Infarctus du myocarde chez la femme : symptômes, facteurs de risque, séquelles neuropsychologiques et impact physiologique en situation de stress

Myocardial Infarction in Women: Symptoms, Risk Factors, Neuropsychological Impairment, and Stress-Induced Physiological Changes

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Résumé

Les maladies cardiovasculaires figurent parmi les principales causes de décès mondial des dernières décennies (Roth et al., 2015; WHO, 2021a). Dans les pays où le produit intérieur brut est moyen ou élevé, les accidents vasculaires cérébraux et l'infarctus du myocarde (IM) représentent les causes de mortalité prévalentes. Au fil des ans, la communauté scientifique a déterminé des répercussions cognitives et émotionnelles significatives chez les survivants de maladies coronariennes et de maladies cardiovasculaires. Nous savons que le vieillissement des populations et les niveaux de stress élevés associés au mode de vie contemporain jouent un rôle déterminant dans le pronostic et le recouvrement des personnes atteintes d'un infarctus du myocarde. Ces facteurs sont associés à un accroissement du fardeau sociétal lié à la prise en charge des survivants. En vieillissant, une proportion plus élevée de femmes que d'hommes sont atteintes de maladies coronariennes, incluant l'infarctus du myocarde. Toutefois, les femmes demeurent sous-représentées dans les études portant sur la récupération associée aux infarctus du myocarde. L'objectif principal de cette thèse est d'élargir les connaissances sur l'association de divers facteurs environnementaux et physiques chez des femmes canadiennes ayant un historique d'infarctus du myocarde. Les travaux scientifiques accomplis sont présentés sous forme de deux études empiriques effectuées auprès d'échantillons de femmes canadiennes ayant ou non un historique d'un infarctus du myocarde ainsi que de deux revues systématiques de la littérature.

La première étude a établi l'état des connaissances sur le paradigme du Trier Social Stress Test que nous avons utilisé comme outil au sein de notre étude en laboratoire. Via une analyse approfondie des protocoles de différents groupes de recherche ayant utilisé le TSST, cette recherche systématique de la littérature a permis d'identifier les éléments essentiels à des conclusions valides et de proposer un ensemble de recommandations visant une standardisation de l'utilisation du Trier Social Stress Test en recherche. La deuxième revue systématique a quant

à elle permis la mise à jour des connaissances actuelles concernant les impacts cognitifs répertoriés chez la femme ayant une maladie coronarienne. Bien que les maladies cardiovasculaires, dont les maladies coronariennes, demeurent sous-étudiées chez la femme, les recherches effectuées durant la dernière décennie suggèrent des altérations cognitives. Les femmes avec un historique de maladies coronariennes rapportent différents problèmes cognitifs suivant leur incident cardiaque. Cette revue systématique a permis une interprétation mieux informée des résultats obtenus dans la quatrième étude.

Au niveau de la collecte de données auprès de population de femmes, un questionnaire en ligne (N = 366) auprès de femmes canadiennes a permis de valider la présence de facteurs de risques et symptômes spécifiques associés à l'infarctus du myocarde. Finalement, une étude en laboratoire a permis de comparer la réponse physiologique (c.-à-d., variabilité du rythme cardiaque et sécrétion salivaire du cortisol) associée à une exposition à un stress social (c.-à-d., Trier Social Stress Test) chez des femmes ayant un historique d'infarctus du myocarde comparé à un groupe contrôle (N = 29).

Cet ensemble de données issu de travaux auprès de participants et des revues systématiques contribue à enrichir la connaissance des affectations physiologiques et cognitives des femmes ayant un historique d'infarctus du myocarde. Notre recherche participe également au raffinement des méthodologies disponibles dans l'examen de ces déficits et l'identification des domaines dans lesquels des recherches supplémentaires sont nécessaires. Nos résultats ont permis de confirmer que les femmes présentent des symptômes différents de ceux décrits par les hommes ; nous soulignons également l'importance que ces symptômes ne soient donc plus qualifiés d'« atypiques ». Nos travaux indiquent la présence de facteurs de risque (p. ex., hypertension) similaires chez les femmes canadiennes et celles d'autres parties du monde. Au niveau de l'étude en laboratoire, nos résultats indiquent que les niveaux subjectifs/perçus de

stress sont semblables entre les groupes des femmes ayant un historique d'infarctus du myocarde et celles n'ayant pas cette condition. Toutefois, nos résultats ne soulignent que des tendances au niveau des changements observés pour les mesures physiologiques prises.

Mots-clés : femmes, infarctus du myocarde, Trier Social Stress Test, fonctions cognitives, Cortisol, variabilité du rythme cardiaque

Abstract

Cardiovascular disease has been a leading cause of death worldwide over the last decades (Roth et al., 2015; WHO, 2021a). In countries with middle or elevated gross domestic product indices, stroke and myocardial infarction represent the prevalent causes of death. Over the years, the scientific community has identified significant cognitive and emotional impacts on survivors of coronary heart disease and cardiovascular disease. We know that ageing populations and high-stress levels associated with contemporary lifestyles play a crucial role in the prognosis and recovery of individuals with myocardial infarction. These factors are associated with an increased societal burden related to survivors' care. As they age, a higher proportion of women than men are affected by coronary heart disease, including myocardial infarction. Nonetheless, women remain under-represented in studies addressing trajectories of recovery associated with myocardial infarction. The arching goal of this thesis is to expand the knowledge on the association of various environmental and physical factors with a history of myocardial infarction in a sample of Canadian women. The accomplished research is presented in the form of two empirical studies carried out on samples of Canadian women with and without a history of myocardial infarction, as well as two systematic reviews of the literature.

The first study established the state of knowledge on the Trier Social Stress Test paradigm, a tool that we later used in our laboratory study. Through an in-depth examination of the protocols used by different research groups, this systematic review identified essential elements for valid conclusions and proposed a set of recommendations for standardizing the use of the Trier Social Stress Test in research. The second systematic review updated the current scientific knowledge concerning the cognitive consequences of women with a history of coronary heart disease. Despite cardiovascular disease, including coronary heart disease, remains

understudied in women, the last decade has seen an emergence of research supporting cognition to be affected. Our findings support subtle cognitive impairments in women with a history of coronary heart disease. Our literature review was conducted to facilitate interpreting the results obtained in a sample of women with a history of MI in this thesis' fourth study.

Regarding data collection, an online questionnaire validated the presence of specific risk factors and symptoms associated with myocardial infarction in a sample of middle-aged Canadian women (N = 366). Finally, a laboratory study measured alterations in the physiological responses (i.e., heart rate variability and salivary cortisol secretion) associated with exposure to a social stressor (i.e., Trier Social Stress Test) in women with a history of myocardial infarction and age-matched controls (N = 29).

This body of data and analytic reviews contribute to expanding the knowledge of physiological and cognitive impairments in women with a MI history. Our research also helps improve testing paradigms to examine deficits and identify areas where further research is needed. Our findings support women experiencing different symptoms than those described in men, and it pleads for these to be no longer described as "atypical." Our work highlights a similar prevalence of certain factors (e.g., hypertension) in Canadian women and women from other parts of the world. In terms of the laboratory study, our results indicate subjective/perceived levels of stress intensity to be comparable between the myocardial infarction and non-myocardial infarction women groups. However, we only found tendencies in changes related to measured physiological variables.

Keywords: *women, myocardial infarction, Trier Social Stress Test, cognitive functions, Cortisol, heart rate variability*

Remerciements

Oh, wow ! Six ans se sont écoulés depuis le commencement de mon programme doctoral, en aucun cas, ce que j'avais prévu ne s'est vraiment pas réalisé. Faire un doctorat m'a appris que dans la vie, il est plus important de s'adapter, changer ses idées et être ouverts à des idées différentes des nôtres pour réussir non seulement ce programme, mais notre vie personnelle.

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À ma famille immédiate, ici au Canada comme au Pérou, merci pour votre soutien. Vous ne vous êtes jamais plaint et m'avez toujours appuyé dans toutes les manières que vous pouviez. J'en serais toujours reconnaissant ! Même si mes animaux ne pourront jamais lire ce message, leur constant soutien émotionnel m'a certainement permis de passer au travers des hauts et des bas. Astro, Yoda et Nora, merci pour tout !

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This doctoral thesis is dedicated to my number one fans, my grandfather and mother. I will never have the chance to celebrate this moment with you because you left this world too early. However, I know that the day I will defend this thesis, you will be with me. Thank you for everything, this is for you.

-Tu Nicopico

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Liste d'abréviations

ACS	Arrêt cardiaque soudain
ACTH	Adrénocorticotrophine
CORT	Cortisol
CRF	Facteur de libération de la corticotropine
DT2	Diabète de type 2
HHS	Axe hypothalamique-hypophysaire-surrénalien
IM	Infarctus du myocarde
MC	Maladies coronariennes
MCO	Maladies du cœur
MCV	Maladies cardiovasculaires
RG	Récepteurs glucocorticoïdes
RM	Récepteurs minéralocorticoïdes
TSST	Trier Social Stress Test

Impact de la pandémie sur mes recherches

La pandémie de COVID-19 obligeant la fermeture de l'université en mars 2020 a eu un impact significatif sur la progression des études 3 et 4. Par exemple, l'échantillon de l'étude 4 a dû être reconsidéré en raison de l'impossibilité de poursuivre les tests en laboratoire. De par la durée de trois heures de l'étude excluant la préparation du matériel et le protocole de passation du TSST nécessitant des juges, mes travaux de recherche exigeaient entre 6 et 10 étudiant(e)s travaillant de manière continue aux différents éléments de ma thèse. Il a donc été impossible de poursuivre la collecte de données des études 3 et 4, réduisant les échantillons des deux études. Les étudiant(e)s n'ayant plus accès à l'université, j'ai dû prendre en charge le travail de l'ensemble de mon équipe afin de compléter l'ensemble des modules de cette thèse. De par la durée des restrictions liées à la pandémie, la composition de cette thèse a dû être repensée en collaboration avec les membres de mon comité. Le document dont vous ferez la lecture présente donc les résultats de quatre composantes ciblées au sein de l'ensemble du projet doctoral. Certains éléments liés à la collecte de données ont dû être omis de ce document. Ces éléments feront l'objet de publications qui seront complétées et soumises dans une phase ultérieure.

Contributions

I divided my thesis into six chapters, including four research chapters. I contributed to the conceptualization, methodology, formal analysis, writing the original draft, and project administration of each article. Dr. Plamondon and I discussed all aspects of this research. She assured the research's supervision, reviewed the manuscripts, and funded the projects.

It is well known that females/women encounter several obstacles to overcome in publishing scientific articles (Duch et al., 2012; Holman et al., 2018; Huang et al., 2020; Larivière et al., 2011). I had the chance to supervise many undergraduate students during my doctoral studies. Their research contribution deserved to be mentioned. It was a pleasure to acknowledge the work they produced via authorships on articles and research communications and support female/women and/or individuals of Colour.

On the cover page of every article, the Contributor Roles Taxonomy (CRediT) can be found (Allen et al., 2019). The CRediT allows to recognize the contribution of every author. For your information, I am providing the table from Allen et al. (2019), which explains every term.

Table 1 *(Table 1 for the Prologue of the thesis)* Contributor Roles Taxonomy (CRediT)

Term	Definition
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims
Formal analysis	Application of statistical, mathematical, computational, or other formal techniques to analyse or synthesize study data
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection
Resources	Provision of study materials, reagents, materials, patients, laboratory

Term	Definition
	samples, animals, instrumentation, computing resources, or other analysis tools
Data curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use
Writing – original draft	Preparation, creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation)
Writing – review and editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team
Project administration	Management and coordination responsibility for the research activity planning and execution
Funding acquisition	Acquisition of the financial support for the project leading to this publication

Status of Scientific Papers

First paper

The first paper, 'A Systematic Review of the Trier Social Stress Test methodology: Issues in promoting study comparison and replicable research,' is published. We published this paper in Neurobiology of Stress, https://doi.org/10.1016/j.ynstr.2020.100235

Second paper

The second paper, 'Neuropsychological Sequelae of Coronary Heart Disease in Women: A Systematic Review,' is published. We published this paper in Neuroscience & BioBehavioural Reviews, https://doi.org/10.1016/j.neubiorev.2021.05.026

Third paper

The third paper, 'Myocardial Infarction in a sample of Canadian Women: An exploratory study of symptomology and prominent risk factors,' will be restructured following the thesis defence recommendations. Therefore, the publication is pending.

Fourth paper

The fourth paper, 'The Impact of Myocardial Infarction on basal and stress-induced heart rate variability and cortisol secretion in Women: A pilot study,' is published. We published this paper in Comprehensive Psychoneuroendocrinology, https://doi.org/10.1016/j.cpnec.2022.100113

Chapitre I – Introduction générale

1.0 Introduction générale

En 2019, un tiers des décès mondiaux répertoriés étaient liés aux maladies cardiovasculaires (MCV), touchant 17,9 millions d'individus (WHO, 2021a). Le terme MCV représente la grande famille de maladies qui affectent le cœur et les vaisseaux sanguins y étant associés. Au sein des MCV, les maladies du cœur (MCO), incluant les maladies coronariennes (MC) – aussi appelées coronaropathies ou cardiopathies ischémiques – représentent le type le plus communément répertorié en Amérique du Nord et en Europe (Virani, et al., 2020). Au Canada, les MC occupent le deuxième rang des causes de décès dans la population générale (Public Health Agency of Canada, 2017). Aux États-Unis, l'incidence des MC au sein de la population a rapidement cru ; d'une incidence de décès très rare au début du 20^{e} siècle, les MC ont atteint, à peine trois décennies plus tard, la première position du palmarès des principales causes de décès (Dalen et al., 2014). Le nombre de personnes atteintes de MC continue de croître annuellement (Virani et al., 2020).

Les MC sont étroitement liées à la formation d'athérosclérose dont la présence induit un durcissement et un rétrécissement des artères coronaires (Davis, 2005). L'accumulation des plaques athéromes entraîne une réduction significative de l'apport en nutriments et oxygène vers le cœur (Pepine et al., 2006). Cette présentation clinique peut ultimement causer un infarctus du myocarde (IM ; Naik et al., 2006; Thygesen et al., 2012). L'IM - communément appelé crise cardiaque - est le type de MC le plus prévalent (Nichols et al., 2014). Les IM et les accidents vasculaires cérébraux sont responsables de plus de 85,0 % des décès reliés aux MCV (WHO, 2021a). Aux États-Unis, une personne décède d'un IM toutes les 39 secondes (Virani, et al., 2020). Au Canada, parmi les 2,4 millions de Canadien(ne)s vivant avec une MC, près du quart d'entre eux ont un historique d'IM (Public Health Agency of Canada, 2018). Les dépenses

associées à la détection, la prise en charge, les traitements hospitaliers et le soutien post-hospitalier promulgués aux individus affectés par une MCO, MC ou IM représentent un fardeau économique et social considérable. Annuellement, les États-Unis dépensent environ 219 milliards de dollars dans la prévention et la prise en charge des MCO – dont 12,1 milliards pour les IM et 9 milliards pour les MC (CDC, 2020) - alors qu'au Canada, les dépenses associées aux MCV sont estimées à 22,2 milliards (Smolderen et al., 2010). Les MC représentent le groupe de maladies qui affectent le plus les femmes (Virani., 2020). Toutefois, les études sur les conséquences associées à ce groupe de maladies chez les femmes demeurent peu nombreuses (Heart & Stroke, 2018; Khan et al., 2020). L'omission de l'inclusion des femmes dans la recherche humaine (Jin et al., 2020; Liu & Mager, 2016; Nowogrodzki, 2017; Pinn, 2003) et animale (Becker et al., 2016; Beery & Zucker, 2011; Kim et al., 2021; Prendergast et al., 2014) pendant plusieurs décennies a contribué à des constats et des recommandations scientifiques biaisés.

1.1 Une sous-représentation des femmes dans la recherche contemporaine

Les caractéristiques et réactions physiologiques distinctes des femmes et des hommes sont liées à des différences connues dans la manière dont les maladies s'expriment chez les deux sexes[1]. Malgré cette connaissance, les recherches continuent de privilégier l'étude d'échantillons humains/animaux composés d'hommes/mâles (Nature, 2010), un biais de sélection qui s'avère extrêmement préjudiciable pour les femmes (Upchurch, 2016). Malgré une augmentation de leur représentation au sein des études scientifiques depuis les années 2000, la représentation des femmes demeure loin d'atteindre des proportions équivalentes à celle des hommes (Kim et al.,

[1] Dans cette thèse, lorsque nous utilisons les termes « femmes » et « hommes », nous faisons référence aux caractéristiques biologiques de l'être humain, à moins d'indication contraire. En d'autres mots, nous faisons allusion aux termes anglais « *females* » et « *males* ».

2010). Un écart est également présent dans les études animales (Marts & Keitt, 2004). Par exemple, Beery & Zucker (2011) ont revu près de 2000 études animales et ont constaté un biais dans l'utilisation de sujets mâles : les ratios mâles/femelles des échantillons étant de 5,5 : 1 pour les études en neuroscience, de 5 : 1 en pharmacologie et de 3,7 : 1 en physiologie. Afin de contrer ce problème, plusieurs initiatives ont été adoptées visant à augmenter le nombre de femmes dans les études cliniques, incluant la création de l'Office of Research on Women's Health et l'adoption du *National Institutes of Health Revitalization Act* aux États-Unis (Kim et al., 2010). Au Canada, nous avons le *Document d'orientation : Considérations relatives à l'inclusion des femmes dans les essais cliniques et à l'analyse des données selon le sexe* ainsi que la Politique en matière d'analyse comparative fondée sur le sexe et le genre (Yakerson, 2019). Néanmoins, l'inclusion des femmes dans les études cliniques n'a pas augmenté de manière significative (Geller et al., 2018). Par conséquent, les professionnels de la santé, de même que les responsables des politiques de santé, continuent de prendre des décisions et baser leurs recommandations diagnostiques et thérapeutiques visant les femmes en s'appuyant sur un compendium d'études effectuées auprès des hommes (Ballantyne & Rogers, 2011; Bryant et al., 2018; Mansukhani et al., 2016; Woitowich et al., 2020; Yoon et al., 2014).

1.1.1 Les femmes et la recherche sur les maladies cardiovasculaires

Les études sur les MCV, incluant les MC, ne sont pas épargnées par un biais dans la représentation des sexes. Historiquement, l'exclusion des femmes des essais cliniques a contribué à perpétuer une croyance de la prépondérance de ces maladies chez les hommes (Clayton & Arnegard, 2018; Miracle, 2010; Pathak et al., 2017), malgré une connaissance dès le début du 21^{e} siècle de l'existence de proportions équivalentes, voire plus élevées, de MCV chez les femmes - en lien avec la ménopause et le vieillissement (Mikhail, 2005; Wenger, 2012). Ce

n'est qu'au cours des deux dernières décennies que la communauté scientifique a sonné l'alarme, soulignant le fait que les MCV occupent le premier rang mondial des causes de décès chez les femmes (Gholizadeh & Davidson, 2008; Woodward, 2019). Cette récente reconnaissance explique en partie le fait que plus des deux tiers des résultats des recherches cliniques sur les MCO sont issus d'analyses effectuées à partir d'échantillons majoritairement composés d'hommes (Heart & Stroke, 2018). Une recension récente effectuée par Gong et al. (2019) montre une augmentation progressive du pourcentage de femmes participant à des essais cliniques sur les MCV, passant de 20,7 % pour la période de 1986 à 1990 à 32,6 % pour la période de 2011 à 2015. Néanmoins, nous sommes forcés de constater que le nombre de participantes demeure non représentatif en rapport à la proportion de femmes atteintes de MCV dans la population générale. Les répercussions d'un tel écart se manifestent au niveau des connaissances que les femmes elles-mêmes peuvent avoir en ce qui touche le développement des MCV, notamment à leur présentation clinique. À ce sujet, un récent rapport de l'American Heart Association (Virani et al., 2020) souligne des améliorations; alors que moins du tiers (30,3 %) des femmes savaient que les MCV représentaient la première cause de décès chez cette population en 1997, un peu plus de la moitié (56,0 %) des femmes étaient au fait de cette information en 2012.

Ce manque d'information quant à la santé des femmes a des répercussions significatives, liées entre autres au faible niveau de connaissances des médecins quant à l'incidence et la présentation clinique des MCV chez les femmes (Maas et al., 2011). Mosca et al. (2005) ont rapporté que moins de 20 % des médecins étaient au courant de la plus grande vulnérabilité des femmes aux MCV en comparaison aux hommes. Une décennie plus tard, cette proportion demeure stable avec un peu plus d'un médecin de famille sur cinq (22,0 %) et un peu plus du

deux cinquièmes (42,0 %) des cardiologues se déclarant suffisamment qualifiés pour évaluer le risque de MC chez les femmes (Bairey Merz et al., 2017). Ce biais des connaissances semble davantage préjudiciable lorsque le médecin traitant une femme ayant subi un IM est un homme. Greenwood et al. (2018) ont découvert que les femmes avaient de meilleures chances de survie à la suite d'un IM lorsque le médecin traitant était une femme, s'exprimant par une réduction de 12,0 % du taux de mortalité lié à l'IM. Incidemment, ces chercheurs ont également remarqué que plus les hommes médecins avaient de l'expérience à promulguer des soins aux femmes, ou lorsque ces derniers côtoyaient un nombre important de collègues médecins femmes au sein de leur pratique, plus les taux de mortalité lors d'IM diminuaient chez leurs patientes. Considérant ces différences quant à la prise en charge médicale selon le sexe, il n'est pas étonnant de constater qu'en moyenne, les femmes encourent un risque accru de 30,0 % de mourir d'un IM en comparaison aux hommes (Public Health Agency of Canada, 2018), ce qui se traduit par un taux de mortalité plus élevé à long terme (Bucholz et al., 2014; Li et al., 2016).

Une autre raison vient du fait que les femmes et les hommes présentent des symptômes distincts associés à l'IM (McSweeney et al., 2010). Les symptômes des femmes sont fréquemment considérés « atypiques » par les médecins ce qui constitue une barrière importante dans le diagnostic d'un IM (Kosuge et al., 2006; Mosca et al., 2011). Par exemple, Lichtman et al. (2018) ont rapporté qu'un plus grand nombre de femmes que d'hommes (29,5 % *vs* 22,1 %, respectivement; $p < 0.001$) ont cherché de l'aide médicale avant d'être hospitalisés pour leur IM. Ces chercheurs ont également identifié qu'un peu plus de la moitié des femmes (53,4 %) – comparé à 36,7 % des hommes ($p < 0.001$) – ont indiqué que les médecins consultés ne pensaient pas que leurs symptômes étaient liés à un IM, alors qu'elles vivaient un événement cardiovasculaire au moment de la prise en charge clinique. La microvasculature coronaire des

hommes et des femmes présente des différences qui sont elles-mêmes associées à une prédisposition et des répercussions variables à l'IM selon le sexe (Coutinho et al., 2018). En effet, les vaisseaux coronaires plus fins des femmes engendrent un débit sanguin plus élevé que chez les hommes les plaçant davantage à risque de dommages des vaisseaux sanguins lors d'IM, ainsi qu'une augmentation des effets néfastes sur l'anatomie et la fonction du cœur (Patel et al., 2016). Cette différence physiologique représente également un facteur contribuant à un taux plus élevé d'IM chez les femmes en comparaison aux hommes (Kothawade & Merz, 2011). Ainsi, un ensemble de facteurs contribuent à une présentation différente de l'IM selon le sexe. À cet égard, l'éducation des professionnels de la santé ainsi que de la population générale demeure un réel enjeu pour une sensibilisation, une prise en charge et des traitements adéquats (Cushman et al., 2021).

1.1.2 Les particularités de l'infarctus du myocarde chez la femme

Tel que mentionné, les différences entre les sexes dans la présentation clinique de l'IM demeurent méconnues des femmes (McDonnell et al., 2014) et des professionnels de la santé (Woodward, 2019), une situation en partie liée au maintien de la croyance que les hommes sont davantage affectés par l'IM que les femmes (Clayton & Arnegard, 2018). Bien que l'angine de poitrine – aussi connue sous le nom de « douleur thoracique » - soit l'un des seuls symptômes classiques associés à un IM autant chez l'homme et la femme (Arora & Bittner, 2015; Ferry et al., 2019; Lichtman et al., 2018), les femmes présentent une panoplie de symptômes qui sont différents de ceux des hommes. Ceux-ci tendent à être plus diffus en nature, tels que : a) une fatigue extrême; b) de l'anxiété; c) des difficultés reliées au sommeil; d) des vertiges; e) des étourdissements; f) l'évanouissement; g) l'essoufflement; h) une douleur ou une pression dans le haut du dos, à la mâchoire, dans la partie supérieure de l'abdomen ou dans la partie inférieure du

thorax; i) des brûlures d'estomac; et i) des sueurs (Dey et al., 2009; Lichtman et al., 2018; Mehta., et al., 2016; Virani, et al., 2020; Woodward, 2019). Ces symptômes étant plus subtils et méconnus, les femmes ont tendance à les associer à des troubles, à des maladies ou à des conditions moins graves, n'affectant pas la survie, comme le reflux acide, la grippe, l'anxiété ou même le vieillissement normal (Albarran et al., 2007; Dempsey et al., 1995; O'Donnell & Moser, 2012). Il n'est donc pas étonnant d'apprendre que 8 femmes sur 10 omettent les signes précoces d'un IM (Heart & Stroke, 2018); ces femmes ayant des symptômes « atypiques », leur trouble est également plus susceptible d'être mal diagnostiqué ou de ne pas l'être du tout (Cushman et al., 2021). De plus, une autre particularité de l'IM chez la femme et que ce dernier tend à être moins prévalent avant la ménopause alors qu'une augmentation graduelle de l'incidence est observée vers la fin de la décennie suivant la ménopause. Ainsi, Savonitto et al. (2018) ont suggéré que les résultats contradictoires dans la littérature scientifique quant aux taux de mortalité des IM rapportés chez les femmes sont probablement dus au manque de rigueur dans le suivi des populations chez la femme ainsi que des intervalles examinés.

1.1.3 La ménopause et l'infarctus du myocarde chez la femme

La ménopause, définie opérationnellement comme la cessation spontanée des menstruations pour une période de 12 mois consécutifs, commence entre 49 et 52 ans chez la majorité des femmes (Morabia & Costanza, 1998). Cependant, certains facteurs sont associés à une ménopause prématurée ou précoce comme la consommation de tabac, un faible indice de masse corporelle, une nulliparité (c.-à-d., ne pas avoir eu d'enfant) et/ou un faible niveau d'éducation (Gold et al., 2001; Parazzini & PMIS Group, 2007). De plus, il est important de noter que la ménopause ne se déroule pas sur un intervalle temporel précis, mais se matérialise à la suite d'une transition de plusieurs changements physiologiques au cours des années précédant

cette transition physiologique chez la femme. En effet, Harlow et al. (2012) ont établi l'ensemble de conditions et règles quant aux stades liés au processus de maturation du système reproductif chez la femme selon le *Stages of Reproductive Aging Staging System.* Ce système identifie trois principales phases, soit (a) la reproduction, (b) la périménopause (transition vers la ménopause) et (c) la ménopause; ainsi que sept différentes étapes au sein de ces trois phases. La périménopause est la période de transition où la femme va avoir ses dernières règles; l'âge moyen du début des irrégularités menstruelles est de 47,5 ans (Ferrell et al., 2006). En moyenne, la périménopause dure 5 ans, mais les symptômes peuvent commencer jusqu'à 8 ans avant les dernières règles (McNamara et al., 2015). La dernière phase, la ménopause, arrive en moyenne vers 51 ans, lorsque la femme n'a plus de saignements vaginaux liés aux menstruations (Kato et al., 1998).

Une controverse demeure quant aux mécanismes physiologiques de la ménopause étant liés à l'accroissement du risque de MC (Kim et al., 2015). Plusieurs études suggèrent qu'une ménopause qui se déroule de manière naturelle n'augmente pas le risque, mais si une femme a une ovariectomie bilatérale ou une hystérectomie avec ou sans ovariectomie, ce risque augmente (Atsma et al., 2006; Colditz et al., 1987; Gordon et al., 1978; Howard et al., 2005; Parker et al., 2009). Par ailleurs, l'âge de la ménopause a un impact significatif, les femmes étant ménopausées jeune (avant 45 ans) ayant un risque accru de développer une MCV (Wellons et al., 2012). À cet effet, les données de 15 études soulignent des risques accrus de développer une MC chez les femmes ayant eu une ménopause prématurée (< 40 ans) ou précoce (40 à 44 ans) en comparaison aux femmes ayant eu leur ménopause à un âge plus avancé (50-51 ans ; Zhu et al. , 2019). Toutefois, la littérature existante ne permet pas de statuer fermement le rôle de l'âge ou de l'induction subite de la ménopause par chirurgie sur le développement des MC (Jacoby et al.,

2009, 2011; Lobo, 2007).

Depuis la fin des années 1990, il est connu que la ménopause constitue un facteur de risque quant au développement des MC (Tunstall-Pedoe, 1998). Jusqu'à cette étape de maturation physiologique, les niveaux d'œstrogènes plus élevés chez la femme confèrent un effet cardioprotecteur (Iorga et al., 2017; Mendelsohn & Karas, 1999), nourrissant la croyance que les femmes sont protégées des MC (Gouva & Tsatsoulis, 2004). En effet, l'œstrogène permet aux vaisseaux sanguins d'avoir une élasticité supérieure facilitant une meilleure circulation sanguine (Xing et al., 2009). En situation de ménopause, la diminution de l'œstrogène peut augmenter les possibilités de différentes maladies incluant l'athérosclérose, qui figure comme un précurseur à l'IM (Reslan & Khalil, 2012). Étant donné une diminution graduelle des taux d'œstrogène, le diagnostic de MC survient en moyenne 8 à 10 ans suivant la ménopause (Saeed et al., 2017; Leening et al., 2014). Toutefois, le risque demeure tout aussi élevé au fil du temps (Leening et al., 2014). À cet effet, McSweeney et al. (2016) rapportent que la proportion de MC diagnostiquées est équivalente chez les deux sexes lorsque les comparaisons entre les groupes sont ajustées en fonction de l'âge, permettant ainsi de tenir compte de l'apparition d'un diagnostic plus tardif des MC chez les femmes. Bien que le vieillissement augmente le risque des MC chez les deux sexes, l'apparition de la ménopause à un âge moyen de 50 ans (Nelson, 2008) représente à elle seule un facteur majeur augmentant le risque de développer une MC chez la femme (Mehta, Beckie Theresa M., et al., 2016; Newson, 2018; Wake & Yoshiyama, 2009).

Dans les années 1980 et 1990, les recherches ont suggéré qu'un traitement hormonal substitutif pouvait diminuer l'incidence des MCV (Grady et al., 1992; Guetta & Cannon, 1996). L'initiation d'une série d'essais cliniques entre 1993 et 1998, au sein du *Women's Health Initiative* visait à tester les effets de suppléments hormonaux chez des milliers de femmes

ménopausées. Ces essais cliniques ont toutefois été interrompus en 2002 à la suite d'observations quant à la prise de suppléments d'œstrogène et de progestérone chez les femmes âgées entre 50 et 79 ans. En effet, les chercheurs ont trouvé que les effets de suppléments hormonaux augmentaient de 41,0% et 29,0% les risques de subir un accident vasculaire cérébral ou de développer une MC, respectivement (Writing Group for the Women's Health Initiative Investigators, 2002). Plusieurs études publiées subséquemment ont souligné des problématiques dans les analyses et l'interprétation des données mettant en doute la validité des conclusions initiales (Lobo, 2013). Notamment, certains résultats présentant des tendances vers des différences furent interprétés comme étant des observations significatives (Manson et al., 2003). De plus, des résultats ont été rapportés différemment d'une étude à l'autre (Stevenson et al., 2009). À titre d'exemple, lors d'analyses subséquentes d'un ensemble de données, Salpeter et al. (2006) ont trouvé que le traitement hormonal substitutif réduisait le risque de MC chez les femmes ménopausées qui étaient plus jeunes, alors que chez les femmes ménopausées qui étaient à un âge plus avancé, le risque d'une MC augmentait avant de diminuer au fil du temps. Pour ce qui est du risque relié au cancer du sein, Anderson et al. (2006) ont indiqué qu'ils n'avaient pas assez de données longitudinales pour pouvoir dresser un portrait clair concernant les liens du traitement hormonal substitutif et l'incidence du cancer du sein. Dans tous les cas, les résultats de cette large étude ont bouleversé la communauté scientifique, et à ce jour la présentation de ces résultats continue d'influencer la perception des femmes (p.ex., croyance populaire) quant aux effets bénéfiques des suppléments hormonaux. Depuis, plusieurs groupes de recherche n'ont montré aucun accroissement des risques de développer une MC ou subir un IM associé à la prise de suppléments hormonaux (Manson et al., 2013; Rossouw et al., 2007; Yang et al., 2013), malgré une utilisation qui demeure controversée (Manson et al., 2013; Marjoribanks et al., 2017).

1.1.4 Facteurs de risque et maladies coronariennes

Outre la ménopause, plusieurs facteurs sont associés à l'accroissement du risque de subir un IM (Pedersen et al., 2016), dont certains sont davantage préjudiciables pour les femmes que les hommes (Anand et al., 2008; Andrés et al., 2011; Mosca et al., 2011). Dès les années 80, les chercheurs ont indiqué que certaines conditions médicales incluant l'hypercholestérolémie, l'hypertension et le diabète de type 2 (DT2) augmentaient davantage le risque de développer une MC, incluant l'IM, et d'engendrer des conséquences plus néfastes chez les femmes (Abbott et al., 1988; Brezinka & Padmos, 1994; Eaker et al., 1989; Mehta, Beckie Theresa M., et al., 2016; Wilson, 2001). Plus récemment, Lu et al. (2019) ont conduit une des rares études avec un grand échantillon (N = 11,036; n_{femmes} = 5705; 51,7%) afin d'évaluer la prévalence de l'hypercholestérolémie, l'hypertension et du diabète de type 2 (DT2) quant aux effets cumulatifs de ces derniers permettant d'expliquer le développement d'un IM ou d'un accident vasculaire cérébral. Ces chercheurs ont souligné que l'hypertension et l'hypercholestérolémie sont des facteurs importants à prendre en considération puisqu'ils jouent un rôle important dans la probabilité de subir un IM, surtout à un âge plus avancé. Cette recherche associée à plusieurs autres ayant des échantillons plus petits ont permis de déterminer que ces facteurs de risque (c.-à-d., hypertension, hypercholestérolémie et DT2) exercent un rôle prépondérant dans le développement de MCV et MC chez les femmes en comparaison aux hommes (Bloomgarden, 2007; Petrie et al., 2018; Sehestedt et al., 2011; Barrett-Connor & Bush, 1991; Hokanson & Austin, 1996; Os et al., 1993) et que leur présence chez ces dernières est associée à un pronostic de récupération moins favorable et une mortalité accrue (Huxley et al., 2006; Jonsdóttir et al., 2002; Klempfner et al., 2016; Millett et al., 2018; Smith & Vale, 2006). Par exemple, le DT2 augmente de 50,0% les risques de subir un IM chez l'homme alors que chez la femme, cette

condition augmente ce risque de 150,0% (Barrett-Connor et al., 2004). En 2015, une analyse systématique de 64 études, contenant plus de N = 900,000 individus, a indiqué que la présence de D2T triplait le risque d'avoir une MC chez les femmes alors que ce facteur augmentait doublait ce risque chez les hommes (Peters et al. , 2015). Simultanément, des chercheurs ont noté que la transition vers la ménopause jouait un rôle important dans l'expression de ces différences entre les sexes due au rôle protecteur de l'œstrogène (voir section 1.1.3; Chiha et al., 2012; Gudmundsdottir et al., 2012; Pardhe et al., 2017).

Davantage de recherches sont nécessaires pour comprendre les mécanismes physiologiques sous-jacents à ces différentes entre les sexes. De plus, malgré une augmentation du nombre de travaux scientifiques conduits dans un contexte canadien (Heart & Stroke, 2018; Izadnegahdar et al., 2014; Norris, Yip, Nerenberg, Clavel, et al., 2020; Norris, Yip, Nerenberg, Jaffer, et al., 2020), les recommandations établies sont largement basées sur les résultats d'études effectuées en Europe ou aux États-Unis. Nous savons que le vieillissement est lié à une augmentation de l'expression de problèmes cognitifs, incluant la démence, et que ce risque croit plus l'individu avance en âge (WHO, 2012). Ainsi, sachant que les MC surviennent à un âge plus avancé chez les femmes, il est important de mieux caractériser et isoler le degré d'atteinte cognitive lié aux MC. Ceci est également pertinent par le fait qu'un plus grand nombre de femmes que d'hommes sont atteintes de démence ou de la maladie d'Alzheimer (Beam et al., 2018).

1.2 Les maladies coronariennes et le cerveau : conséquences cognitives

Dans les années 80, il devenait de plus en plus clair que les maladies affectant les organes périphériques, incluant les MC, avaient également des répercussions sur le fonctionnement du cerveau (Natelson, 1985). Au fil des ans, des recherches pluridisciplinaires ont permis de

confirmer des répercussions importantes et mesurables sur les processus cognitifs (c.-à-d., atteintes de processus mentaux liés à l'acquisition et au maintien des connaissances) liées aux MCV. Au cours de la dernière décennie et malgré un nombre toujours limité d'études, le lien entre les MC et les répercussions cérébrales s'est concrétisé (Abete et al., 2014; Qiu & Fratiglioni, 2015; van Buchem et al., 2014). Chez l'animal, l'impact de l'IM sur les circuits cérébraux a également été exploré. Par exemple, Kaplan et al. (2018) ont trouvé que les rats ayant subi un IM demeuraient à risque d'avoir des dysfonctions cognitives dues à des problèmes de vascularisation jusqu'à 30 jours suivant l'IM. Malick et al. (2018) et Liu et al., (2014) ont également souligné des impacts cognitifs post-IM, particulièrement dans les régions cérébrales du système limbique, affectant la mémoire spatiale, les comportements sociaux reliés à l'anxiété et induisant des comportements d'anhédonie et de l'impuissance acquise (comportements nommés « depressive-like behaviours » chez l'animal). Ces dommages cérébraux démontrent la vulnérabilité des cellules nerveuses cérébrales aux changements d'oxygène et aux substrats de glucose induits par un IM (Buja, 2005; Carden & Granger, 2000). Par ailleurs, l'intensité et la durée de l'IM détermine la privation de l'apport sanguin au cœur et l'étendue des dysfonctions cérébrales (Willie et al., 2014; Daga et al., 2011; Karwowski et al., 2017; Basit et al., 2021).

L'hippocampe, une région cérébrale du système limbique, s'avère particulièrement sensible au manque d'oxygène en raison de la vulnérabilité des neurones pyramidaux qui composent ses couches cérébrales (Cervós-Navarro & Diemer, 1991; Nitsch et al., 1989; Papp et al., 2008). Des dommages sélectifs affectant l'hippocampe à la suite d'un IM (Liu et al., 2014; Malick et al., 2018) ou une ischémie cérébrale globale (Bantsiele et al., 2004; Corbett et al., 2006; Gerhardt & Boast, 1988; Petito et al., 1987; Wang & Corbett, 1990) affectant l'animal ou l'humain engendrent des dysfonctionnements émotionnels et cognitifs (Neumann et al., 2013).

L'hippocampe étant interconnecté à différentes régions du cerveau via les voies méscorticolimbiques (p. ex. amygdale, noyau accumbens, cortex préfrontal), l'impact des MC est diffus et susceptible d'affecter différentes fonctions cognitives (Barekatain et al., 2014; Natelson, 1985; Roberts et al., 2010; Talman, 1985). À ce jour, les études ayant utilisé des techniques d'imagerie afin de détecter des changements cérébraux chez les personnes vivant avec une MC ont trouvé que des changements affectant la matière grise (au sein de plusieurs noyaux cérébraux) et blanche (faisceaux de fibres et projections), la quantité de tissu cérébral (volume de matière cérébrale) ainsi que le volume du liquide céphalorachidien non ventriculaire sont corrélés à des déficits au sein de plusieurs domaines cognitifs (Ottens et al., 2017; Santiago et al., 2015; Vidal et al., 2010; Zheng et al., 2012). À titre d'exemple, Ottens et al. (2017) ont comparé les scans cérébraux d'individus avec et sans une MC ayant accompli des tâches cognitives évaluant la mémoire de travail à court terme et la capacité d'attention partagée. Ces chercheurs ont suivi durant plus de 7 ans un groupe d'individus ayant une MC (n = 102; 75,0 % d'hommes) et un groupe contrôle n'ayant pas de MC connue (n = 48; 40,0 % d'hommes). Les résultats obtenus ont indiqué un volume cérébral global du groupe MC inférieur de 2,0 % à celui du groupe contrôle, accompagné d'une augmentation du liquide céphalorachidien non ventriculaire. Les auteurs ont noté une association entre l'atrophie cérébrale et une déficience cognitive (c.-à-d., un terme ici utilisé pour définir un individu ayant des difficultés à se remémorer de l'information, à apprendre de nouvelles choses, ou à fonctionner quotidiennement de façon autonome et sans aide); ils ont toutefois également suggéré une contribution à cette détérioration neurocognitive de facteurs pathogéniques (c.-à-d., athérosclérose). En effet, différentes conditions médicales, tels l'hypertension artérielle (McGuinness et al., 2009; Razay et al., 2009) et le diabète (Ahtiluoto et al., 2010; Matsuzaki et al., 2010) associées aux MCV, aux MC et aux

IM (particulièrement chez les femmes; Moshki et al., 2015) sont liés à une augmentation des risques de développer une démence (c.-à-d., « syndrome dans lequel on observe une dégradation de la mémoire, du raisonnement, du comportement et de l'aptitude à réaliser les activités quotidiennes » [WHO, 2021b]).

Dans la dernière décennie, les recherches ont en effet confirmé une accélération du déclin cognitif (Gharacholou et al., 2011; Xie et al., 2019) et une augmentation des risques de développer un diagnostic de démence (Deckers et al., 2017) étant associées aux MC. De façon analogue, l'IM est associé à une augmentation significative d'incapacité cognitive fonctionnelle à long terme, s'exprimant parfois plus de dix ans suivant l'incident (Levine et al., 2014). Ces chercheurs ont recueilli de l'information sur 12 ans sur $N = 450$ patients ayant eu un IM, dont $n = 345$ ont eu besoin de plusieurs hospitalisations relatives à leur IM. Ils ont trouvé que les patients avaient des limitations supplémentaires peu de temps après l'IM, et que l'IM a accentué les problèmes cognitifs de ceux qui en présentaient avant cet évènement cardiaque et augmenté le pourcentage de survivants présentant des troubles cognitifs modérés à sévères (9,6 % *vs* 15,1 %). De manière générale, il est attendu que les personnes atteintes d'un IM démontrent des difficultés reliées à l'attention, la résolution de problèmes, la mémoire, les habilités visuospatiales et les fonctions exécutives (Antony & Joseph, 2013; Roberts et al., 2010; Sherin et al., 2010; Singh-Manoux et al., 2003, 2008).

À ce jour, la recherche de Haring et al. (2013) est la seule étude visant à élucider les conséquences des MC et des IM sur les fonctions cognitives étant composé exclusivement d'un échantillon composé de femmes ($N = 7479$). Ces chercheurs ont trouvé un risque accru chez les femmes vivant avec une MC de présenter un déclin cognitif (ratio de risque, 1,29; 95 % IC : 1,00, 1,67), ce risque étant plus élevé chez les femmes ayant un historique d'IM (2,10; 95 % IC :

1,40, 3,15). Par ailleurs, ces chercheurs ont souligné que les femmes présentant de l'hypertension et du D2T en l'absence de pathologie cardiovasculaire avaient également un risque accru de déclin cognitif (Haring et al., 2013). Ces deux conditions sont notamment souvent présentes chez les individus ayant un IM et connues pour avoir des impacts au niveau cognitif. Malheureusement, l'expression de ces conditions étant souvent préalables à l'IM, une isolation des conséquences directes de l'IM sur les fonctions cognitives chez la femme demeure à définir.

En somme, les MC représentent un facteur de risque indépendant dans le développement d'une déficience cognitive légère non amnésique (c.-à-d. avec une mémoire intacte, mais une détérioration significative d'une ou plusieurs autres fonctions cognitives), dont l'association est plus grande chez les femmes (Roberts et al., 2013). De plus, il semble que des facteurs associés à une augmentation des niveaux de stress et/ou d'anxiété puissent agir comme déclencheurs d'un IM. À ce sujet, Witte et al. (2000) ont rapporté une augmentation significative du taux de mortalité lié à des accidents cardiovasculaires chez les hommes le jour de l'élimination l'équipe néerlandaise du championnat européen de soccer en 1996, sans augmentation significative chez les femmes. Par ailleurs, une récente analyse des données de deux études prospectives (N = 918 participants ayant vécu un IM - 34 % de femmes) souligne une association significative entre le niveau de stress psychologique élevé rapporté par les participants et une augmentation du taux de mortalité cardiovasculaire ou d'IM non fatal (Vaccarino et al., 2021). Ainsi, les niveaux de stress ressentis chez un individu semblent être un facteur pouvant jouer un rôle sur la récupération ou le pronostic lors d'un IM.

1.3 Dysfonctions de l'axe hypothalamo-hypophysaire surrénalien lors d'un IM

Nous connaissons de longue date les dérèglements possibles de l'axe hypothalamo-hypophysaire-surrénalien (HHS) suivant un arrêt cardiaque (Hékimian et al., 2004; Kim et al.,

2011; Schultz et al., 1993). À ce jour, il n'existe pas de recherche examinant les conséquences de l'IM sur le fonctionnement de l'axe HHS. Lors d'un arrêt cardiaque ou d'un IM, la diminution du flux sanguin et le manque d'oxygénation cérébrale associés entrainent des répercussions sur le fonctionnement des réseaux neuronaux. Les études sur les animaux indiquent qu'il y a un impact neuronal suivant un IM. Dès lors, il est envisageable que l'IM ait des impacts similaires, possiblement minimisés en rapport à ceux associés à l'arrêt cardiaque, mais cet impact n'a pas encore étudié chez l'humain.

1.3.1 L'impact du stress sur l'activation de l'axe hypothalamo-hypophysaire-surrénalien

Un changement de la réponse au stress associé à une MC ou MCV peut engendrer des répercussions néfastes sur les fonctions cognitives, voire accélérer le déclin cognitif (Scott et al., 2015). L'activation de l'axe HHS en réponse à un stress constitue une réponse physiologique plus lente que celle liée à la sécrétion quasi immédiate d'adrénaline par la glande médullosurrénale. L'activation de l'axe HHS est conséquente à l'exposition à un stress, qu'il soit de nature physique ou psychologique. Cette activation provoque la sécrétion d'un peptide appelé facteur de libération de la corticotropine (CRF) par le noyau paraventriculaire de l'hypothalamus (Rivier & Vale, 1983; Vale et al., 1981). La sécrétion de CRF via l'activation de deux sous-types de récepteurs, le CRF de type 1 ou de type 2, déclenche une cascade de réactions physiologiques (Smith & Vale, 2006). Les récepteurs CRF de type 1 exercent un rôle prédominant au niveau cérébral et lors d'un stress - étant particulièrement exprimés dans la glande pituitaire, le cortex cérébral, le cervelet et l'hippocampe (Kishimoto et al., 1995; Potter et al., 1994; Van Pett et al., 2000). Le CRF libéré de l'hypothalamus atteint la glande pituitaire via la veine porte et engendre la sécrétion de l'adrénocorticotrophine (ACTH), qui elle emprunte la circulation sanguine et stimule la sécrétion de glucocorticoïdes par la portion corticale de la glande surrénale, soit le

cortisol (CORT) chez l'être humain ou la corticostérone chez les rongeurs. Lorsque l'exposition au stress perdure ou que l'activation de cet axe devient dysfonctionnelle, des répercussions sur les processus d'apprentissage et de mémorisation, ainsi que la réponse émotionnelle sont manifestes (Kim et al., 2006; Sapolsky, 2003; Sousa, 2016).

Les glucocorticoïdes jouent un rôle primordial dans la régulation de la durée et de l'intensité de l'activation de l'axe HHS (De Kloet et al., 1998; S. Keller & Seraganian, 1984; Reul et al., 2000). Ainsi, la cessation de l'activité de l'axe HHS une fois le stress éclipsé implique un rétrocontrôle négatif exercé par les glucocorticoïdes sur la sécrétion de CRF et d'ACTH par l'hypothalamus et l'hypophyse (De Kloet et al., 1998; Reul & de Kloet, 1986; Keller & Seraganian, 1984). Cette rétroaction est initiée par une action du CORT sur les structures de l'hippocampe et du noyau paraventriculaire riches en récepteurs pour les glucocorticoïdes (Kova´cs & Makara, 1988; Kovács et al., 2000; Marques de Souza & Franci, 2010; Sawchenko, 1987; Watts, 2005) qui mène à la cessation de la sécrétion de CORT par les glandes surrénales (Diorio et al., 1993; Jacobson & Sapolsky, 1991; McEwen, 2000; Radley & Sawchenko, 2011). Un dérèglement de la sensibilité des récepteurs des glucocorticoïdes perturbe la rétroaction négative, entrainant une sécrétion prolongée de glucocorticoïdes (principalement de CORT) qui contribuent au développement de différentes pathologies, incluant la dépression (Nandam et al., 2020) et la démence (Lara et al., 2013; Ouanes & Popp, 2019). Notamment, des lésions ou dommages à l'hippocampe ont comme effet d'élever le niveau basal de la circulation des glucocorticoïdes (Sapolsky et al., 1991) et de prolonger le relâchement de l'ACTH et du CORT lors d'une réponse au stress (Han et al., 2007; Herman et al., 1992).

1.3.2 Dérèglement de la réponse de l'axe hypothalamique-hypophysaire- surrénalien suivant un infarctus du myocarde

Lindner et al. (1992) furent parmi les premiers groupes de recherche à étudier les altérations de différentes hormones de stress (c.-à-d., ACTH, CORT, vasopressine et rénine) suivant un arrêt cardiaque. Ces chercheurs ont comparé des patients qui ont eu un arrêt cardiaque à l'extérieur de l'hôpital, dont 20 sur un total de 34 purent être réanimés. Des échantillons sanguins ont permis de quantifier la sécrétion des différentes hormones au cours du processus de réanimation pour l'ensemble des sujets et chez les survivants durant un intervalle médian de 60 minutes suivant la réanimation. Les niveaux de CORT se sont avérés significativement plus bas chez les patients dont l'intervalle entre l'effondrement et le début de la réanimation était plus long. Lorsqu'ils ont comparé les différentes hormones durant la réanimation entre les patients réanimés et non réanimés, les chercheurs ont trouvé que les concentrations hormonales étaient globalement plus faibles chez les patients non réanimés; indiquant une altération différentielle du fonctionnement du système endocrinien associée à la récupération. Depuis ces travaux, d'autres études ont indiqué des dysfonctions de l'axe HHS suivant un arrêt cardiaque (Adrie et al., 2004; Hékimian et al., 2004; Kim et al., 2011; Schultz et al., 1993).

Il est raisonnable de penser qu'un stress physiologique puissant comme celui lié à un IM puisse aussi engendrer des répercussions sur l'activation de l'axe HHS susceptibles d'avoir un impact au niveau émotionnel et/ou cognitif (Dimsdale, 2008), ressemblant à celui noté lors d'un arrêt cardiaque (Batelaan et al., 2022). Néanmoins, les connaissances scientifiques à cet effet demeurent quasi inexistantes. Une étude de Jackson et al. (2018) ayant caractérisé sur une période de 5 ans les niveaux de détresse psychologique de 221,677 individus et le risque d'encourir un IM a permis de découvrir que les participantes ayant subi un IM, étaient celles qui

rapportaient une détresse psychologique élevée/très élevée, et que ce facteur augmentait de 20 % le risque d'encourir un second IM. De façon similaire, Roest et al. (2010) rapportent que les individus ressentant des niveaux d'anxiété élevés post-IM présentent 36,0 % plus de risque d'avoir des complications cardiaques (p. ex., mortalité, risque d'avoir un autre IM). Ces résultats pointent sur d'importants changements physiologiques et émotionnels suivant un IM. Il est important de souligner qu'il existe certaines études ne soutenant pas de telles associations (Larsen et al., 2014; Welin et al., 2000), bien que les études appuyant de tels liens soient plus nombreuses. Parmi celles-ci, une récente méta-analyse de Wen et al. (2021) a regardé l'association entre l'anxiété et le pronostic à court et à long terme d'individus ayant un historique d'IM. Ces chercheurs ont trouvé un lien entre des niveaux élevés d'anxiété et une présentation clinique moins favorable. À court terme, ils ont noté des complications plus importantes accompagnées à long terme par un pronostic de récupération moins favorable et un taux de mortalité plus élevé. En raison de l'aspect systématique et des critères de rigueur méthodologique des études incluses lors de méta-analyses, il faut mentionner que seules 16 études furent retenues sur un total de 9373 publications. Toutefois, les constats émis concordent avec le fait que l'activation plus soutenue de l'axe de stress souvent associé à des symptômes significatifs d'anxiété ou de dépression (Stetler & Miller, 2011) semble représenter un facteur affectant la récupération à un IM (Holsboer, 1999, 2001; Iob et al., 2020; P. A. Keller et al., 2006; Vreeburg et al., 2009).

Des niveaux de dépression et d'anxiété élevés affectent d'autres systèmes, notamment le système rénine-angiotensine-aldostérone qui est essentiel à la régulation du volume sanguin et contribue à la résistance vasculaire systémique (Fountain & Lappin, 2022). Ainsi, l'incidence d'IM chez un individu présentant des niveaux élevés d'anxiété et/ou de dépression est

susceptible de survenir au sein d'un organisme présentant déjà un dérèglement de l'activité de l'axe HHS. Dans ce contexte, l'activation soutenue de ces deux systèmes lors de l'IM risque d'augmenter la réponse inflammatoire (Steptoe et al., 2013), la réactivité des plaquettes sanguines (Zafar et al., 2010), une réduction du réflexe des barorécepteurs (Watkins et al., 2013), accompagnée d'une augmentation de la variabilité de la fréquence cardiaque (Martens et al., 2008); ces deux derniers facteurs agissant comme modulateurs du système nerveux autonome. Sachant que des corrélats physiologiques liés aux troubles d'anxiété ou de dépression (dérèglement des réponses du système nerveux autonome ou de l'axe de réponse au stress) semblent associés aux MCO, il semble justifié d'approfondir les liens entre le statut psychologique et physiologique d'un individu et les répercussions de l'IM chez cette personne. Ce type de lien permettrait de mieux saisir l'importance du statut émotionnel et physiologique de la personne dans le pronostic de rétablissement suivant un IM.

1.3.3 Le Trier Social Stress Test – un paradigme d'induction de stress validé chez l'humain

Le Test social de Trier (TSST) a été développé en 1993 et est utilisé depuis afin de mesurer les effets comportementaux, cognitifs et psychobiologiques de l'induction d'un stress psychologique modéré chez des sujets humains sains ou ayant des conditions pathologiques (Kirschbaum et al., 1993). Son développement a été motivé par le fait que les tests utilisés jusqu'alors disponibles engendraient une grande variabilité interindividuelle des réponses physiologiques : les effets observés étaient de plus souvent très faibles et impossibles à mesurer de manière fiable (Berger et al., 1987; Kirschbaum et al., 1993). Le TSST demeure à ce jour l'un des tests les plus utilisés dans le milieu psychobiologique pour étudier les effets du stress chez l'humain (Labuschagne et al., 2019). Kudielka et al. (2007) ont notamment recensé plus de 4000 séances utilisant le TSST, soulignant l'efficacité du test à mesurer les paramètres d'activation de

l'axe HHS et du système cardiovasculaire en réponse au stress et la validité de comparaisons interétudes que son utilisation permet. En effet, plusieurs études sur l'activation de l'axe HHS ont constaté que l'exposition au TSST déclenchait de deux à trois fois la libération de CORT chez environ 70 à 80 % des participants en comparaison à un groupe témoin (Dickerson & Kemeny, 2004; Het et al., 2009). En plus de stimuler une élévation de la sécrétion de CORT, le TSST engendre des changements cardiovasculaires et immunologiques, tout en occasionnant une élévation des niveaux de stress et d'anxiété autorapportés (Frisch et al., 2015). Le TSST apparait donc comme un paradigme de recherche de choix pour les chercheurs désirant étudier des dérégulations possibles de l'axe HHS associées à diverses présentations, incluant les MCV (Brosschot et al., 2014), le déclin potentiel des capacités cognitives en raison de l'âge (Scott et al., 2015) ou les effets néfastes sur le bien-être physique et psychologique que le stress peut causer (Deak et al., 2015). Il est à noter que peu de recherches ont évalué la validité écologique du TSST, soit la ressemblance de cette exposition au stress vs à divers évènements stressants vécus au quotidien (Henze et al., 2017). Ceci limite donc la généralisation des résultats obtenus à la suite du test à un ensemble de situations stressantes affectant ces personnes dans la vie de tous les jours.

Plusieurs autres données physiologiques peuvent être recueillies lors de la passation du TSST, incluant la variabilité de la fréquence cardiaque. Comme mentionné à la section 1.3.2, la réponse au stress enclenche l'activation de divers systèmes, dont l'axe HHS et le système nerveux autonome – incluant la branche sympathique et parasympathique. Le fonctionnement de ces systèmes est interdépendant et coordonné en réponse à un stresseur (Rotenberg & McGrath, 2016). En situation d'exposition aiguë au stress, le système nerveux autonome - sympathique et parasympathique - sera séquentiellement sollicité et impliqué dans la régulation de la fréquence

cardiaque selon l'intensité de l'événement perturbateur. Cette activation constitue un indicateur de l'état de santé de la personne, une variabilité élevée de la variabilité de la fréquence cardiaque indiquant des mécanismes du contrôle autonome pleinement fonctionnels (Pumprla et al., 2002). La variabilité de la fréquence cardiaque peut être analysée soit par des paramètres du domaine temporel ou fréquentiel. Dans le domaine temporel, l'arythmie respiratoire sinusale peut être utilisée pour indexer la variabilité de la fréquence cardiaque (Sevoz-Couche & Laborde, 2022). La variabilité de la fréquence cardiaque est habituellement mesurée grâce à un électrocardiogramme qui permet de mesurer l'activité cardiaque du cœur en utilisant des capteurs collés sur la peau. Lorsque la variabilité de la fréquence cardiaque est dérivée à partir de l'arythmie respiratoire sinusale, celle-ci est calculée à partir de la différence entre l'intervalle minimal et maximal entre les battements cardiaques par respiration (Berntson et al., 1997). L'axe HHS et le système nerveux autonome sont connus pour avoir un lien fonctionnel avec plusieurs problèmes dont les MC, DT2 et la dépression (Kajantie & Phillips, 2006). Par exemple, Peltola et al., (2008) ont développé un algorithme permettant de prédire une mort cardiaque subite en utilisant l'arythmie respiratoire sinusale chez des patients ayant eu un IM (N = 1631; 7,4; 95 % IC 3,6 – 15,1 ; $p < 0.0001$) et soulignant l'utilité de cette mesure dans un contexte de récupération post-MI. Ainsi, la variabilité de la fréquence cardiaque semble être une mesure physiologique intéressante à prendre en considération lorsqu'on veut étudier des changements physiologiques in vivo. Dès lors, étant donné que la combinaison des deux tâches utilisées dans le TSST permet l'activation de l'axe HHS ainsi que celle du système nerveux automne (Kajantie & Phillips, 2006), ce paradigme robuste semble être le choix par excellence.

De manière générale, la durée maximale associée à une évaluation avec le TSST est de deux heures. Ce paradigme constitue donc une exposition temporaire à une situation stressante.

Un temps de repos d'au moins 30 minutes est exigé des participants à leur arrivée. Durant cette période, le participant remplit les formulaires souhaités par l'expérimentateur et prend du temps pour se détendre. Deux minutes avant de débuter le test comme tel, un échantillon de salive est prélevé et le participant est dirigé à la salle d'examen. Lors de son entrée, le participant est placé devant un microphone et une caméra, puis un juge, parmi un panel de trois, lui demande de préparer un discours de cinq minutes pour postuler à un emploi. Une caméra est en place et un des juges lui mentionne que la séance sera filmée afin d'être évaluée par la suite. Cette directive vise à augmenter le niveau de stress ressenti par le participant. Les juges portent une blouse de laboratoire blanche et doivent agir de manière réservée, ne donnant aucune rétroaction faciale ou verbale. Le participant a cinq minutes pour préparer son discours en utilisant une feuille de papier et crayon afin d'organiser ses idées; toutefois, cette feuille ne sera pas disponible durant le discours que le participant livrera au panel de juges. Durant cinq minutes, le participant doit fournir des raisons et convaincre le panel de juges qu'il serait le candidat idéal pour le poste vacant. À la suite du discours, un des juges demande au participant d'effectuer une épreuve mathématique ou il doit soustraire par bonds de 13 le chiffre 1022 jusqu'à 0 à voix haute. Lorsque le participant se trompe, un juge lui demande de recommencer à 1022 jusqu'à écoulement du temps, soit 5 minutes. Pour la phase finale, le participant est redirigé dans la salle d'accueil pour une période de 90 minutes afin d'atténuer son stress (Kirschbaum et al., 1993; Kudielka et al., 2007).

Le protocole et les tâches du TSST sont considérés robustes pour étudier les effets du stress lorsqu'un individu doit livrer une performance orale (Dickerson & Kemeny, 2004). Nonobstant son utilisation répandue dans les études psychoneuroendocrines, un manque de standardisation dans l'utilisation de ce paradigme a été souligné (Allen et al., 2014, 2017;

Goodman et al., 2017; Labuschagne et al., 2019). Par exemple, les recherches ayant utilisé le TSST pour étudier les effets de l'embonpoint ont trouvé soit une hyper- ou une hypo- réaction de l'axe HHS en réponse au stress (Herhaus & Petrowski, 2018; Odeniyi et al., 2015) qui peut être en partie lié à des modifications du protocole ou de certains détails méthodologiques. Par exemple, alors que Herhaus & Petrowski (2018) ont accepté des participantes prenant des contraceptifs oraux, Odeniyi et al. (2015) ont adopté des critères excluant les femmes présentant ce profil. Considérant l'influence significative des contraceptifs oraux sur la sécrétion de CORT (Buchanan & Tranel, 2008; Hertel et al., 2017; Kuhlmann & Wolf, 2005; Maki et al., 2015; Mordecai et al., 2017), un tel changement méthodologique est susceptible de contribuer aux différences observées dans la littérature scientifique de même qu'aux conclusions divergentes entre des études évaluant un même facteur - l'embonpoint dans l'exemple ci-dessus. Ainsi, bien que le TSST permet d'étudier la réponse de l'axe HHS, il est important d'avoir une méthodologie et protocole basés sur les données probantes afin de pouvoir obtenir des résultats qui sont fidèles, valides et réplicables.

1.3.4 Le TSST comme outil dans l'étude de la régulation d'un stress suivant un IM

Le déroulement d'un IM implique une cascade physiologique impliquant une réponse de l'axe HHS. Les études animales ou humaines caractérisant la récupération à la suite de problèmes cardiovasculaires suggèrent que ces atteintes produisent des perturbations émotionnelles et cognitives à long terme, liées à des changements du fonctionnement de l'hippocampe (Liu et al., 2014; Malick et al., 2018; Petito et al., 1987;) et à une dérégulation de l'axe de la réponse au stress (de la Tremblaye et al., 2016; Milot & Plamondon, 2009; Plamondon & Khan, 2005). Ainsi, considérant la privation d'oxygène et de nutriments au cerveau est différente en intensité, mais communes à l'IM et l'arrêt cardiaque, il semble possible

que l'IM engendre des changements de la réponse physiologique (p. ex., variabilité du rythme cardiaque, sécrétion de CORT) lors de l'exposition à un stress et perturber les performances cognitives. À ce jour, l'étude de participants ayant un historique d'IM sur l'activation de l'axe HHS (notamment la sécrétion de CORT basal et induit à la suite d'un stress) a reçu peu d'attention au niveau scientifique. Sachant que l'IM atteint une proportion plus élevée de femmes avec l'âge, que ces dernières tendent à vivre plus longtemps, qu'elles rapportent des niveaux de stress supérieurs et ont des complications plus sévères que les hommes suivant un IM (p. ex. développement d'une maladie mentale), l'étude approfondie des changements de la réponse physiologique à la suite d'un chez cette population est susceptible de fournir des informations cruciales du point de vue de santé des populations. L'utilisation du TSST représente un outil de choix pour évaluer les changements physiologiques suivant sa passation chez des femmes ayant subi ou non un IM.

1.4 Buts et hypothèses de cette recherche doctorale

La vie quotidienne au sein des sociétés contemporaines, marquées par une augmentation des demandes sur les individus et de la rapidité des réponses attendues, expose les individus à davantage de stress au quotidien (Almeida et al., 2020; APA, 2020; Gerstorf et al., 2020; Piazza et al., 2019). Dans cette optique, il apparaît important d'étudier les conséquences d'un IM sur les femmes en adoptant une approche multifactorielle dans la recherche des effets possiblement associés à ce type d'événement (p.ex., changement dans la régulation de la réponse émotionnelle, de l'expression de déterminants physiologiques du stress). En abordant ma recherche sur les conséquences liées aux MC et à l'IM, j'ai rapidement observé un manque important d'informations scientifiques sur le retentissement fonctionnel de l'IM chez la femme en comparaison aux informations existant pour les hommes, particulièrement dans un contexte

canadien. Au sein de cette recherche, nous avons jugé essentiel d'obtenir au préalable une connaissance aiguisée des meilleures pratiques et des connaissances actuelles du profil de récupération des femmes affectées par les MC afin d'appliquer ces connaissances au développement des protocoles empiriques. Cet objectif explique l'inclusion de deux revues systématiques au sein de cette thèse, présentée sous forme de deux articles scientifiques. Un second volet, comprenant une étude par questionnaire et une étude en laboratoire permet d'aborder l'étude des facteurs prédisposant chez la femme canadienne et des effets associés à l'IM sur la réponse à un stress social. Les travaux de recherche accomplis s'inscrivent au sein de quatre composantes d'analyses distinctes. Les études 3 et 4 ont reçu l'approbation éthique du comité d'éthique de la recherche de l'université d'Ottawa (certificat H-06-18-639; voir certificats après section 1.4).

1.4.1 Étude 1 – Chapitre II

La première composante de la thèse consiste en une revue systématique de la littérature. La rigueur méthodologique associée à ce type de travail permet de faire une synthèse compréhensive de la littérature scientifique (Moher et al., 2015).

La revue systématique permettra d'examiner l'importance de chacun des éléments de la tâche stressante du TSST, ainsi que de commenter la standardisation méthodologique du protocole de passation de ce test. Cet examen systématique assurera de baser l'élaboration des directives de passation du TSST sur un ensemble de données scientifiques probantes et de maximiser le contrôle des variables reconnues influençant la réponse de l'axe HHS.

Le but principal de cette première recherche vise à établir une méthodologie et un protocole d'administration du TSST qui soient des plus rigoureux pour une utilisation ultérieure dans l'étude 4. Cette revue permettra également de créer un questionnaire permettant de

recueillir de l'information chez chacun des participants sur un ensemble de variables pouvant influencer la réponse au stress évaluée lors du TSST (p.ex., consommation de café, cycle menstruel). À cet effet, cette recherche permettra de placer une emphase particulière sur les facteurs déterminants à considérer lors de l'inclusion de femmes au sein de recherches utilisant le TSST.

1.4.2 Étude 2 – Chapitre III

L'accomplissement d'une deuxième revue systématique permettra de dégager un profil des atteintes neuropsychologiques observées chez les femmes ayant un historique de MC. Ceci nous permettra de présenter un portrait inclusif des répercussions cognitives précises des femmes vivant avec une MC. Nous désirons également via cette recension examiner la standardisation adoptée dans la définition des variables au sein des études. Nous nous attarderons particulièrement à la définition opérationnelle des MC entre les études afin de souligner que cette problématique, si présente, est un facteur compromettant les comparaisons entre les études. En effet, des conclusions erronées et des comparaisons non valides sont déjà observées en raison d'une inclusion de multiples types de maladies et/ou d'un manque de standardisation au sein des études sur les MC. Cet examen systématique permettra d'élaborer une série de recommandations pouvant orienter les chercheurs et neuropsychologues qui s'intéressent à cette population clinique.

1.4.3 Étude 3 – Chapitre IV

La troisième composante consiste en une étude effectuée en ligne via un questionnaire. Cette étude transversale vise à sonder un échantillon de femmes canadiennes afin d'établir la prévalence de certains facteurs liés à l'IM, ainsi que les symptômes ressentis lors d'un IM. Cette enquête par questionnaire permettra de documenter les symptômes ressentis par des femmes

canadiennes et de comparer ces résultats à ceux d'études réalisées aux États-Unis et en Europe. De plus, nous regarderons si certains facteurs de risque connus dans la littérature (p.ex., diagnostic d'hypertension avant le premier IM; consommation d'alcool) sont également présents dans notre échantillon. Ceci permettra de déterminer si les femmes ayant vécu un IM présentent un profil différent de celui des femmes n'ayant pas vécu pas un d'IM quant à ces facteurs (p.ex., moins de consommation de tabac). Cette enquête par questionnaire permettra d'examiner la prévalence au sein de l'échantillon des principaux facteurs de risque associés à un IM ainsi que des symptômes ressentis lors d'un IM. Seule une partie des données seront présentées au sein de cette thèse.

1.4.4 Étude 4 – Chapitre V

La quatrième composante consiste en une étude transversale de type quasi expérimentale effectuée en laboratoire. Ce type d'étude scientifique permet d'étudier l'effet de la manipulation d'une variable spécifique. Dans le cas de cette recherche, je n'ai pas manipulé de variable, mais étudié la différence entre des femmes qui ont eu un IM et celles qui n'en ont pas. Ainsi, j'ai souhaité connaitre l'impact d'un stresseur sur la réponse physiologique et la performance cognitive chez les participantes. L'étude de la réponse physiologique est présentée dans cette thèse. Cette étude s'intéresse principalement à deux changements physiologiques (c.-à-d. les niveaux de CORT et la variabilité du rythme cardiaque) et de leur mesure à différents points d'ancrage spécifiques (intervalles) durant l'étude en laboratoire. En plus des données physiologiques, le niveau de stress ressenti sera déterminé grâce à des questionnaires, permettant d'examiner une association entre la réponse physiologique et le statut émotionnel des femmes, ainsi que l'impact de l'incidence d'IM sur ces variables. À ce jour, aucune étude en laboratoire de ce type n'a été publiée, l'examen de telles variables s'étant concentré sur d'autres maladies

cardiaques, principalement l'arrêt cardiaque – une condition plus sévère.

La principale hypothèse de cette étude stipule que la réponse physiologique au stress (c.-à-d. niveaux différents de CORT et de variabilité du rythme cardiaque) sera plus élevée pour les femmes ayant un IM, bien que celles-ci rapporteront des niveaux de stress ressentis comparables à celles du groupe contrôle.

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Chapitre II – Recension systématique de la littérature sur le protocole de stress du Trier Social Stress Test

A Systematic Review of the Trier Social Stress Test methodology: Issues in promoting study comparison and replicable research

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Abstract

Since its development in 1993, the Trier Social Stress Test (TSST) has been used widely as a psychosocial stress paradigm to activate the sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPAA) stress systems, stimulating physiological functions (e.g. heart rate) and cortisol secretion. Several methodological variations introduced over the years have led the scientific community to question replication between studies. In this systematic review, we used the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) to synthesize procedure-related data available about the TSST protocol to highlight commonalities and differences across studies. We noted significant discrepancies across studies in how researchers applied the TSST protocol. In particular, we highlight variations in testing procedures (e.g., number of judges, initial number in the arithmetic task, time of the collected saliva samples for cortisol) and discuss possible misinterpretation in comparing findings from studies failing to control for variables or using a modified version from the original protocol. Further, we recommend that researchers use a standardized background questionnaire when using the TSST to identify factors that may influence physiological measurements in tandem with a summary of this review as a protocol guide. More systematic implementation and detailed reporting of TSST methodology will promote study replication, optimize comparison of findings, and foster an informed understanding of factors affecting responses to social stressors in healthy people and those with pathological conditions.

Keywords: Trier Social Stress Test, Stress paradigm, Protocol, Systematic Review, Standardization

List of Abbreviations

Cortisol	CORT
Cortisol awakening response	CAR
Heart rate	HR
Hypothalamix-Pituitary-Adrenal Axis	HPAA
Min	Minutes
Preferred Reporting Items of Systematic Reviews and Meta-Analysis	PRISMA
Standard deviation	SD
Trier Social Stress Test	TSST

2.1.0 Introduction

Prior to the development of the Trier Social Stress Test (TSST; Kirschbaum, et al., 1993), researchers used diverse psychological stressors to assess the impact of stress on Hypothalamic-Pituitary-Adrenal axis (HPAA) activation (Berger et al., 1987). Given major concerns that these different stressors were associated with important inter-individual variability in physiological responses and that effects were often too small to be measured reliably, Kirschbaum et al. (1993) developed the TSST to provide researchers with a standardized psychophysiological paradigm for assessing the impact of psychosocial stress. Since then, researchers worldwide have used the TSST as a robust experimental protocol proven to produce reliable physiological outcomes (Dickerson & Kemeny, 2004). Since its publication and up to 2007, the TSST was used in over 4000 studies, supporting its well-established status as a stress paradigm (Kudielka et al., 2007). TSST tasks (speech and arithmetic) are remarkably efficacious in studying stress effects on performance (Dickerson & Kemeny, 2004). Physiological measures, including heart rate (HR) and salivary cortisol (CORT), have helped researchers understand human stress responses, with findings suggesting that people experience up to a 70-80 % increase in CORT secretion following TSST exposure (Kudielka et al., 2007).

Dysregulation of HPAA activation is a hallmark feature of various pathological conditions; chronic HPAA activation contributes to cardiovascular diseases (Brosschot et al., 2014), cognitive decline in aging populations (Scott et al., 2015), and exerts detrimental effects on physical and psychological well-being (Deak et al., 2016). Thus, it is vital that researchers use valid and reliable tools to better understand the functional dynamics influencing HPAA activation and behavioral responses in humans (Rubinow et al., 2012). Since its development, researchers have introduced several TSST variants to study different populations, maximize

efficiency, and limit inter-individual variability. These variants include the children's version (Buske-Kirschbaum, et al., 1997), the virtual TSST (Jönsson, et al., 2010), the TSST for groups (Von Dawans et al., 2011), and the friendly TSST (Wiemers et al., 2013).

2.1.1 Objectives of the current review

Over 25 years have passed since Kirschbaum et al. (1993) developed the TSST. Although the paradigm appears at first glance unchanged, several researchers have pointed to methodological variations in the TSST protocol, raising concerns about validity and reproducibility of the measurements (Labuschagne et al., 2019; Allen et al., 2014; Allen et al., 2017; Goodman et al., 2017). Although there have been some attempts to examine the effects of some modifications or failure to control variables that are known to affect the TSST (e.g. morning TSST vs. afternoon TSST; Kudielka et al., 2004), to our knowledge, these attempts have been limited in scope.

Existing reviews (Labuschagne et al., 2019; Allen et al., 2014; Allen, et al., 2017) addressing elements of the TSST paradigm have significantly raised awareness of the important factors to consider in studying the human stress response. These critical reviews have proposed selective assessments, which deviate from the validated protocol used by narrative systematic review. Goodman et al.'s (2017) meta-analysis focused primarily on the impact of protocol variations on CORT collection, not reviewing other variations of the TSST methodology. Additionally, authors did not use a registered standardized protocol, like the PRISMA-P statement or provide a systematic methodology for the review process (i.e., single vs double reviewer, risk of bias assessment). In this context, Labuschagne et al. (2019) acknowledged limitations of a critical review in that it does not provide a comprehensive assessment of the key elements of the TSST and related variabilities. At present, there is an important need for

systematic reviews using "explicit, systematic methods to minimize bias in the identification, selection, synthesis, and summary of studies" (Moher et al., 2015, p. 3). Our review contributes to such a goal, providing a complementary but distinctive approach from that adopted by other review articles.

Considering the widespread and diverse use of the TSST, it is vital that we understand the ways in which methodological variations can affect outcomes. Indeed, such variations, if not considered, can account for divergent findings that researchers otherwise interpret as related to their study hypotheses. For example, hormonal fluctuations associated with menstrual cycles impact the HPAA (Kirschbaum, et al.1999). Maki et al. (2015) found that women in the luteal phase (high levels of estradiol and progesterone) compared to those in the follicular phase (low levels of estradiol and progesterone) performed better on a cognitive task and demonstrated significantly lower levels of cortisol following the TSST. Although the effects of menstrual cycle on HPAA have been documented for more than 20 years, researchers do not consistently consider menstrual cycle phase in their studies using the TSST (e.g., post-traumatic stress disorder research; Summer et al., 2017; cardiac arrest research; Agarwal et al., 2018); researchers may misinterpret their findings if they do not control for menstrual cycle. Taylor et al. (2010) found that participants exposed to an unsupportive *vs.* supportive audience showed elevated CORT secretion compared to participants in the no audience condition; the difference between the audience conditions approached significance (Taylor, et al., 2010). However, because the researchers did not assess for women's menstrual cycles, it is unclear whether any of the observed differences were attributable to sex or hormonal differences. Finally, the original TSST protocol contained only a brief description of its methodology (Kirschbaum, et al., 1993). As such, it is not surprising that researchers interested in studying stress have introduced variations

in the protocol over time, given increasing knowledge and innovation in the field of stress and psychoneuroendocrinology. A formal update of the protocol, therefore, is warranted.

Thus, we aimed first to review various factors (e.g., exclusion criteria, sex/gender differences, menstrual cycle phase) that can impact stress induction and its associated outcomes. Second, we documented systematically the variations in how researchers have applied the TSST protocol since its development. Finally, we used our findings to generate guidelines for reporting TSST methodology, with the goal of fostering reliable comparisons between findings and maximizing replication efforts. We added a theoretical framework section before the methods and the results sections to provide a background rationale for the proposed methodological decisions for our systematic review.

2.2.0 Theoretical framework

2.2.1 Administration of the TSST and stress-sensitive factors

Before describing our findings in detail, we briefly review the various factors that are known to exert effects on the stress response and its associated effects on HPAA regulation (Hellhammer et al., 2009).

2.2.1.1. Women participants and hormonal status

The influence of hormonal status on women's stress responses is well documented (see Fang et al., 2014; Kajantie and Phillips, 2006, for reviews). For instance, women in the non-luteal phase show reduced CORT levels compared to women in the mid-luteal phase (Kirschbaum et al., 1999), and fluctuations of progesterone and estrogen levels can impact women's emotional and cognitive responses to a stress-inducing task (Felmingahm et al., 2012). Among pre-menopausal and menopausal women, researchers have shown a variability on CORT

measures depending on when it is measured (e.g., morning *vs.* afternoon; Kudielka et al., 2004). Similarly, Rotermann and colleagues (2015) found that approximately 15% of Canadian women and girls between the ages of 15 and 49 years reported using oral contraceptives in the previous month; oral contraceptive use is associated with reduced CORT secretion, and affects the diurnal neuroendocrine rhythm, particularly morning CORT levels (Roche et al., 2013). Notably, researchers have demonstrated elevated HPAA activation in men following a psychosocial stressor compared to women in the ovarian follicular phase (Stephens et al., 2016), highlighting the potential importance of considering this factor in data analysis and interpretation.

Further, pregnant women experience higher anxiety levels, depressive symptoms, and significantly elevated CORT levels compared to non-pregnant women (Mustonen et al., 2018). Relatedly, breastfeeding may be protective against stress responses. Johnston et al. (2017) found that women who breastfeed also demonstrate lower levels of CORT secretion, particularly in the moments following lactation.

2.2.1.2 Exclusion criteria

2.2.1.2.1 Medication. Pharmacological treatments come with therapeutic and side effects that can alter people's behavioral and physiological responses (e.g., CORT secretion). Many drugs can influence (a) HPAA activation, (b) associated biochemical systems (e.g., regulate sympathetic activation), or (c) participants' subjective experiences (Granger, et al., 2009). In a study using the TSST for groups, Houtepen et al. (2015) demonstrated that participants diagnosed with bipolar disorder and taking antipsychotic medication showed a blunted CORT response compared to their siblings who were also diagnosed with bipolar disorder, but not taking medication (Houtepen et al., 2015). Compiling drug prescriptions from the medical records of 142,377 American citizens, Zhong et al. (2013) found that 68.1% of individuals

received a prescription for at least one type of medication, while 51.6% and 21.2% received prescriptions for a minimum of two and five medication types, respectively (Zhong, et al., 2013).

2.2.1.2.2 Mental Health Status. Every year, 1 in 5 Canadians - Worldwide, 1 in 4 individuals (WHO, 2001) - is affected by a psychological disorder, and half the Canadian population will have experienced a psychological disorder before the age of 40 years (Mental Health Commission of Canada, 2013). Even though people with psychological disorders also tend to show reduced research participation rates, there is likely psychological health/disorder variability across samples (Loue & Sajatovic, 2008). Importantly, researchers have demonstrated that dysfunctional HPAA activation is associated with various mental health conditions (Wingenfeld & Wolf, 2010). For instance, researchers reported that diagnoses of: (a) Major Depression with melancholic features (referred as melancholic depression in the article), panic disorder, obsessive-compulsive disorder, and schizophrenia could all exert a long-term impact on HPAA activation (Jacobson, 2014); (b) social anxiety disorder, autism spectrum disorder (Jacobson, 2014), post-traumatic-stress disorder and atypical depression(Wichmann et al, 2017) can be associated with increased sensitivity to stress and/or lead to altered HPAA activation. As such, the decision to include/exclude individuals who are or have been affected by a mental disorder needs careful consideration, not only for ethical reasons, but also when the association of the particular condition with stress responses is not the primary objective of the study (Allen et al., 2014).

2.2.1.2.3 Tobacco use. Assessments of the relationship between CORT secretion and tobacco smoking have generated mixed findings. In a sample of 4231 people (73% men/27% women), Badrick et al. (2007) evaluated smoking status and salivary CORT measures and they found that current smokers demonstrated increased salivary CORT secretion (also observed in

Cohen et al., 2019) compared to ex-smokers or people who had never smoked or quit smoking. Such findings support delayed impact of smoking on CORT secretion and smoking a single cigarette is sufficient to induce CORT secretion and HPAA activation (i.e., increased HR; Rohleder & Kirschbaum, 2006). Despite the importance of smoking status, researchers define smoking status in various ways; there is no consensus on operational definitions of 'regular' or 'past' smokers (Ryan et al., 2012).

2.2.1.2.4 Substance use. Substance use disorders and psychoactive substance consumption are known to show differentials effect on the neuroendocrine system. The central and peripheral nervous systems work in tandem to maintain homoeostasis, a crosstalk that may be compromised by drug intake. For example, researchers have observed immediate increases in CORT secretion (1-2 fold in magnitude) following 3,4-Methylenedioxymethamphetamine (MDMA) consumption; people who reported regular MDMA consumption for 3 months also demonstrated a 400% increase in cortisol secretion compared to people who did not consume MDMA (Parrot et al., 2014). Other psychostimulants, including amphetamines and cocaine, similarly increase plasma CORT levels, and can affect mood and cardiovascular functions (Manetti et al., 2014). Findings are mixed among people who use cannabis, with some supporting both increased and decreased HPAA activation, as well as effects on basal and awakening CORT secretion profiles (Cservenka et al., 2018). Finally, one of the most common substances used is caffeine. The influence of caffeine on the HPAA is well documented. For example, Patz et al. (2006) found that although low to moderate doses did not modulate HPAA, they led to significant increases in corticosterone levels, which took 60 min to return to their initial levels. Higher doses impacted the HPAA for up to 120 minutes. Burke et al. (2015) found that caffeine consumption impacted the circadian cycle and suggested that it could impact the

secretion of other hormones. Additionally, there has been an increase among youth and college students in consumption of energy drinks, which not only contain higher doses of caffeine, but also contain other ingredients that are likely to have an impact on people's health (Malinauskas, et al. 2007; Ibrahim & Ifitkhar 2014; Shah et al., 2019).

2.2.1.2.5 Body Weight. In North America, excluding Mexico, approximately two thirds of adults aged 20 to 64 years are overweight, and one in three people is considered obese (Flegal et al., 2012; Government of Canada, 2018). Worldwide about two in five people are overweight and one in ten are obese (WHO, 2016). At present, the impact of body weight on neuroendocrine system functioning remains uncertain (Incollingo Rodrigues et al., 2015); being overweight has been associated with hyper- (Odeniyo et al., 2015) and hypo- (Herhaus & Petrowski, 2018) responsiveness of HPAA. On the other end of the continuum, Schorr et al. (2015) found that participants with a low body mass index (BMI; Kg/m^2) demonstrated increased CORT secretion compared with participants with a BMI in the normal weight range. More specifically, Monteleone et al. (2016) found an enhanced cortisol awakening response (CAR) in severely underweight participants with anorexia nervosa, but not in weight-restored participants; in other words, a dysregulation of CAR appears highly correlated with weight (Monteleone et al., 2016). Moreover, Pasquali et al. (2006) suggested that participants' BMI remains an important variable in understanding how diverse weight ranges may impact the stress response.

2.2.1.2.6 Chronic Diseases. Chronic diseases include diverse medical conditions that persist across time and cause impairments in daily living. Such diseases represent the leading cause of death and disability worldwide (WHO, 2019). Diabetes, coronary heart disease, cancer and chronic obstructive pulmonary disease (Dis-Chaves et al., 2016; Matura et al., 2018) have all been associated with increased CORT secretion. In North America, an estimated 25-33% of the

adult population live with one or more chronic health conditions (Ward et al., 2012; Branchard et al., 2018), often associated with dysregulations of HPAA activation (Allen, et al., 2014). Furthermore, in a recent Danish study (N = 4,555,439), Hvidberg et al. (2020) reported that two-thirds of people aged 16 years and older (65.6%) had at least one chronic disease.

2.1.2.7. Working Night Shifts. Given that irregular shifts are a staple of a 24/7 global economy, 15 to 30% of American and European adults report working night shifts, and an additional 19% report working regularly for periods extending over 2 h between 10 pm and 5 am (Boivin & Boudreau, 2014). Researchers have demonstrated that night shifts and irregular working schedules impact circadian cycles (Boivin & Boudreau, 2014) and exert profound effects on physical and psychological health associated with dysregulation of HPAA and diurnal CORT secretion profiles (Charles et al., 2016; Gonnissen et al., 2013). Therefore, more rigorous screening of work shifts is important to consider, especially if the sample of participants are undergraduate students. For example, in a longitudinal study, Lund et al. (2010) found that undergraduate students reported chronically limited sleep, which appeared to lead to other problems (e.g., more frequent consumption of alcohol and drugs). Thus, it is important to take this factor into consideration.

2.2.1.3 Restriction of activities prior to participation

When assessing CORT secretion using blood or saliva samples, environmental factors can interact with the collected measures (Garde et al., 2009). Various activities performed prior to a saliva sample have been shown to enhance endocrine measures (Kudielka et al., 2008), including: brushing or flossing teeth, receiving false results due to blood contamination (Kudielka et al., 2012; Stalder et al., 2016), physical exercise (Rahman et al., 2010), food consumption, (Stalder et al., 2016), caffeinated beverages (Patz et al., 2006), smoking (Rohleder

& Kirschbaum, 2006) and any substance (Zhou et al., 2010) or alcohol (Badrick et al., 2008) use. Additionally, heavy alcohol consumption can negatively impact cognitive functions and performance on everyday tasks (Gunn et al., 2018) and therefore affect TSST performance (Badrick et al., 2008).

2.2.2. TSST protocol application

2.2.2.1 Selected resting period

Researchers typically include a rest period before the TSST to account for multiple factors involved when participants take part in a laboratory session, including the participants' means of transportation being possibly associated with stress or increased sympathetic activation, general stress related to participating in a study, or anxiety associated with the performance task or with interacting with unknown people including the researcher (Kudielka et al., 2007). Additionally, Rahman et al. (2010) found that it takes the body up to 60 min to return to a homoeostatic state after vigorous physical activity. Indeed, letting participants acclimatize to the research environment ensures that they have the lowest physiological activation possible before the TSST to assess the real impact on CORT secretion.

2.2.2.2 Period of the day

The circadian rhythm of CORT is the gold standard measure to establish an optimal starting time in neuroendocrine studies (Liu et al., 2017). CORT levels are lower in the afternoon than in the morning (Matsuda et al., 2012). Specifically, 30 to 45 min following awakening, people's CORT levels increase by 50 to 156% before declining throughout the day (Stalder et al., 2016). Recent research demonstrated that morning CORT measures tend to be more accurate and representative, and less affected by external factors (e.g., caffeine intake; Matsuda et al., 2012). Women's and older individuals' CORT levels tend to differ from normalized values (e.g.,

women demonstrate a greater and prolonged response than men); researchers suggest paying close attention to these differences (Stalder et al., 2016). Finally, because the body will naturally tend to re-establish homeostasis after a certain period, the duration of the TSST session may impact the TSST outcome measures.

2.2.2.3 Self-report anxiety/stress questionnaires

Researchers frequently use self-report questionnaires to assess participants' subjective experience of anxiety and its relation to their observed behavioral and physiological responses. There is some evidence that individual differences across a variety of factors can influence under- or over-reporting of subjective anxiety. For example, Karlson et al. (2011) found that women who reported higher job stress demonstrated higher CAR, whereas men who reported lower job stress demonstrated higher CAR. In other words, both sex and perceived work stress impacted upon HPAA activation (Karlson et al., 2011).

Measuring subjective anxiety may be important not only for understanding its effect on psychophysiological functioning, but also for understanding the role of psychophysiological functioning on real-life distress or impairment. Indeed, there are multiple examples in the literature demonstrating a *lack* of relationship between subjective and objective measurement of anxiety (e.g., Campbell-Sills et al., 2006; De Los Reyes et al., 2012; Puigcerver et al., 1989; Wilhelm & Roth, 2001). Some of these discrepancies are likely related to how people interpret their own physiological symptoms (i.e., as dangerous or not), and to the type of subjective anxiety that researchers measure (i.e., specific or general; De Los Reyes et al., 2012). Thus, it is possible that variations in subjective measurement result in different patterns of findings across studies using the TSST.

2.2.2.4 Panel of judges and video recording

Notwithstanding the gender of a participant, Allen et al. (2014) concluded in their critical review that a same gender across the panel of judges significantly influenced responses on a threat evaluating situation, especially when testing young men or women. Additionally, men and women demonstrate different HPAA responses to stressors (Dickerson & Kemeny, 2004; Kudielka et al, 2007). Specifically, men tend to exhibit higher CORT levels than women, whose responses vary depending on menstrual cycle or hormonal contraceptive use. Duschesne et al. (2012) demonstrated that both men and women exhibited increased CORT secretion only when performing in front of judges of the opposite gender. However, this effect was present only in women in the follicular phase (Duschesne et al., 2012). Moreover, many researchers videorecord participants' performance, which is associated with amplified feelings of threat and elevated stress response (Biondi & Picardi, 1999). Thus, whether or not a TSST protocol includes videorecording may impact upon TSST outcomes.

2.2.2.5 Speech and arithmetic tasks

In a review article addressing the effects of public speaking on fear and anxiety and its impact on people's physiology and perception, Garcia-Leal et al. (2014) found that 30 to 50% of people reported a fear of public speaking with approximately 40% of those reporting anxiety about being negatively evaluated by others (Stein et al., 2010). Speech tasks are common across different research areas given their ability to create a social-evaluative threat (Dickerson & Kemeny, 2004). Buchanan et al. (2014) demonstrated that people who engaged in the TSST demonstrated reduced speech fluency and increased physiological reactivity compared to those in a non-stressful condition. Participants in the TSST condition showed higher word productivity (i.e. the ratio of productive words to total words) and paused more often during their speech than

those in the non-stressful condition. This effect was pronounced in participants who evidenced higher cortisol and heart rate responses to the TSST, highlighting that speech tasks effectively induce stress and cause physiological changes in participants (Buchanan et al., 2014). Similarly, close to 20% of the general population experiences some level of anxiety related to performing mathematical tasks (Dowker et al., 2016). Indeed, in a review performed by Caviola et al. (2017), they found that participants who performed an arithmetic task under timed conditions tended to show a weaker performance than participants under untimed conditions, a phenomenon related to the interference of different task-associated cognitive domains, including working memory (Caviola et al., 2017).

2.2.2.6 Recovery period

A recovery period following the TSST enables researchers to measure CORT variation until its return to baseline levels, when the effects of the TSST are attenuated. Physiological stress persists after stress exposure, but the duration of the effects is still unclear (Brosschot et al., 2014). Therefore, researchers have included a recovery period following the TSST (Kirschbaum, et al., 1993) to quantify these differences subsequent to a stressor.

2.2.3 Physiological measures

2.2.3.1 Heart Rate

HR measures represent a sensitive tool enabling researchers to determine sympathetic nervous system activation in an experimental context. The Task Force of the European Society of Cardiology (1996) recommends taking HR measures every 5 minutes (cluster) for a short clinical study like the TSST. HR is a valid physiological measure to assess stress levels. Hellhammer and Schuber (2012) found that HR measures were significantly higher before and during the TSST and significantly lower during the recovery period, indicating a peak in

physiological stress during the TSST.

2.2.3.2 Cortisol collection

Assessing salivary cortisol is a reliable, quick, and non-invasive way to determine changes in CORT levels (Hellhammer et al., 2009), making this method the most popular in human studies (Liu et al., 2017). Following a short-term stressor like the TSST, participants show increased salivary cortisol levels, reaching peak levels 15-20 min after the stressor (Kudielka et al., 2008; Kirschbaum, et al., 1993). Recommendations according to Kirschbaum et al. (1993) and a meta-analysis conducted by Liu and colleagues (2017) are that baseline cortisol measures be taken 30 min before the TSST, with time intervals between 10 and 25 min and the last measure occurring between 30 and 70 min following the start of the TSST. Juster et al. (2012) and Dickerson and Kemeny (2004) validated that cortisol reaches peak levels after the 20 min following the beginning of the TSST.

2.2.3.3 Blood collection

Blood collection can help characterize endogenous biochemical changes (e.g., neurotransmitter and/or hormones) to address specific objectives. To standardize and facilitate study replication, recommended time intervals for blood collection mirror those of cortisol. However, researchers who collect blood samples should minimize participant discomfort to avoid additional unwanted stress (Birkett, 2011) given its invasiveness.

2.3.0 Method

2.3.1 Protocol and registration

Prior to beginning our review, we registered our protocol in accordance with the PRISMA-P checklist (Moher, et al., 2015) with PROSPERO (CRD42017069908). The protocol was

registered on June 21, 2017 and was last updated on April 15, 2019. There were three updates to clarify the wording and update the status of the systematic review; no changes to the protocol were made.

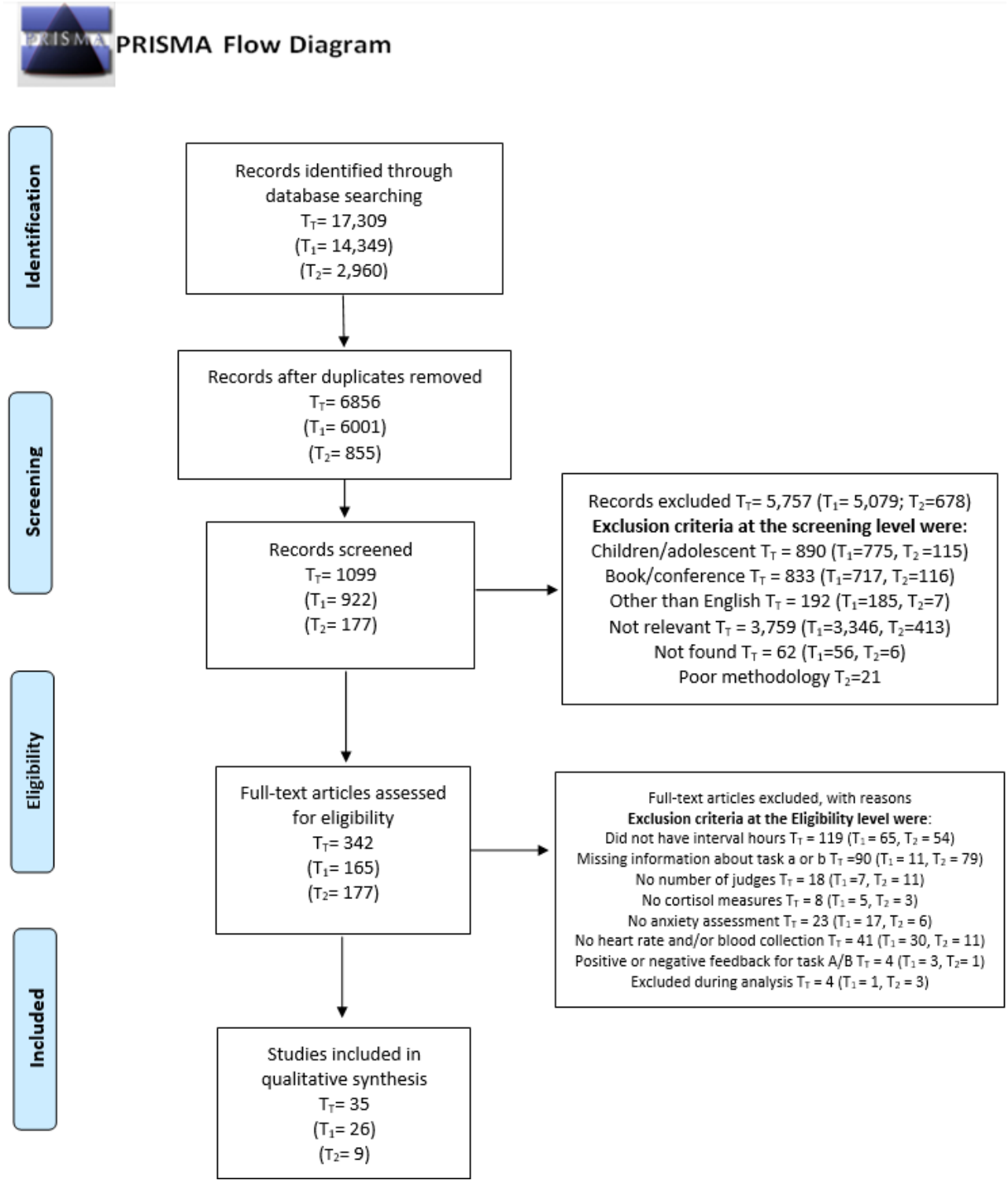
2.3.2 Literature search strategy

We focused our review on studies wherein researchers used the original version of the TSST (Kirschbaum et al., 1993) with adult populations (18 years and older). A social sciences research librarian (P.R.L.) with expertise in knowledge synthesis assisted in drafting, developing, and implementing a search strategy that would retrieve relevant results from the following databases: APA PsycInfo (Ovid), Medline (Ovid), Web of Science, and Scopus. We developed a keyword search across multiple fields specific to the concepts of the TSST, psychosocial stressors, and speech tasks (See Appendix D for the complete search strategy). Database limits were not used at this stage of the review. The search was initially conducted in December 2017 (T_1) and updated in July 2019 (T_2). Articles collected at those time points were reviewed using the same criteria. We used Zotero (Roy Rosenzweig Center for History and New Media) and Covidence (Veritas Health Innovation) to manage references and complete the research for T_1 and T_2, respectively (see Figure 1).

2.3.3 Procedure

A group of undergraduate and graduate students were trained to screen the references. First, two independent reviewers screened the titles and abstracts to assess their relevance. In case of doubt or uncertainty, N.F.N.L. reviewed the title and abstract. If an article did not include an abstract, N.F.N.L. attempted to locate it online using Google Scholar, Pubmed, journal Web sites, and other databases. If unsuccessful, the study was categorized as not found and excluded. Studies with a brief or vague summary were triaged by N.F.N.L. to review and classify.

Figure 1 *(Figure 1 for Chapter II)* Flow Diagram of the selection of the studies included in the systematic review (Moher, et al., 2015). T1 and T2 - refer to the dates when the literature searches were conducted



During the second phase, all references that remained were screened by two independent reviewers according to the study eligibility criteria, section 3.4. The third phase consisted of a second full-text screening by two independent reviewers in conformity with study selection, section 3.5.

For clarification purposes, note that T_1 and T_2 refer to the dates when the literature searches were conducted. Only for T_1, the principal authors (N.F.N.L. & V.C.) added an extra step to increase efficiency during data extraction by removing articles that did not provide adequate information about their use of the TSST, making data extraction and interpretation impossible. Specifically, while doing full-text screening for the first time (section 3.4), studies that reported using the TSST but provided limited or no procedural details (e.g., failed to report information concerning the speech or arithmetic tasks, only referred to the original article) we removed.

2.3.4 Exclusion criteria

During the title/abstract and full-text screening phases we used the following criteria to exclude ineligible studies. Studies were excluded if one of the following characteristics applied: (a) inclusion of participants 17 years old or younger, mixed sample of adults and children, or longitudinal studies with participants under 17 years or younger; (b) presented as a conference publication (given methodological information is summarized and not detailed) or erratum study (c) book chapter or graduate thesis (not peer-reviewed); (d) not published in English; (e) did not use the original TSST, for example: group TSST, virtual TSST, Toxic Shock Syndrome, animal studies, meta-analysis or systematic reviews, research on stress not using the TSST, research on psychosocial factors, program evaluations, Tubien Scotopic Threshold Test, and adaptations of the TSST (i.e, using a single task, or completely modifying all tasks from the original TSST version).

2.3.5 Study eligibility criteria

To be included, articles had to report on several specific methodological aspects. We assessed inclusion using sequential steps in order of importance from a to e: (a) testing time window; (b) number of judges (we also noted if there was a mention of judges giving positive or negative feedback at any point during the TSST); (c) nature of speech and arithmetic tasks; (d) collection of cortisol and at least one type of self-report measure (e.g., anxiety questionnaires); and (e) HR or blood collection. Specifically, articles failing to provide information about the testing time window were eliminated. Then, articles failing to indicate information about the judges were eliminated. Then, criteria related to reporting about the speech or arithmetic task (e.g., speech's type and duration, initial number for the arithmetic task), cortisol measures, anxiety questionnaires, HR or blood collection measurements were screened.

2.3.6 Data extraction

The following information was extracted from retained studies: (a) title of the article, authors' name, and year of publication; (b) number of participants for each sex[2] (men, women, or the combination of both), mean age and standard deviation for each sex, menstrual cycle stage for women if provided and any exclusion or inclusion criteria related to menstrual cycle; (c) exclusion criteria; (d) self-report measures and associated administration time; (e) number and gender of judges; (f) presence of recording equipment; (g) modifications to the TSST protocol; (h) TSST administration time; (i) resting period duration from arrival to TSST initiation; (j) controlled or prohibited activities (e.g., drinking or smoking) and required abstinence period prior testing; (k) instructions for participants' speech preparation and delivery, and feedback received from judges; (l) characteristics of the arithmetic task, i.e., initial number used, number

[2] We use the term 'sex' to refer to biological sex at birth. We use the term 'gender' to refer to an individual's socially-constructed gender role and gender expression.

to be subtracted, and task duration; (m) resting period duration following TSST; (n) physiological measures (e.g., sampling frequencies and intervals).

2.3.7 Risk of bias

Given our goal of extracting methodological information rather than specific outcomes or effect sizes, we did not conduct a typical risk of bias assessment. In addition, we did two full text-screens to ensure accuracy.

2.4.0 Results

The database search (section 3.2) yielded a total (T_T) of 17,309 studies (T_1= 14,349; T_2 = 2,960). After eliminating duplicates, 6,856 (T_1=6,001; T_2=855) studies remained in the database. Following the title and abstract screening, 5,757 (T_1=5,079; T_2=678) studies were excluded. The remaining 1,099 (T_1 = 922; T_2 = 177) studies proceeded to the full-text examination portion of the procedure (section 3.5). As reported in the procedural section 3.3, following an initial review of studies, we added one supplementary exclusion criterion related to poor reporting of TSST details for T_1. This step eliminated 757 articles, leaving 165 articles for T_1. For T_2, we applied these criteria during the study eligibility phase (section 3.4). Finally, we retained 39 articles (T_t) following the study selection phase (section 3.5). The first authors excluded an additional four studies because the described methodology appeared inconsistent with the findings reported in the figures or in the result section. For example, the times at which cortisol measures were taken did not match what was reported in the methodology section and/or the figures. Therefore, 35 articles were ultimately included in this review. We provided a summary table of the study characteristics in appendix C and an excerpt in Table 1. In the reference list, articles included in the review are identified by an *.

Table 2 *(Table 1 for Chapter II)* Speech Task, Arithmetic Task and Judges and videotape - Example of information provided in Appendix C

	Speech task			Arithmetic Task			Judges and videotape			
Study	Preparation period (min)	Time to deliver speech (min)	Type of speech	Digit number used	Digit number used for subtraction	Time to complete the task (min)	Number of judges used for the panel	Number of judges that were men	Number of judges that were women	Mentioned it was videotaped
(Abelson, et al., 2014)	3	5	Job interview	1,022	13	5	2	1	1	Yes
(Bae, et al., 2019)	5	5	Job interview	2,043	17	5	2	-	-	Yes
(Böbel, et al., 2018)	3	5	Job interview	3,079	17	5	2	-	-	Yes
(Buchanan, Laures-Gore, & Duff, 2014)	5	5	Accusation defense	1,022	13	5	1	-	-	No
(Drake, et al., 2017)	10	5	Job interview	1,022	13	5	3	Both males and females	-	Yes
(Erickson, et al., 2017)	3	5	Job interview	1,022	13	5	2	-	-	Yes
(Elzinga & Roelofs, 2005)	5	5	Job interview	1,587	13	5	3	-	-	Yes
(Fries, Hellhammer, & Hellhammer, 2006)	3	5	Job interview	2,083	17	5	3	2	1	Yes
(Giles, et al., 2014)	10	5	Job interview	1,223	17	5	3	-	-	Yes
(Gröpel, Urner, Pruessner, & Quirin, 2018)	5	5	Job interview	2,010	13	5	2	-	-	Yes
(Het, et al., 2015)	5	5	Job interview	2,043	17	5	2	-	-	No
(Inagaki & Eisenberger, 2016)	5	5	Administrative assistant position	2,083	13	5	2	1	1	Yes
(Jiang, et al., 2017)	5	5	Accusation defense	1,022	13	5	3	-	-	Yes
(Kern, et al., 2008)	3	5	Job interview	2,043	17	5	2	-	-	Yes
(Klatzkin, et al., 2018)	5	5	Job as a campaign manager for a local politician	1,022	13	5	3	-	-	Yes
(Klatzkin, Baldassaro, & Hayden, 2018)	5	5	Job interview	2,000	7	5	3	-	-	Yes
(Klatzkin, Baldassaro, & Rashid, 2019)	5	5	Job interview	2,000	7	5	3	-	-	Yes
(Li, et al., 2015)	5	5	Job interview	2,043	17	5	2	1	1	Yes
(Lupis, Lerman, & Wolf, 2014)	5	5	Job interview	2,043	17	5	2	-	-	Yes
(Maki, et al., 2015)	10	5	Job interview	1,687	13	5	3	-	-	Yes
(McInnis, et al., 2014)	3	5	Job interview	2,043	17	5	2	-	-	Yes

	Speech task			Arithmetic Task				Judges and videotape		
(McInnis, et al., 2015)	3	5	Job interview	2,043	17	5	2	-	-	Yes
(Oswald, Mathena, & Wand, 2004)			Describe qualifications for hospital							
	10	5	administrator	2,322	13	5	3	-	-	Yes
(Polheber & Matchock, 2014)								*mix-		
	3	5	Job interview	2,023	17	5	3	gendered*	-	Yes
(Reinelt, et al., 2019)	5	5	Job interview	2,043	17	5	2	1	1	Yes
(Shalev, et al., 2011)	5	5	Job interview	1,687	13	5	2	-	2	Yes
(Smith, et al., 2016)	10	5	Job interview	1,022	13	5	3	-	-	Yes
(Souza, et al., 2015)			Good candidate for a future peacekeeping							
	10	5	mission (army)	910	7	5	2	2	-	Yes
(Thomas, et al., 2011)	5	5	Job interview	1,022	13	5	3	-		No
(Veer, et al., 2011)			one's positive and negative							
	10	5	characteristics	1,033	13	5	3	-	-	No
(Wand, et al., 2007)			Describe qualifications for hospital							
	10	5	administrator	2,322	13	5	2	-	-	Yes
(Wiegand, et al., 2018)	10	5	Job interview	1,022	13	5	2	-	-	Yes
(Xin, et al., 2017)	5	5	Accusation defense	1,022	13	5	3	1	2	Yes
(Yao, et al., 2016)	5	5	Accusation defense	1,022	13	5	3	1	2	Yes
(Zhang, et al., 2019)	5	5	Accusation defense	1,022	13	5	3	1	2	Yes

As explained in section 3.5, articles were excluded in sequential steps. However, we remained interested in the number of articles excluded based on the distinctive criteria. Overall, of the 165 articles examined in T_1, insufficient details were found concerning the: testing time window (100 articles - 60.6%); speech or arithmetic tasks (13 articles - 9.7%); number of judges (23 articles - 13.9%); or self-report (13.9%), blood (93 articles - 56.4%) or HR (132 articles - 80%) measures. We excluded 12 articles (7.3%) because the judges provided positive or negative feedback during the speech or arithmetic task. Several articles fell into more than one of the exclusion criterion categories, thus demonstrating a general lack in systematic reporting of methodological details.

2.4.1 Administration of the TSST and stress-sensitive factors

Please consult Appendix C for complete characteristics of all the screened studies

2.4.1.1 Women participants and Hormonal status

Twenty-three studies included women participants. Among these studies, seven omitted mention of the menstrual cycle while 16 controlled for estrous cycle phases. Specifically, five included women in the luteal phase only, four included women in the follicular phase only, and three included women in either phase. Among the three studies wherein researchers did not control for either phase, only Maki, et al., 2015 found a significant difference in stress responses between women in the follicular and luteal phase, average age in both groups 25.60 (5.39 SD) and 28.05 (5.83 SD), respectively. Twelve of the 23 studies (52%) controlled for oral contraceptive use and 10 controlled for pregnancy, lactation, or breastfeeding. Finally, two studies controlled for post-menopausal status while the other studies excluded women who were post-menopausal, ovulating, in the follicular phase, or had irregular estrous cycles

2.4.1.2 Exclusion criteria

In total, 26 different exclusion criteria were reported in the 35 articles. A total of 303

exclusion criteria were screened in the complete sample; studies used approximately nine exclusion criteria (mean = 8.66 ± 3.11 SD), some of the most susceptible to impact results being detailed here. ***2.4.1.2.1. Medication.*** Thirty-two studies reported excluding participants taking prescribed drugs (i.e., psychoactive medication, all medication, or any medication consumed on a regular basis). ***2.4.1.2.2. Mental Health Status.*** Twenty-seven studies reported excluding individuals with mental illness, psychiatric disorder and/or DSM-IV Axis 1 disorders. ***2.4.1.2.3. Tobacco use.*** Twenty-two studies reported excluding participants based on nicotine/tobacco consumption. Specifically, seven controlled for no smokers, five excluded people who reported smoking more than five cigarettes per day, three excluded "regular smokers", two excluded "current smokers" and one excluded people with "low levels" of smoking. For the last three categories, the studies did not report the specific criteria used to define each state. Finally, four studies did not provide information about nicotine/tobacco consumption. ***2.4.1.2.4. Substance use.*** Nineteen studies reported excluding participants based on (problematic) substance use or a substance use disorder. ***2.4.1.2.5. Body Weight.*** Twelve studies reported excluding participants based on their BMI; seven of these excluded participants who did not meet a minimum BMI threshold, while ten excluded participants for exceeding a specific BMI value. Generally, the BMI of the study participants ranged between a minimum of 18-20 kg/m^2 and a maximum of 26-35 kg/m^2. ***2.4.1.2.6. Chronic Diseases.*** Ten studies reported excluding participants if they had a chronic disease, but provided no additional detail. ***2.4.1.2.7. Working Night Shifts.*** Only four studies reported excluding participants if they worked night shifts.

2.4.1.3 Restriction of activities prior to participation

In order for participants to be eligible for the TSST studies, abstinence from certain behaviors was required. Although restrictions varied, some were recurrent. Researchers asked

participants to refrain from: eating (24 studies), drinking anything other than water (16 studies), engaging in physical exercise (16 studies), drinking coffee (14 studies), drinking alcohol (nine studies), using drugs (six studies), smoking (six studies), and brushing or flossing their teeth (two studies). Given the samples for each activity are either relatively small or the difference in time is large, it was difficult to assess an average of time to refrain from each activity. Overall, the restriction period varied widely for the different behaviors extending between 60, 90, 120, 240, 270, 720, 1440, 2880, and 4320 min prior to participation, a consideration that will be addressed in relation to the specific activities in the discussion section.

2.4.2. Differences in the TSST protocol application among the sampled studies

2.4.2.1 Selected resting period

Nine studies reported having modified certain aspects of the TSST from the original protocol. Across reviewed studies, 12 different resting/habituation periods prior to TSST exposure were used, many substantially extending the initially proposed habituation time. In the original article, participants rested 30 min following a catheter placement or 10 min when no blood samples were collected (Kirschbaum et al., 1993). On average, participants waited 55 ±7.42 min. However, no consensus emerged between studies; the resting periods were: 5 min (one study), 10 min (three studies), 20 min (two studies), 30 min (13 studies), 40 min (one study), 45 min (two studies), 60 min (six studies), 70 min (one study), 90 min (three studies), 180 min (one study), 210 min (one study), and 240 min (one study).

2.4.2.2 Period of the day

Eleven studies reported initiating daily testing at the same time for every participant. Researchers often provided a time window for participants to be tested, rather than one specific time. For example, "Participants reported to the laboratory between 1200 and 1600" (Buchanan

et al., 2014, section 2.4), "the TSST experimental sessions were run between the hours of 1100 and 1600" (Drake et al., 2017, TSST protocol section), or "TSSTs were administered in the afternoon between 2 pm and 5 pm" (Het et al., 2015, Procedure section).

On the one hand, providing time windows (rather than specific times) to participants allows researchers to accommodate different participant needs and increase study feasibility. On the other hand, time windows likely increase the variability of the stress response data, given that physiological measures are not taken at the exact same time of the day. Researchers reported sixteen times for participants to begin the study, varying from 08:30 to 18:30, with a window of 3.16 ±1.77 hours in average. Forty-six ending times were reported, varying from 10:30 to 21:40. For example, if participants arrive between 14:00 and 17:00 (3-hour interval) and the experiment lasts ~70 min, the study end time will vary between 15:10 and 18:10. As shown in table 2, providing such flexibility to participants increases the variability between studies given that both the initiation times for each study and the duration of each study (i.e., resting period, duration of TSST, and recovery period) vary. This variation in time may be an important reason explaining why systematic reviews/meta-analyses report conflicting results. We found that in half of the studies we reviewed, researchers asked participants to stay for an additional 60.29 (+/- 7.64) min following the TSST, enabling them to evaluate the delayed impact of the test on physiological measures.

Table 3 *(Table 2 for Chapter II)* Procedural timeline- Example of information provided in Appendix C

	Initiation time for each			Duration of each study				Termination time for each study	
Study	Initiation time	End of provided time window	Window (width)	Rest Period before TSST	Recovery period (duration)	TSST Duration	Experiment (Total duration)	Termination time	End of provided time window
	Time 1 (24h)	Time 2 (24h)	In hours	Min	Min	Min	Min	Time 1 (24h)	Time 2 (24h)
(Abelson, et al., 2014)	13	-	-	60	75	13	148	15.47	-
(Bae, et al., 2019)	12	-	-	210	130	15	355	17.92	-
(Böbel, et al., 2018)	13	-	-	60	120	15	195	16.25	-
(Buchanan, Laures-Gore, & Duff, 2014)	12	16	4	30	40	15	85	13.42	17.42
(Drake, et al., 2017)	11	16	5	45	40	20	105	12.75	17.75
(Erickson, et al., 2017)	13.5	-	-	60	60	13	133	15.72	-
(Elzinga & Roelofs, 2005)	9	-	-	45	50	15	110	10.83	-
(Fries, Hellhammer, & Hellhammer, 2006)	15	17.5	2.5	180	60	13	253	19.22	21.72
(Giles, et al., 2014)	13	15	2	5	20	20	45	13.75	15.75
(Gröpel, Urner, Pruessner, & Quirin, 2018)	13	16	3	30	60	15	105	14.75	17.75
(Het, et al., 2015)	14	17	3	30	25	15	70	15.17	18.17
(Inagaki & Eisenberger, 2016)	13.5	16.5	3	90	75	15	180	16.50	19.5
(Jiang, et al., 2017)	13.5	18.5	5	30	30	15	75	14.75	19.75
(Kern, et al., 2008)	12	16.5	4.5	60	90	13	163	14.72	19.22
(Klatzkin, et al., 2018)	14	17	3	10	45	15	70	15.17	18.17
(Klatzkin, Baldassaro, & Hayden, 2018)	16	17	1	10	80	15	105	17.75	18.75
(Klatzkin, Baldassaro, & Rashid, 2019)	14	16	2	10	30	15	55	14.92	16.92
(Li, et al., 2015)	9	12	3	70	40	15	125	11.08	14.08
(Lupis, Lerman, & Wolf, 2014)	14	17	3	30	45	15	90	15.50	18.50
(Maki, et al., 2015)	13	17	4	60	10	20	90	14.50	18.50
(McInnis, et al., 2014)	13.5	18.5	5	30	120	13	163	16.22	21.22
(McInnis, et al., 2015)	13.5	18.5	5	30	120	13	163	16.22	21.22
(Oswald, Mathena, & Wand, 2004)	12	-	-	90	55	20	165	14.75	-
(Polheber & Matchock, 2014)	15	16	1	40	30	13	83	16.38	17.38
(Reinelt, et al., 2019)	11.75	-	-	240	115	15	370	17.92	-
(Shalev, et al., 2011)	15	18	3	20	60	15	95	16.58	19.58
(Smith, et al., 2016)	15	16	1	30	30	20	80	16.33	17.33
(Souza, et al., 2015)	13	17	4	20	20	20	60	14.00	18
(Thomas, et al., 2011)	16	-		60	90	15	165	18.75	-
(Veer, et al., 2011)	8.5	10.5	2	30	70	20	120	10.50	12.5
(Wand, et al., 2007)	12	-	-	90	65	20	175	14.92	-
(Wiegand, et al., 2018)	15	-	-	30	60	20	110	16.83	-
(Xin, et al., 2017)	13.5	-	-	30	60	15	105	15.25	-
(Yao, et al., 2016)	14	17	3	30	30	15	75	15.25	18.25
(Zhang, et al., 2019)	14	17	3	30	60	15	105	15.75	18.75

2.4.2.3 Self-report anxiety/stress questionnaires

Researchers used 18 different questionnaires to assess participants' subjective state anxiety. On average, studies measured subjective state anxiety using more than a single questionnaire (2.23 ± 1.24). All studies used at least one measure, 20 used at least two measures, 15 used three measures, and eight used four measures. The State-Trait Anxiety Inventory (Spielberger et al., 1983), the Positive and Negative Affect Schedule (Watson et al., 1988), and Visual Analogue Scales (e.g., Heller, et al., 2016) were the most popular questionnaires; they were used in 18, 14 and 11 studies, respectively. Other scales included the Perceived Stress Scale (nine studies; Cohen et al., 1983) and the Beck Anxiety Inventory (nine studies; Steer & Beck, 1997); the remaining questionnaires were used in fewer than two studies and some of them seem to have been used as screening tools. Seventeen different questionnaire combinations were listed, although no consensus for a particular combination of questionnaires was observed. The majority of studies used questionnaires before and after TSST completion allowing researchers to determine changes in subjective state anxiety due to the stressors.

2.4.2.4 Judges' number, gender and Video recorded sessions

In most studies (31 out of 35), researchers told participants that the TSST session would be videorecorded for further analysis. Only one study used a single judge, whereas the other studies reported using two (17 studies) or three (17 studies) judges. As for the judges' gender, 10 studies used both men and women on the panel, one study used only women, one study used only men, and twenty-four studies failed to report the genders of the judges.

2.4.2.5 Speech task

For the speech task, we noted three preparation times. Eight, eighteen, and nine studies allotted 3, 5, and 10 min of preparation time, respectively. All studies reported a speech duration

period of five min. Seven types of speeches were reported. The majority (24 studies) used a specific job interview task (asking participants what makes them the best candidate for their dream job), five used an accusation defense task, two asked participants to describe personal qualifications in an administrative job at a hospital, one asked participants to comment on their qualifications for a future peacekeeping mission, one asked participants to present positive and negative personal characteristics, one asked participants to present their qualifications as a future administrative assistant, and one asked participants to describe their qualifications as a campaign manager for a local politician. We identified nine combinations of preparation times and speech types. The preparation times for studies using a job interview were three (8 studies), five (11 studies), and ten min (5 studies). Five studies used an accusation defense speech and provided 5 min of preparation time and two studies provided 10 min preparation time for participants to describe qualifications as a hospital administrator. The remaining studies used either 5 min (i.e., administrative assistant or campaign manager for a local politician) or 10 min of preparation time (i.e., qualifications for future peacekeeping mission, personal positive and negative characteristics).

2.4.2.6 Arithmetic task

Researchers used 13 different initiation and subtraction numbers in the arithmetic task across 14 different number combinations. The two number sets predominantly selected (initial and subtraction numbers) were 1022 and 13 (12 studies) and 2043 and 17 (8 studies). For the remaining studies, 1687/13, 2322/13, 2000/7 were used in two studies each, respectively; and 910/7, 1033/13, 1223/17, 1787/13, 2010/13, 2023/17, 2083/13 were used in one study each, respectively. All arithmetic tasks lasted five min.

2.4.2.7 Recovery period following TSST

We observed a wide range of resting periods across studies. Sixteen studies used recovery periods that were shorter than one hour (from 10 to 55 min); seven used over one-hour post testing recovery, and seven used recovery periods lasting over 90 min. On average, recovery periods lasted 60.29 ±7.76 min.

2.4.3 Physiological measures

Collection times are preceded by minus '-' or plus '+' signs to indicate whether the physiological measures were collected prior or after TSST exposure, respectively, 0 min corresponding to TSST initiation. Given that studies used multiple collection intervals for the physiological measures, we decided to round up the stated collection times when needed. For instance, 18 min and 31 min were rounded up to the most proximal number, 20 min and 30 min, respectively.

2.4.3.1 Heart rate

Twenty-seven studies measured HR and thirty-four different time intervals were reported for recording initiation. On average, researchers collected nine HR measures (9.42 ± 5.14). The time interval for HR collection varied greatly, HR sampling ranging from an initial collection at -70 min and a final measure at + 105 min post initiation of the TSST. Five studies recorded HR throughout the study but did not specify time (i.e., baseline, pre-TSST, TSST, post-TSST).

2.4.3.2 Cortisol collection

Researchers reported 38 different CORT collection times. On average, studies collected 6 CORT samples (6.29 ± 3.06) over the experimental procedure. However, we found inconsistencies in CORT time sampling procedures across the 35 studies. No consensus emerged on when the initial salivary sample was collected (i.e., initial measurement), the number of

collected measures, or the interval between collections. As an illustration, two studies collected the 'initial' CORT level at -280 min, one study at -180 min, one study at -70 min, one study at -50 min, two studies at -45 min, one study at -40 min, six studies at -30 min, four studies at -20 min, two studies at -15, four studies at -10 min, four studies at -5 min, one study at -1 min, and 6 studies at 0 min (immediately preceding TSST initiation - noted as 0 min sample).

2.4.3.3 Blood collection

Twelve studies collected blood samples and thirty-three collection times were identified. On average, researchers collected seven samples (7.67 ± 3.52). Similar to salivary cortisol sampling, blood collection showed a wide range of intervals, with no consensus as to a validated sampling procedure. For example, only five studies collected a blood sample at the initiation of the TSST at 0 min, two collected at +5 min, two collected at +10 min, six collected at +15 min, two collected at +20 min, seven collected at +25 min, two collected at +30 min, five collected at +35 min, two collected at +40 min, seven collected at +45 min, three collected at +50 min, one collected at +55, five at +60 min, two collected at +65 min, two collected at +70 min, three collected at +75 min, and 15 collected blood samples between +80 min and +133 min. As for the method of collection, seven studies reported collecting blood samples using an intravenous catheter, three studies used an indwelling catheter, and two studies used a peripheral venous catheter. In all cases, the technique involved introducing a catheter to collect venous blood samples while minimizing the discomfort and stress effect associated with repeated venepuncture.

2.5.0 Discussion

We conducted a systematic review to examine the degree to which researchers report

various methodological details when using the TSST. We aimed to document reporting practices, identify differences in protocols that may be limiting comparison across studies—and thus—replication efforts, and make recommendations to increase standardization in future research using the TSST. Overall, we found that most researchers: 1) did not provide sufficient details to enable replication, 2) ignored a variety of discrete variables that could influence their findings (e.g., alcohol use, number of judges), and 3) when testing women, often failed to consider menstrual cycle phases, peri- and menopausal periods, and oral contraceptive use. For example, the results in section 4.3.2. Cortisol collection provide support that researchers have introduced several changes to the initial protocol over time, resulting in a lack of standardization of the actual testing procedure. Initial CORT levels are important because they establish the baseline to which future levels are compared, to determine whether the TSST produces an increase or decrease of HPAA. Therefore, if initial CORT levels are measured at different times and different rates, it is difficult—if not impossible—to compare HPAA responses across time. This comparison difficulty increases if we also take into consideration the variation in testing windows (section 4.2.2). Consequently, in the following sections, we provide a set of guidelines based on the literature and on our findings with the ultimate goal of facilitating strong replication practices by reducing the impact of known confounding variables in HPAA responses to stress.

2.5.1 Researchers should control stress-sensitive factors when using the TSST

2.5.1.1 Women participants and Hormonal status

Guideline 1. Knowing that hormonal fluctuations in women can strongly influence responses to a stressor, *researchers should assess and report women's menstrual cycle phase or menopausal state.* Moreover, they should include these variables in their statistical analyses (e.g., by creating separate groups or specifying a covariate; Gaffey et al., 2014). Ignoring or failing to

report these variables can reduce sound study replication. If groups are too small to control for hormonal status in data analyses, researchers should—at a minimum—report frequencies for this variable so that the information is available for future knowledge synthesis efforts. Researchers could alternatively determine inclusion or exclusion criteria based on menstrual cycle, contraceptive use, pregnancy, or breastfeeding status.

2.5.1.2 Exclusion criteria

Guideline 2. *Researchers using the TSST should assess and report*: (a) medication use (type/duration of treatment), (b) mental or psychiatric disorders, (c) history of substance use, nicotine/tobacco and alcohol intake, (d) Body Mass Index range, (e) chronic diseases, (f) poor health/physically unhealthy, (g) cardiovascular diseases, and (h) working night shifts. Reporting decisions about whether to include participants, exclude participants, or implement statistical controls based on these factors will enable clearer interpretation of the effects of any independent variables on HPAA, and will also enhance the validity and replication of studies (Lilienfeld, 2017). Moreover, researchers should clearly indicate how they are measuring each of these factors. For example, how did they assess for current psychological disorders? What chronic diseases were considered?

In 1946, the WHO defined health in their constitution as "the state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity" (WHO, 1946, p. 1). As such, health is often assessed via participant self-report (e.g. any medical conditions, medication, mental health symptoms, etc.). For research with human participants, it is up to the experimenters to decide *a priori* how they will define the health status of participants and, based on their definition, determine eligibility criteria for the study. Again, depending on the specific research goals, inclusion and exclusion criteria may vary. Regardless of how researchers define

health for a given study, it is crucial to clearly report the definition in the methodology section, which was not the case for most of the studies reported in this systematic review. In the conclusion (section 6.0), we offer some ideas for how researchers can account for different confounding variables when interpreting their findings, using a guidance document we created. According to participants' responses, researchers can operationalize their own definition of poor health/physically unhealthy and exclude participants from participation or analysis accordingly.

2.5.1.3 Restriction of activities prior to participation

Guideline 3. Brushing or flossing teeth, smoking, using substances, drinking alcohol or caffeinated beverages, engaging in physical exercise, and eating are all behaviors that, to some extent, have an impact on HPAA. However, we found that researchers do not apply consistent standards for accounting for these behaviors. Therefore, we recommend that *researchers systematically ask participants to report engagement in these behaviors prior to participating in the TSST* (Stalder et al., 2016). Moreover, researchers should ask all participants to abstain from engaging in these behaviors at least 60 min prior to arriving at the laboratory. For alcohol and substance consumption, this period should be extended to 24 hours. Thus, including the rest period prior to beginning the TSST, 90 to 120 min should elapse before researchers collect physiological measures to assess the impact of the TSST. That time frame will provide sufficient time for CORT secretion to stabilize prior to engaging in the TSST.

Additionally, caffeine withdrawal occurs when abstinence from caffeine leads to primary onset of symptoms 12 to 24 hours after the last consumption, with the peak between 20 to 51 hours, and a duration of 2 to 9 days (Juliano et al., 2004). Therefore, researchers should carefully plan their TSST with consideration of how to restrict caffeine consumption while avoiding a withdrawal state for participants.

2.5.2. Differences in the TSST protocol

2.5.2.1 TSST protocol alterations and selected resting period

Guideline 4. Considering our guideline to restrict the above-mentioned activities for 60 min prior to testing, we recommend that *researchers implement at least 30 min resting time for participants upon arriving at the lab and prior to initiating the TSST* to allow the individual's physiological responses to stabilize. When participants initially arrive, their physiological activity may vary because of different personal, situational, and environmental factors (e.g., walking to the lab, anxiety about being in a strange environment or participating in research). During this period, researchers can greet participants, complete the consent process, and/or administer preliminary questionnaires—especially those that measure the various factors for which researchers should control (e.g., oral contraceptive use, medical history). We believe the acclimatization period is very important and we recommend a minimum of 30 min be implemented for every study.

2.5.2.2 Period of the day

Guideline 5. *Researchers should choose a specific time of day at which participants can begin the study.* We suggest avoiding wide time intervals as starting points, given that collected measures might not be comparable, and people's circadian rhythms can influence CORT values. The variability in time windows that we observed may explain some inconsistencies found in the current research. Additionally, researchers should review the literature related to CORT circadian rhythms relevant to their target population (i.e., age and sex) prior to setting a starting point. Finally, researchers should carefully analyze and interpret measures taken beyond 90 min post-TSST to confirm that these values are associated with the experimental conditions and not to extraneous factors.

Lastly, to our knowledge, there are no studies on the impact of waking time and cortisol levels during the day on TSST outcomes. However, in one study, Williams et al. (2005) measured CAR in 32 men and women over 6 days across three conditions: 2 early shift days, 2 day-shift days, and 2 control (leisure) days. They found that waking time had no effect on CAR even when controlling for stress and sleep disturbances. Future studies are warranted to investigate the impact of awakening time on diurnal cortisol levels. At present, researchers may ask participants to wake up at a specific time or within a defined morning time window to minimize influence of this possible confounding variable. However, at this time, no scientific research is available to sustain this claim.

2.5.2.3 Self-report anxiety/stress questionnaires

Guideline 6. *Researchers should use a minimum of two different self-report questionnaires to assess participants' subjective anxiety or stress state* to ensure accurate estimates of anxiety experiences. Researchers should administer the questionnaires before and after the TSST to measure the impact of the TSST on participants' subjective state anxiety (i.e., change in anxiety due to TSST). Given the large volume and variety of self-report state anxiety measures, researchers should carefully consider their research goals to select the measure(s) that best measures their target variables. For assessing in-the-moment state anxiety, we recommend the State-Trait Anxiety Inventory (STAI), the Positive or Negative Affect Schedule (PANAS), or the Visual Analogue Scale (VAS) because there is evidence that they are sensitive to change, some are available for free, and available in several languages (e.g, STAI in French [Gauthier & Bouchard, 1993]; STAI in Spanish [Virella, et al., 1994]). Furthermore, given evidence that subjective and physiological anxiety measurements often diverge, researchers can better understand the impact of the TSST on different components of anxiety experiences across time

by using these questionnaires at multiple timepoints and comparing subjective and physiological responses.

2.5.2.4 Judges' number, gender, and video recorded sessions

Guideline 7. The original TSST included a panel of 3 judges. However, researchers have deviated considerably from this suggestion, using a smaller panel of 2 judges, primarily due to study feasibility. To our knowledge, there are no research findings suggesting significant effects of this procedural difference. However, given the large number of studies that have used two judges and the real need to facilitate study feasibility, *adopting a standard of two judges would promote reliable effects that could easily be compared*. We suggest using one man and one woman, rather than two same-gendered judges given findings that a mixed panel more effectively induces optimal HPAA activation (Allen, et al., 2014; Duschesne, et al., 2012). Because videorecording is effective in enhancing perceived stress and HPAA activation (Kudielka, et al., 2007), we recommend telling participants that their performance will be recorded and judges will evaluate their non-verbal communication.

2.5.2.5 Speech and arithmetic tasks

Guideline 8. As shown in table 1, we found considerable variability in the TSST speech task administration. In a meta-analysis, Goodman et al. (2017) found few differences between preparation times, but did not assess speech length or type. Therefore, in the interest of increasing consistency between studies, *researchers should implement the following standard speech task process:* 5 min preparation using a piece of paper and pencil to organize their thoughts, 5 min speech (without their notes) about why the participant considers themselves the best candidate for the job of their dreams.

Guideline 9. We observed a wide variety of number combinations. To ensure researchers

induce similar stress levels across participants and across studies, we recommend that *researchers adopt a standard initial number and subtraction variable.* We suggest maintaining the initial arithmetic combination described by Kirschbaum et al. (1993), asking participants to repeatedly subtract 13 from an initial number of 1022. Some systematic reviews/meta-analysis have tried to determine whether variation in the arithmetic task impacts CORT measures, but have not yielded significant findings (see Goodman et al. (2017) for an example), and one could not ascertain whether observed differences were accounted by the selection of the initial number, the subtracting number or the combination/interaction of both. Furthermore, given the variability observed across several variables (e.g., window time, menstrual cycle, exclusion criteria), current knowledge synthesis efforts may not accurately estimate differences based on a single variable because of these multiple confounds.

2.5.2.6 Recovery period

Guideline 10. We must remain cautious about the possible lasting impact of the TSST on HPAA activation in certain populations, especially when there is so much variation across variables (e.g., menstrual cycle, age, time windows). Nonetheless, *researchers should analyze and interpret with caution* any physiological measures taken more than 90 min following TSST completion. To our knowledge, no researchers have demonstrated HPAA activation related to TSST exposure above this time interval. In other words, researchers investigating HPAA dysfunction, which is not typically observed at delayed intervals should do so through re-exposure to a second TSST session or to another acute stressor. Finally, researchers should include a post-test recovery period lasting at least 60 min to enable them to collect additional physiological measures and examine optimal recovery intervals in diverse populations.

2.5.3 Physiological measures

2.5.3.1 Heart rate

Guideline 11. HR measures are a practical, non-invasive method to quantify physiological activation of HPAA and a way to supplement salivary and/or blood measures (Liew, et al., 2016). Based on the reviewed research and considering that HR can be taken continuously throughout the session without disturbing the TSST administration, we suggest that *researchers collect HR measures at* time intervals of –30 min, – 5 min, 0 min, +5 min, +10 min, +15 min, +20 min, +30 min, +40 min, +50 min and +60 min. Collecting HR measurements at sufficient time intervals will help better appreciate rapidly occurring changes in participants' physiological arousal.

2.5.3.2 Cortisol collection

Guideline 12. *We recommend that researchers take 6 CORT samples* at -30 min, 0 min, +15 min, +25 min, +35 min and +45 min. The proposed time intervals have proven effective in the reviewed studies and appear optimal with protocols involving repeated blood or saliva sampling. As researchers know, theory and practice do not always map onto one another. Thus, instead of taking a sample at +10 min, which would occur between the end of the speech task and the beginning of the arithmetic task, we recommend taking it at +15 min. By shifting the interval collection by 5 minutes, we may not be able to separate contribution of the speech and arithmetic task to cortisol secretion, but this strategy will enable the TSST to be completed without interruption. Indeed, some participants experience difficulty giving a saliva sample (i.e., participants taking medication or older adults; see Dickerson & Kemeny, 2004; Juster et al., 2012). Considering the results in this review and the time profile of endocrine secretions following various moderate psychogenic stressors, including the TSST, the proposed collection

enables to cover an appropriate secretion time range and is aligned with results from previous findings (section 2.3.2).

2.5.3.3 Blood collection

Guideline 13. To our knowledge, no specific recommendations have been proposed for blood collection aimed at CORT measures during the TSST. Therefore, based on CORT secretion profile and numerous studies using TSST induced cortisol detection in saliva samples, we recommend *blood sample collection be perfomed using the same intervals as for salivary CORT detection*. Given that blood collection remains an invasive procedure, researchers should ensure it is completed by a team member with the appropriate qualifications (e.g., a registered nurse). Researchers should consider whether this additional burden on research feasibility is on par with the desired outcome.

Moreover, they should choose a blood sampling method (e.g., repeated venepuncture, indwelling line) taking into consideration the additional activities in which participants will be involved during the study. For example, if participants undergo a neuropsychological assessment, the presence of a needle inserted on the top of the hand could interfere with full arm dexterity and exert unanticipated effects on any neuropsychological task requiring a manipulation of objects. Therefore, researchers should carefully select the proper method to take blood samples based on the study paradigm. In this context, consulting the WHO guide is a good start (WHO, 2010).

Although we focused primarily on the main physiological measures assessed during the TSST (i.e., CORT), it is worth mentioning that saliva and/or blood samples allow researchers to measure several other endocrine responses. For example, researchers could assess the influence of the main sex hormones in women (i.e., estradiol and progesterone) on study outcomes while

other researchers study the impact of the TSST exposure on immune parameters (e.g., cytokines) using collected saliva and/or blood samples (for a review see Allen et al. 2014). These analyses need to be carefully planned in advance for two main reasons: 1) analysis of different endocrine parameters can be very costly, and 2) the amount of saliva and/or blood can differ depending on the number and/or nature of the endocrine/immune responses assessed. Researchers interested in collecting and analyzing endogenous biomarkers should develop a detailed plan before beginning data collection.

2.6.0 Conclusion

The TSST has been a true asset in investigating the impact of social stress exposure on various functional outcomes. Nonetheless, in reviewing these individual studies, we noted no systematic processes among researchers across a number of variables and factors. First, there is considerable variability across studies in exclusion criteria, which makes it difficult to replicate or compare studies. Second, we found substantial variability in time intervals implemented in all phases of the TSST, with a notable lack of similarity across articles, and in whether or not researchers considered hormonal status among women. These two major factors may play a primary role in the wide variety of findings in this research area. We found no standardization across studies of optimal times for collection of various physiological measures, complicating future researchers' ability to select time intervals when designing a study. We acknowledge the cost associated with collecting multiple, repeated physiological measures. However, selecting consistent intervals, even if it is not feasible to use all measures at a high frequency, whether due to costs or participants not being suited for repeated sampling, still represents a minimum standard, and an improvement over the current situation. We strongly believe that establishing

key time collection intervals can set the stage for improved knowledge synthesis and transfer. Throughout the years, researchers have implemented many changes to the original protocol. Several studies reported divergent findings, which may be partly attributable to methodological differences. In this review, we noted that only 20% of the articles eligible for this review (i.e., because they reported a sufficient amount of methodological detail) were published before 2014. Thus, the scientific field may be becoming more aware of this methodological variability, and prioritizing high reporting standards to facilitate research replication (Lilienfeld, 2017).

Given that our findings are similar to those reported in past reviews (Labuschagne et al., 2019; Allen et al., 2014; Allen et al., 2017; Goodman et al., 2017), our work provides additional support to past criticisms of TSST variations using best practices for knowledge syntheses. Using a systematic approach, our review validates the recommendations from previous work, and through rigorous assessment of the controlled factors across studies, enabled us to provide informed guidelines to be used in future research.

Since the inception of our review, we realized that researchers devoted to studying stress have made significant gains to increase our understanding of the consequences and influence of stress in our daily lives. Nevertheless, even one of the most rigorous paradigms like the TSST is not immune to methodological drift following new discoveries. As such, we used this systematic review to develop a TSST researcher's guide—a shortlist of elements researchers should consider prior to using the TSST. Our ultimate goal is to facilitate standardization of the research protocol *via* a detailed methodology, including a proposed timeline for the collected physiological measures (appendix A) and a background questionnaire (appendix B) to guide researchers in considering several factors that could influence findings. Specifically, we aim to raise awareness of the different variables that can influence TSST outcomes. However, specific

research objectives and resource limitations will undoubtedly require adaptations in applying the proposed recommendations. Rather than a strict set of implementation rules, we conceptualize Appendix B as a flexible guide to aid in controlling potentially influential or confounding variables by taking these factors into account when designing the study, collecting a large amount of data, analyzing data, and interpreting their findings. To our knowledge, there are no comparable documents available in the literature. We hope that researchers will use these resources to facilitate data collection, research replication, data analysis, and eventually improve study comparisons and knowledge synthesis (Stark, 2018).

2.7.0 Acknowledgements

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Appendix A – Standardization of the TSST protocol

Recruitment

- When studying both sexes, it is essential to report the number of participants in each sex group and in the overall sample, as well as the average age (±SD) of each sex group;
- Sex-related exclusion or inclusion criteria should be clearly specified for women participants, particularly the menstrual cycle phase (Luteal, Follicular, Luteal & Follicular) for younger women, and menopausal stages for middle-aged women (perimenopause, menopause, and postmenopause);
- Although specific inclusion/exclusion criteria will vary from study to study depending on specific research questions and variables, all studies should assess and report the following: (a) type of medication, (b) mental disorders, (c) history of drug use (d) nicotine/tobacco and alcohol intake, (e) contraception use, (f) Body Mass Index range, (g) pregnancy or Lactation, (h) chronic Diseases (e.g. cardiovascular), (i)working night shifts;
- Together with the criteria used to include or exclude participants, researchers should report whether they assessed and/or restricted the following pre-TSST activities (a) exercise, (b) eating, (c) drinking (except water), (d) brushing teeth/flossing, (e) caffeine intake, (f) smoking, and (g) drug use. A 60 min restriction interval should be considered for all activities except (c) and (g) that should where inclusion should be considered with minimal 24h intervals;

Pre-TSST

- Any modifications made to the standardized TSST protocol should be clearly reported in the methodology to facilitate replication and knowledge synthesis;
- Age and sex can impact physiological results depending on the time of the day they are collected. Researchers should carefully consider the time window selected, based on prior research. The same time window should be maintained for all participants, starting at the same time and/or select a limited testing time-window;

- To provide the participant sufficient time to acclimatize to the environment, the resting period prior to TSST initiation should minimally last 30 min;
- Researchers should assess subjective anxiety levels by using at least 2 separate forms/scales/questionnaires before and after the TSST. The most common measures are: (a) the State-Trait Anxiety Inventory, (b) the Positive and Negative Affect Schedule, (c) the Visual Analogue Scale;
- Participants should always be informed that their performance will be videorecorded for further analysis by a behavioural specialist (as this factor influences HPAA response);
- Notwithstanding the number of judges included on the judges' panel (2 or 3), both genders should be represented. When using three judges, consider counterbalancing a possible effect of the panel's genders by alternating (2 men & 1 women VS. 2 women & 1 man). Otherwise, maintain the same set of judges for all participants;

Tasks

- For the speech task, the preparation time should be 5 min, the topic should be about a job interview and the speech duration should be 5 min;
- For the arithmetic task, the start number and the subtraction number should be consistent across studies. We recommend using 1022 and 13, respectively. Task duration should be 5 min;

Post-TSST

- The recovery period should be one hour;
- Any tasks assigned during the recovery period should not challenge the participants, unless you control for this in your research. The objective of the recovery period is to collect measurements related to the individual's coping response following stressor exposure;

Physiological measures

- The physiological impact of the TSST should always be validated by including cortisol measurements. Heart rate can be added as a measure of sympathetic system activation;

- Recommended times for physiological measure collection are presented in Figure 1;
- If you are measuring heart rate, 10-12 collection time points are recommended;
- If you are measuring cortisol, 6 samples are recommended, whether collected via salivary or blood sampling.

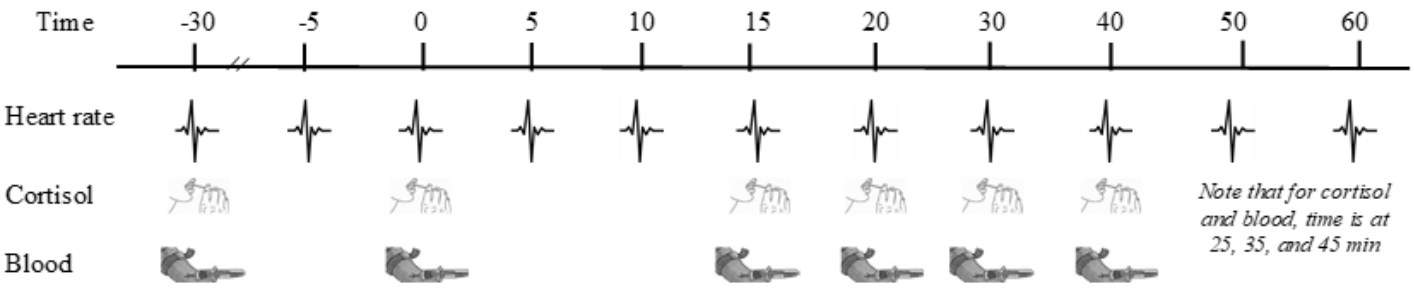


Figure 1. Recommended times in minutes to measure the heart rate, salivary cortisol or blood collection during the TSST

Appendix B –TSST Background Questionnaire

Participant #: _____ Age: _____
Sex: _____ Date: _____/_____/_____

TSST Background Questionnaire

Prior to participation
In the last 24 hours have you…

1. … done any physical exercise?
   ☐ No ☐ Yes, when (time): _____

2. … had any alcohol?
☐ No ☐ Yes, when (time): _____

3. …had any caffeine drinks (e.g., coffee, energy drinks)?
☐ No ☐ Yes, when (time): _____

4. …used any kind of tobacco (e.g., cigarettes, pipe, chewing tobacco)?
☐ No ☐ Yes, when (time): _____ What kind: _____

5. …used any kind of recreational drug (e.g., marijuana, cocaine)?
☐ No ☐ Yes, when (time): _____ What kind: _____

6. … eaten any food?
☐ No ☐ Yes, when (time): _____

7. … brushed or flossed your teeth?
☐ No ☐ Yes, when (time): _____

Sociodemographic Information

8. What is your weight and height?
☐_____cm ☐_____ pounds
☐_____feet, inches ☐_____ kg
Note: we will use this data to determine your Body Mass Index

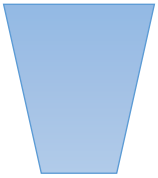
9. Do you have any of the following medical conditions?
☐ Arthritis ☐ Asthma ☐ Cardiovascular Disease
☐ Previous cancer ☐ Diabetes type 2 ☐ Hypercholesterolemia
☐ Hypertension ☐ Obesity ☐ Other:_____

10. Are you a night worker?

☐ No ☐ Yes, since when (year): _____

11. How often do you drink coffee **per week**?

☐ Less than once a week
☐1–2 times a week
☐3–4 times a week
☐ 5–6 times a week
☐ Daily



The standard size for a cup of coffee is 8oz or +/-250 ml or the smallest size of your preferred coffee brand.

12. How much coffee do you drink **daily**?

☐ I do not drink coffee regularly
☐1–2 cups
☐3–4 cups
☐ 5–6 cups
☐ More than 7 cups

13. Do you currently smoke or have you ever smoked tobacco products such as cigarettes, cigars or pipes?

☐ No, I have never smoked cigarettes
☐ Yes, I do smoke cigarettes
  ☐ I smoke _____cigarette(s) per day
  ☐ I smoke _____ pack(s) per week
  ☐ I have been smoking for _____year (s)

☐ Yes, I smoked cigarettes
  ☐ I smoked _____cigarette(s) per day
  ☐ I smoked _____pack(s) per week
  ☐ I smoked for _____ year (s)
  ☐ I stopped _____year (s)

14. How often do you drink alcohol **per week**?

☐ Less than once a week
☐1–2 times a week
☐3–4 times a week
☐ 5–6 times a week
☐ Daily

*Adding pictures of what is considered a standard drink can be informative to the participant when answering question 14-15

15. When you drink alcohol, how much do you **typically** drink?

☐ I do not drink alcohol regularly

☐1–2 drinks
☐3–4 drinks
☐ 5–6 drinks
☐ More than 7 drinks

16. Have you ever been diagnosed with an alcohol use disorder?

☐ No ☐ Yes

17. Do you use recreational drugs (e.g., marijuana, cocaine)?

☐ No ☐ Yes, what kind: _____

18. Have you ever been diagnosed with a substance use disorder?

☐ No ☐ Yes

19. In the **last year**, have you received a mental health diagnosis (e.g., depression, anxiety), or have you been treated for a mental health disorder?

☐ No ☐ Yes

20. Please list the name and dosage of the drugs that you have taken in the last 24h?

Name of medication	Dosage
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____
_____	_____

<u>Thank you for answering these questions</u>

Note: If you are a woman, do not forget to answer the questions on the back of this page

Women participants only: please respond to the following questions

A. Do you have a regular menstrual cycle?

☐ No

☐ Yes

a. If you have a regular menstrual cycle, the last day of your period was _____ days ago

B. Are you on any Hormonal Contraception?

☐ No

☐ Oral Contraceptive Pill

☐ Contraceptive Patch

☐ Vaginal Ring

☐ Intrauterine Contraception (IUC)

☐ Injectable Contraception

If you checked any answer, please indicate since when (year)? _____

C. Are you pregnant or have you ever been pregnant?

☐ No

☐ Yes, I am pregnant

How many weeks have you been pregnant ? _____

☐ Yes, I have been pregnant

When was your last childbirth, abortion or miscarriage (year)? _____

a. Are you currently breastfeeding??

☐ No

☐ Yes, when did you start (month/year)? _____

D. Are you menopaused?

☐ No

☐ Yes, I am in the process of the menopause period

☐ Yes, my menopause is over

Since when (year)? _____

a. If you are menopaused, are you on the Hormone Replacement Therapy?

☐ No

☐ Yes, since when (year)? _____

Appendix C – Results

Follow the following link to access the data : https://doi.org/10.1016/j.ynstr.2020.100235

Appendix D - Search Strategy

The following is a list of the search strategies that were executed in each database used in this review. These searches were conducted in December 2017 and July 2019.

PsycINFO (Ovid)

1. social stress test*.mp
2. social stress task*.mp
3. (tsst not toxic shock syndrome toxin).mp
4. psychosocial stressor*.mp
5. speech task*.mp
6. or/1-5

MEDLINE (Ovid)

1. social stress test*.mp
2. social stress task*.mp
3. (tsst not toxic shock syndrome toxin).mp
4. psychosocial stressor*.mp
5. speech task*.mp
6. or/1-5

Web of Science

1. social stress test*.mp
2. social stress task*.mp

3. (tsst not toxic shock syndrome toxin).mp
4. psychosocial stressor*.mp
5. speech task*.mp
6. #1 or #2 or #3 or #4 or #5

Scopus

1. TITLE-ABS("social stress test*")
2. TITLE-ABS("social stress task*")
3. (TITLE-ABS("tsst")) AND NOT (TITLE-ABS("toxic shock syndrome toxin"))
4. TITLE-ABS("psychosocial stressor*")
5. TITLE-ABS("speech task*")
6. #1 or #2 or #3 or #4 or #5

Supplementary Material – PROSPERO Registration

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

A Systematic Review of the Trier Social Stress Test methodology: Issues in promoting study comparison and replicable research

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

05/12/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

29/03/2018

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

PROSPERO
International prospective register of systematic reviews

NHS
National Institute for Health Research

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Mr Narvaez Linares

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr.

7. * Named contact email.

Give the electronic email address of the named contact.

[redacted]

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

[redacted]

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

[redacted]

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Ottawa

Organisation web address:

http://sciencessociales.uottawa.ca/psychologie/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Nicolas Francisco Narvaez Linares. University of Ottawa (Canada)
Dr Hélène Plamondon. University of Ottawa (Canada)

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

A doctoral research scholarship was awarded to Nicolas Francisco Narvaez Linares from the Fonds de recherche du Québec – Nature et technologies (FRQNT)

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

Miss Valérie Charon. University of Ottawa
Miss Paulette Ehimen Ewalefo. University of Ottawa
Miss Matilda Berr. University of Ottawa

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

Identify the protocol variances most commonly used in the TSST.

Clarify whether the TSST protocol is used in a standardized way.

Illustrate how diversity in the use of the TSST through research can have an impact on results.

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

We will search the following electronic bibliographic databases: MEDLINE, PsycINFO, Web of Science (science and social science citation index) and Scopus.

The key words that we will use are : « social stress test* », « social stress task* », « (tsst not toxic schock syndrome) », « psychosocial stressor* », « speech task* » and « or/1-5 »

There will be no language restrictions.

Studies published between 1993 and the date the searches are run will be sought.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Not applicable.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Exclusion criteria:

a) Poor methodology (e.g., only mentioned the TSST, gave general information (e.g., 5 minutes speech task), only cited the 1993 study without given more information)

b) Articles not found

c) Repetitive articles

d) Children/adolescent studies

e) Thesis_presentation_books_reviews_meta-analysis

f) Not relevant

g) Studies other than English

h) Studies Erratum

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Not applicable.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

We will include all the studies that used the TSST in adults.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

This review will aim to provide a standardized protocol with the most commonly used variances in the TSST.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Not applicable.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. The full text of these potentially eligible studies will be retrieved and independently assessed for eligibility by two review team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with a third reviewer.

A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: participant's demographic information, exclusion criteria, type of anxiety assessment, gender and number of judges, type of task A, type of task B, cortisol measure, heart rate measure, blood measure. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion (with a third author where necessary). Missing data will not be requested from study authors.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Every step will be reviewed by a peer. In case of disagreement between two individuals, a third review author will be involved.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and

software package to be used.

The general approach to synthesis for this review will be narrative (descriptive). Quantitative synthesis will be used if the included studies are sufficiently homogenous.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None planned.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
Yes

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest

No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Canada

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are

included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

systemic review

TSST

adults

standardization

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.
Please provide anticipated publication date

Review_Completed_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Pre-print: https://psyarxiv.com/9wtre/

Give the link to the published review or preprint.

Peer-reviewed: https://doi.org/10.1016/j.ynstr.2020.100235

2.8.0 References

All cited references can be found in Chapter 8 – Références de la thèse.

Chapitre III – Recension systématique de la littérature d'études par échantillonnage ayant étudié l'influence des maladies coronariennes sur le profil neuropsychologique des femmes

Neuropsychological Sequelae of Coronary Heart Disease in Women: A Systematic Review

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Abstract

Heart disease, such as coronary heart disease (CHD), is the leading cause of death among aging women. However, over the past years, the mortality rate has declined, resulting in an increased number of CHD survivors. In this context, research has uncovered relationships between cardiovascular disease (CVD) and the development of neurodegenerative diseases, suggesting that CHD can act as a precursor. Despite heart disease affecting both sexes, CVD research has significantly neglected women. Therefore, we conducted the first systematic review of neuropsychological sequelae of CHD in women to gain a clear portrait of the current knowledge of the association of CHD on women's neuropsychological status. We found that studies continue to include an insufficient number of women in their research. Our work also uncovered that there is variability in the definition of CHD by researchers (i.e., operationalization of the variable), which could explain inconsistencies across studies. Overall, we found evidence that supports the heart-brain disease hypothesis. To conclude, we provide several guidelines for future research involving the impact of CHD in women.

Keywords: coronary heart disease, neuropsychological assessment, cognitive function, women, systematic review

Abstract (PRISMA guidelines)

Introduction. Heart disease, such as coronary heart disease (CHD), is the leading cause of death among aging women. However, over the past years, the mortality rate has declined, resulting in an increased number of CHD survivors. In this context, recent research has uncovered relationships between cardiovascular disease (CVD) and the development of neurodegenerative diseases, suggesting that CHD can act as a precursor to the development of the latter (e.g., Alzheimer's disease). Despite heart disease affecting both sexes, CVD research has significantly neglected women. Therefore, we have conducted the first systematic review of the neuropsychological sequelae of CHD in women. This review aims to draw a clear portrait of the current knowledge of the association of CHD on neuropsychological status of women.

Methods. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA) for our review. We screened publications in both the title/abstract and the full-text screening phases and included the ones that met the following characteristics: a) included participants older than 18 years old; b) included women in their sample; c) performed a neuropsychological assessment (including variations [e.g., cognitive assessment]); and d) studied CHD (including variations [e.g., ischemic heart disease]) or subtypes of CHD (e.g., myocardial infarction). Initial searches were conducted in August 2018 and then updated in July 2020 in the following databases: a) MEDLINE (Ovid); b) APA PsycInfo (Ovid); c) Embase (Ovid); d) AMED (Ovid); e) Cochrane CENTRAL (Ovid); f) CINAHL (Ebsco); g) Web of Science; and h) Scopus. We combined the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomised Trials (Higgins et al., 2011) and Stefanidis et al. (2018) to design our risk of bias assessment.

Results. Our initial search yielded 45,855 publications. After removing duplicates, we

screened 26,843 publications and retained 418 for full-text screening. In the end, only 13 studies met our inclusion criteria. We found that studies continue to include a disproportionate number of men compared to women, thereby limiting the assessment of relationships between CHD and cognitive status in women compared to men. We also observed inconsistencies with the types of neuropsychological tests used, which made comparisons of cognitive function more difficult. Our work also uncovered that there is variability in the definition of CHD by researchers (i.e., operationalization of the variable), the terminology used, and the control of confounding variables, which could explain the inconsistency across studies.

Discussion. We primarily found that women continue to be poorly represented in CHD research. Although there were limitations imposed by the small number of women and variability in the neuropsychological tests used, we still found evidence to support the heart-brain disease hypothesis in women. We offer several guidelines for future research interested in studying the impact of CHD in women. Notably, we provide suggestions regarding the inclusion of women, a shared terminology to be used, the reporting of results, and several other variables that would support study replicability and understanding of the pathological state, and guidance for intervention.

We declare no conflict of interest. A doctoral scholarship from the FRQNT supported N.F.N.L.'s research. The NSERC - USRA supported M.P.'s research. The European Social Fund under the No 09.3.3-LMT-K-712 "Development of Competences of Scientists, other Researchers and Students through Practical Research Activities" funded J.B.'s research. A discovery grant to H.P. from NSERC (RG203596-13) supported this review. The registration number for our review in PROSPERO is CRD42019129133

Keywords: coronary heart disease, neuropsychological assessment, cognitive function, women, systematic review

Highlights

1. This systematic review reveals that women are still underrepresented in cardiovascular research.
2. This systematic review emphasizes inconsistencies in how researchers operationalize the definition of coronary heart disease, which could explain the varied results in the literature.
3. This systematic review shows the wide range of neuropsychological tests being used to examine the relationship between cognitive function and coronary heart disease, which could also contribute to the varied results in the literature.
4. This systematic review finds evidence that supports the heart-brain disease hypothesis in women.

List of Abbreviations

Angina pectoris	AP
Body mass index	BMI
Cardiovascular disease	CVD
Coronary artery bypass grafting	CABG
Coronary artery disease	CAD
Coronary heart disease	CHD
Ischemic heart disease	IHD
Mini-Mental State Examination	MMSE
Myocardial infarction	MI

3.1.0 Introduction

Cardiovascular disease (CVD) is a group of diseases that affect the heart and blood vessels. In 2016, the World Health Organization estimated that about one-third of worldwide deaths (31%; 17.9 million people) were due to CVD (WHO, 2017b). The latest report from the European Society of Cardiology found that CVD kills about half of women (47%; 2.22 million) and close to two-fifths of men (39%; 4.84 million) each year; among CVD deaths, ischemic heart disease (IHD) kills 38of women% (844,778 people) and 44% of men (864,424 people; Timmis et al., 2020). Coronary heart disease (CHD) is the most prevalent subtype of CVD in Europe and North America (Virani et al., 2020). For the purpose of this systematic review, the term CHD refers to both IHD and coronary artery disease (CAD), as they are both terms used to describe the same medical condition. In addition to being the number one cause of death in the United States of America (USA; Virani et al., 2020), CHD represents an important economic burden with an annual total direct cost of 89 billion dollars as of 2015, and a projected increase to 215 billion dollars by 2035 (American Heart Association, 2017). In the United Kingdom, of the total direct cost of CHD (£1730.07 million), only 7.4% is allocated to rehabilitation and community care (Liu et al., 2002).

Similar to CVD, CHD regroups different diseases that cause a blockage or a narrowing of the coronary arteries and affect the heart. The different types of CHD include myocardial infarction (MI) – the most prevalent type, also commonly known as heart attack, acute MI, stable and unstable angina pectoris (AP), and sudden cardiac death (Wong, 2014). In the USA, one person suffers from a MI every 40 seconds, of which about one in five are silent MI (Virani et al., 2020). In a silent MI, the person is not aware that damage has been done to the myocardium (Thygesen et al., 2018).

3.1.1 Anatomical Impact of Coronary Heart Disease

When a plaque forms inside the coronary arteries, it results in a build-up on the artery walls that can completely or partially block the blood flow of the major arteries of the heart – typically called atherosclerosis (Ambrose & Singh, 2015). This narrowing of the arteries leads to a reduction of oxygen to the heart, but also to the brain, which is dependent on the rich supply of oxygen and nutrients carried in the blood (Willie et al., 2014). Brain cells are known to be extremely sensitive to alterations in oxygen and glucose substrates, and this reduction in blood flow can ultimately cause cell death and affect brain function (Buja, 2005; Carden & Granger, 2000). In the early 80s, researchers realized that diseases impacting peripheral organs, such as heart disease, could also affect the brain; this realization paved the way for interdisciplinary research to investigate those connections (Natelson, 1985). The last decade has supported this contention, providing strong evidence that beyond impacting heart tissue, CHD has significant repercussions on various brain processes (Abete et al., 2014; Qiu & Fratiglioni, 2015; van Buchem et al., 2014). For example, in one of the rare studies that looked at the impact of MI on brain circuitries in animals, Kaplan et al. (2018) found a potential risk of brain damage caused by a MI and consequently, a contribution to cognitive dysfunction.

One of the most vulnerable brain regions is the hippocampus due to the pyramidal neurons which are most sensitive to oxygen deprivation (Cervós-Navarro & Diemer, 1991). Due to inter-connected circuitries between the hippocampus and different brain regions via the mesocorticolimbic pathways, CHD exerts a widespread impact on behavioral function (Barekatain et al., 2014; Natelson, 1985; Roberts et al., 2010; Talman, 1985). Human and animal studies have shown that selective damage to the hippocampus contributes to emotional and cognitive dysfunctions following global ischemia (de la Tremblaye et al., 2016; Milot &

Plamondon, 2009; Petito et al., 1987; Plamondon & Khan, 2005) and MI (Liu et al., 2014; Malick et al., 2018). These studies found structural changes in hippocampal regions to be associated with altered anxiety, mood, and spatial memory function.

To date, scientific knowledge regarding brain changes following CHD in humans remains limited. Studying a large cohort of participants (N=5764), Vidal et al. (2010) reported older individuals (76.4 years [SD = 5.2)] with coronary artery calcification - an atherosclerosis marker- showed reduced cognitive processing speed and executive function, and were more at risk of dementia, regardless of sex [3]. Notably, these functional changes were associated with reduced volumes of gray and white matter and total brain tissue, as well as evidence of past cerebral infarcts, microbleeds, and white matter lesions (Vidal et al., 2010). In a more recent study, participants with CHD compared to a healthy control group showed considerably smaller total brain volume and substantially increased non-ventricular cerebrospinal fluid volume, two variables significantly correlated with lower cognitive functions (Ottens et al., 2017). These findings are concordant with Santiago et al. (2015)'s cross-sectional study of 49 CHD patients showing alterations in cerebral white matter microstructural integrity to be associated with executive function impairment. This distinction is further exemplified in a prospective multisite longitudinal study of 74 cognitively intact participants, where participants had MRIs and neuropsychological assessments performed at two different time intervals over 6.9 years on average; Zheng et al. (2012) found, after controlling for hippocampal and cortical gray matter, an association with lower scores in verbal memory, global cognition, and executive functions. However, a recent large meta-analysis of studies using functional MRI showed first and second scans of a person's brain to be poorly correlated, thus questioning the reliability of such findings

[3] We use the term 'sex' to refer to biological sex at birth. We use the term 'gender' to refer to an individual's socially constructed gender role and gender expression.

(Elliott et al., 2020). Although imaging research has a lot to contribute to the study of CHD effects on the brain and cognitive function, it is at its early stages. The neurocognitive effects of CHD have been largely deduced from studies using neuropsychological assessments, which are more affordable and allow the inclusion of more participants.

3.1.2 Neuropsychological Impact of Coronary Heart Disease

Although the contribution of brain damage to CHD-induced cognitive impairment in survivors is acknowledged, it has not been the focus of CVD literature. For example, while systematic reviews clarified the impact of cardiovascular risk factors (Harrison et al., 2014; Ligthart et al., 2010), of other CVD, such as stroke (for systematic reviews, see Makin et al., 2013; Sexton et al., 2019), and of cardiac surgical interventions, such as coronary artery bypass grafting (CABG; for systematic review, see Greaves et al., 2019) on cognitive decline, few studies examined the relationship between CHD and cognitive function (C. L. Armstrong & Morrow, 2010). This is intriguing considering a strong association reported between CHD and accelerated cognitive decline (Xie et al., 2019) and accentuated risk of cognitive impairment or dementia (for systematic review, see Deckers et al., 2017). The Whitehall II study (Singh-Manoux et al., 2003), one of the most extensive studies on the matter, found significant associations, albeit with small effect sizes, between CHD (AP and MI) and poor cognitive function on all tests of a comprehensive cognitive battery. More specifically, short-term memory, inductive reasoning, and verbal fluency were all significantly impacted in both sexes, which showed CHD's wide-ranging effects on various domains of neuropsychological functioning. Separate analyses of this longitudinal cohort suggested time elapsed since the CHD event to be associated with decreased cognitive function (Singh-Manoux et al., 2008a). Similarly, Weinstein et al. (2015) found the severity of AP correlates with worse performance on memory, executive

function, and attention tests.

It is important to note that the association between CHD and cognitive decline has not always yielded consistent results (Arntzen et al., 2011; Bursi et al., 2006). For example, a systematic review by Deckers et al. (2017) investigating the link between CHD and cognitive function revealed that a third of the included nine studies failed to show a significant association of MI or AP with cognitive decline. These inconsistencies in the literature may be partially explained by variability in the definition of CHD (i.e., operationalization of the variable) from one study to another (Luepker et al., 2003; Roberts et al., 2010), as well as whether researchers controlled for other concomitant diseases and risk factors, like diabetes or hypertension (Beeri et al., 2009). Moreover, cognitive impairment in individuals with CHD has also been associated with a history of CABG, apolipoprotein E4 genotype, low left ventricular ejection fraction, anticholinergic medication use (Burkauskas et al., 2016; Lanctôt et al., 2014), circulating high-sensitivity C-reactive protein, interleukin-6 and brain-derived neurotrophic factor ([BDNF]; Burkauskas et al., 2018), and thyroid function abnormalities (Burkauskas et al., 2020). Consequently, evaluating the cognitive status of people with a CHD condition requires the consideration of several other factors also able to influence cognitive functions.

The spectrum of the assessed cognitive skills also plays a significant role in the depicted impairments. While some studies have linked CHD with the risk of developing dementia (Heath et al., 2015), others have screened for more subtle changes in cognitive function (Singh-Manoux et al., 2008a) or for the increased risk of mild cognitive impairment (Roberts et al., 2010). These subtle changes may be harder to detect due to the insensitivity of some of the more commonly used screening tools (Shankle et al., 2005). It is possible that not all neuropsychological tests are sensitive enough to detect the cognitive changes associated with CVD. In a systematic review of

cognitive impairment post-stroke, Burton and Tyson (2015) found that the Mini-Mental State Examination (MMSE), a screening tool commonly used to assess the severity of cognitive impairment (Folstein et al., 1975), is adequate to detect the presence of dementia in post-stroke patients, but lacks the sensitivity and specificity required to detect milder cognitive impairments in individuals with stroke. Such findings about the MMSE have been previously reported (Jones et al., 2002; Tombaugh & McIntyre, 1992), indicating that while it can be used to screen for dementia, it might lack the sensitivity to detect mild cognitive changes, especially in younger populations. Since the research linking cognitive function and CHD is sparse, there are few systematic reviews on the topic, and it is harder to determine which neuropsychological tests can accurately detect changes in cognitive function in individuals with CHD. To resolve this issue, the National Institute for Neurological Disorders and Stroke (NINDS) and the Canadian Stroke Network created practical guidelines to use a battery of neuropsychological tests that are valid and reliable (Hachinski et al., 2006).

3.1.3 Coronary Heart Disease and Women

For decades, clinicians, researchers, and the general population have entertained the misconception that CVD is a man's disease (Miracle, 2010; Pathak et al., 2017). Since the early 2000s, researchers have been sounding the alarm that CVD in women is underdiagnosed, undertreated, and under-researched (Mikhail, 2005; Wenger, 2012). Nevertheless, in the last two decades the scientific community realized that as the leading cause of death in women, CVD requires attention (Gholizadeh & Davidson, 2008; Mehta, Beckie, et al., 2016; Woodward, 2019). The importance of enrolling women in clinical trials has long been overlooked, which means that the results from clinical trials largely composed of men were often generalized to women (Maas et al., 2011; Melloni et al., 2010; Saeed et al., 2017). For example, (Geller et al.,

2006) found that on average, women represented only 37 % of participants in federally funded clinical trials and that 87 % of studies did not report results by sex or use sex as a covariate. Over a decade later, Gong et al. (2019) found that the enrolment of women in cardiovascular trials increased significantly from 20.7 % in 1986-1990 to 32.6 % in 2011-2015 ($p < 0.001$). However, the percentage of women with CVD in the general population is still significantly higher than the mean percentage of women included in clinical cardiovascular trials ($p < 0.001$). The 2020 report from the American Heart Association found that women accounted for slightly less than half (48.5%) of the total CHD prevalence in the USA (Virani et al., 2020), emphasizing the importance of including more women in CHD clinical trials and shifting away from the mentality that samples predominantly made of men are representative of the CHD population.

Estrogen has long been shown to have cardioprotective effects (Mendelsohn & Karas, 1999), which entertained the myth that women are 'protected' from CHD (Gouva & Tsatsoulis, 2004). Although estrogen does play a role in delaying the onset of CHD in women for 8 -10 years (Lerner & Kannel, 1986; Saeed et al., 2017), the lifetime risk of CHD is not lessened in women (Leening et al., 2014; Woodward, 2019). While men younger than 65 tend to present more CHD than their age-matched female counterparts (Wilkins et al., 2017), when comparisons are age-adjusted to account for the later onset of CHD in women, the rates of CHD are similar for both sexes (McSweeney, Rosenfeld, Abel, Braun, Burke, Daugherty, Fletcher, Gulati, Mehta, Pettey, Reckelhoff, et al., 2016). Although aging increases the risk of CHD in both sexes, the onset of menopause, typically occurring at a mean age of 50 years (Nelson, 2008), represents a factor significantly contributing to increased risk of CHD in aging women (Mehta, Beckie, et al., 2016; Newson, 2018). For example, as early as the 80s, researchers found that women over the age of 55 have a 10-fold increase in the risk of CHD when compared to women aged 35-54,

whereas the increased risk in men of the same age groups is 4.6 (Lerner & Kannel, 1986). Furthermore, the age of onset of menopause has a significant impact on CHD occurrence. A pooled analysis of 15 observational studies found that women with premature menopause (age < 40) and early menopause (ages 40 - 44) all had higher risks of CHD compared to women who experienced menopause between 50 - 51 years (Zhu et al., 2019). These findings highlight that even if the onset of CHD is delayed in women, the threat to their health remains present.

Unfortunately, in addition to the misconception that women are protected from CHD, practitioner bias can lead to underdiagnoses (Maas et al., 2011). Hyun et al. (2017) concluded that women were significantly less likely to have their CVD risk factors recorded than their male counterparts, showing the persistent effects of the perceived low risk of CVD in women. Moreover, women themselves are not fully conscious of the threat CVD poses to their health. For example, in the 2020 report by the American Heart Association, Virani et al. (2020) found that in 1997, slightly less than a third (30.0%) of women were aware that CVD was the leading cause of death for their sex, compared to over half (56.0%) in 2012. Although awareness is rising, it is not substantial. Adding to this, the clinical presentation of some CHD symptoms differs between sexes. Notably, women who suffer from MI tend to experience back, shoulder, or jaw pain, shortness of breath, nausea, vomiting, and anxiety more often than men (Woodward, 2019). Since the diagnostic standards of MI are mainly extrapolated from research on men (Kim et al., 2010), for which the most commonly reported MI symptom is chest pain (G. Arora & Bittner, 2015), women presenting 'atypical' symptoms are more likely to go undiagnosed (Cushman et al., 2021).

Consistent with a predominance of men's assessments in CVD research fields, characterization of the impact of CHD on cognitive function in women has not received close

attention. However, an increased risk of cognitive impairment in women with CHD has been established (Singh-Manoux et al., 2008a). In a study of 7479 postmenopausal women, Haring et al. (2013) found that women with a history of CHD tended to be at increased risk of cognitive decline, with previous MI being associated with the highest risk. In studies that included both men and women, the risk of cognitive decline in patients with CHD compared to normal controls increased for both sexes (Breteler et al., 1994; Roberts et al., 2010). Although it is clear that CHD affects a great number of women and kills many more, our knowledge of this population is limited. For example, based on data from the Centre of Disease and Control in 2011, a popular infographic article from Vox (Belluz, 2014) showed a significant discrepancy between the total donations raised and the number of people dying from a specific disease condition. Notably, while heart disease accounted for the most deaths, the money raised by fundraising campaigns only reached 54.1 million dollars, compared to 257.8 million dollars raised for breast cancer research, despite a fourth position amongst the most common cause of death in women.

3.1.4 Goals of This Review

The literature surrounding the cognitive changes in individuals with CHD is sparse and changes specific to women have not received sufficient attention. For this reason, we conducted a systematic review of the neuropsychological impact of CHD exclusively in women to highlight the cognitive impact of CHD in this population. In addition, we hope to identify which neuropsychological tests could show increased efficacy in identifying and detecting altered cognitive functions. This could allow clinicians and researchers in this area to routinely implement these tests in their assessment battery. This will help support the implementation of clinical guidelines for neuropsychologists and encourage a more systematic approach to neuropsychological testing in women to provide them improved support and accommodations.

3.2.0 Method

3.2.1 Protocol and Registration

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Moher et al., 2015) to complete this research. Before we began the review, we registered our protocol in accordance with PRISMA-Protocol with the international prospective register of systematic reviews (PROSPERO; CRD42019129133). The registration of the protocol was completed in June 2019, most recently updated in July 2020. We performed two updates to correct spelling errors, to clarify the wording and to update the status of the systematic review. In the last update, we specified the type of risk of bias assessment.

3.2.2 Information Sources and Search Strategy

This review focuses on any studies that investigated the neuropsychological impact of CHD in women, even if the primary goal of the study was not on CHD (e.g., CHD group was a control group). P.R.L., a social sciences research librarian with expertise in knowledge syntheses, developed the search strategy and identified relevant databases. He developed, drafted, and implemented a search strategy to retrieve pertinent studies from the following databases: a) MEDLINE (Ovid); b) APA PsycInfo (Ovid); c) Embase (Ovid); d) AMED (Ovid); e) Cochrane CENTRAL (Ovid); f) CINAHL (Ebsco); g) Web of Science; and h) Scopus.
We designed the strategy itself, in part, by examining previously published reviews on CHD (L. Anderson et al., 2016; Bradt et al., 2013; Kwong et al., 2015; Richards et al., 2017) as well as reviews on cognition (Kennedy et al., 2013; Ooi et al., 2011; Treanor et al., 2016). Although sex- and gender- specific search filters and database limiting options exist, variability in their applications significantly limit their usability (Lorenzetti & Lin, 2017). Therefore, the concept of women was not included in the search strategy but instead used as an inclusion criterion. The

final strategy used relevant keywords as well as database-specific controlled vocabulary relating to the concepts of neuropsychological assessment and CHD. The complete search strategy is available in Appendix A. We conducted the initial search on August 15, 2018 (T_1) and collected all publications until that date. We conducted a second search on July 23, 2020 (T_2) to update results until that date. We added the new articles to the existing database, therefore there was no overlap between the pre-existing database and the newly added articles. At any stage of the review, if the information for a publication was not available, N.F.N.L. sought to find it online using journal websites, Google Scholar, PubMed, and other databases. Given the number of publications included in the title and abstract phase, if N.F.N.L. was unsuccessful, the publication was categorized as not found and excluded. During the full-text screening phase, N.F.N.L. contacted the corresponding authors by email or through ResearchGate. Articles that received no response from the authors were categorized as not found and excluded. During the data extraction phase, M.P. contacted the corresponding authors by email to obtain supplementary data.

3.2.3 Eligibility Criteria

3.2.3.1 Exclusion Criteria Part 1

We excluded publications during the title and abstract, and full-text screening phases if one of the following characteristics applied: a) included participants 17 years old or younger, mixed sample of children and adults, or longitudinal studies with participants under the age of 17; b) studies that only included men in their sample; c) any other CVD that was not part of our definition of CHD and its subtypes (see section 1.0 for our definition); d) medical conditions unrelated to the scope of our review; e) absence of a cognitive assessment (i.e. neuropsychological, psychological, psychiatric, cognitive, psychoeducational assessment); f)

publications that were presented as a conference publication (information is brief and not detailed); g) graduate thesis (not peer-reviewed) or book chapters; h) not published in English; and i) irrelevant study or publication type (i.e. animal research, systematic reviews and/or meta-analysis, erratum articles, program evaluations, case studies).

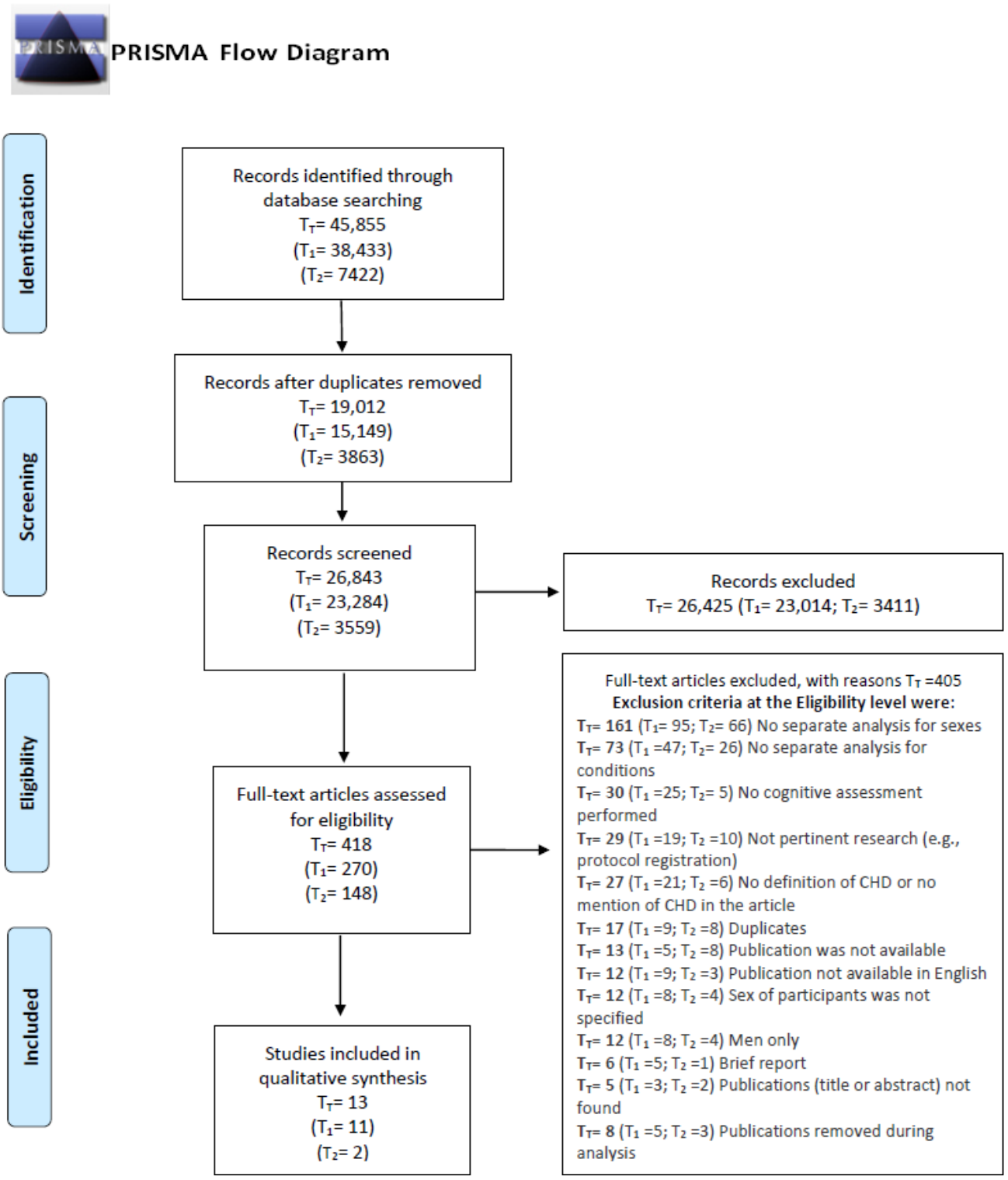
3.2.3.2 Exclusion Criteria Part 2

The full-text screening phase consisted of separate review stages to remain as conservative as possible. First, we excluded articles if one of the following characteristics applied: a) no mention of any CHD in the methods or results sections or no definition of CHD; b) absence of cognitive assessment; c) not published in English; d) sample exclusively made up of men; e) duplicate article; f) article not available; g) not pertinent to this systematic review (e.g., congestive heart disease, clinical trial registrations); h) no mention of the sex of participants; and i) brief reports (too short to extract any information). We reviewed all articles that remained a second time and we excluded some more based on the following criteria: a) no separate analysis by sex; and b) no separate analysis by condition (e.g., participants with CHD were included in the study but were combined with other irrelevant conditions, such as heart failure or CABG, for statistical analyses). The first authors performed a final and third review on the remaining articles to ensure accuracy of full-text screening (see Figure 1). In some cases, publications met more than one exclusion criteria, therefore, N.F.N.L. and M.P. chose the most appropriate category in case of conflict. See Appendix B for the reason for exclusion during full-text screening for each publication.

3.2.3.3 Inclusion Criteria

Throughout both screening phases, we included publications if the following characteristics applied: a) included participants older than 18 years old; b) included women in

Figure 2 *(Figure 1 for Chapter III)* PRISMA Flow Diagram of studies included in the systematic review (Moher et la., 2015). Please note that T1 and T2 refer to the dates of the literature searchers (see Section 2.2)



their sample; c) performed a neuropsychological assessment (including variations [e.g., cognitive assessment]); and d) studied CHD (including variations [e.g., IHD]) or subtypes of CHD (e.g., MI).

3.2.4 Study Records

3.2.4.1 Data Management

We used Covidence (Veritas Health Innovation) to import references from database searches, screen titles and abstracts, evaluate the full-text and perform the risk of bias assessment. We used Microsoft Excel for data extraction.

3.2.4.2 Selection Process

Graduate and undergraduate students trained in using Covidence and correctly applying the exclusion criteria performed the screening of references. During the title and abstract phase, two independent reviewers screened each reference for their relevance. N.F.N.L. reviewed references in cases of uncertainty as well as publications with a brief or vague summary. During the full-text phase, two independent reviewers screened the remaining articles according to the study eligibility criteria (see Section 2.3.3). In cases of conflict between two reviewers, co-first authors reviewed the articles with the original reviewer. Finally, we performed the data extraction phase slightly differently with the intention of avoiding any bias or missing information. The database was separated between the co-first authors who extracted and completed the risk of bias assessment. Then, an independent reviewer verified the extraction and completed the second risk of bias assessment. The co-first authors and the independent reviewer completed the consensus for the risk of bias assessment together. Finally, N.F.N.L. reviewed the split database of M.P. and vice-versa. We proceeded in this way to avoid missing information.

3.2.4.3 Data Collection Process

Co-first authors piloted the data extraction and risk of bias assessment. Following minor adjustments for the data extraction and risk bias assessment documents, senior author H.P. approved the protocol for this phase. Co-first authors trained all independent reviewers to perform data extraction and risk of bias assessment.

3.2.5 Data Items

We extracted the following information from publications that we retained: a) title of article, authors' name, and year of publication; b) how participants were recruited (e.g., cohort sample); c) number of participants for each sex (men, women, or the combination of both) and what terminology was used to describe the sample (i.e., sex, gender, or both), mean age and standard deviation for each sex, menstrual cycle stage for women if provided and any exclusion or inclusion criteria related to menstrual cycle; d) how authors operationalized the definition of CHD and its subtypes, and time between the diagnosis and the neuropsychological assessment; e) exclusion criteria; f) types of cognitive tests and self-report measures of mood and/or anxiety used and associated administration time; g) type of statistical analyses; and h) the results from the cognitive assessment and any other relevant information that was related to CHD and women (e.g., how anxiety results can explain differences between men and women). We contacted corresponding authors to obtain more information about the results of their experiment in relation to the cognitive outcome of CHD in women. If corresponding authors did not answer, we contacted first authors.

3.2.6 Risk of Bias in Individual Studies

We created our version of the risk of bias assessment by combining elements of the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomised Trials (Higgins et al.,

2011) and a tool developed for a systematic and meta-analytic review about the cognitive impact of CVD in a sample of stroke-free survivors (Stefanidis et al., 2018). The definition of our domains and the outcome of the risk bias assessment can be found in Appendix C. We categorized the included studies as 'Low Risk', 'Unclear Risk, and 'High Risk'. We assessed eight domains at the study level: a) ascertainment of CHD and absence of any other type of CVD condition; b) ascertainment of cognitive impairment; c) blinding of personnel; d) blinding of outcome assessment; e) incomplete outcome data; f) selective reporting; g) potential confounds; and h) other sources of bias. The information from this assessment is not used in data synthesis. See Figure 2 for the consensus outcome.

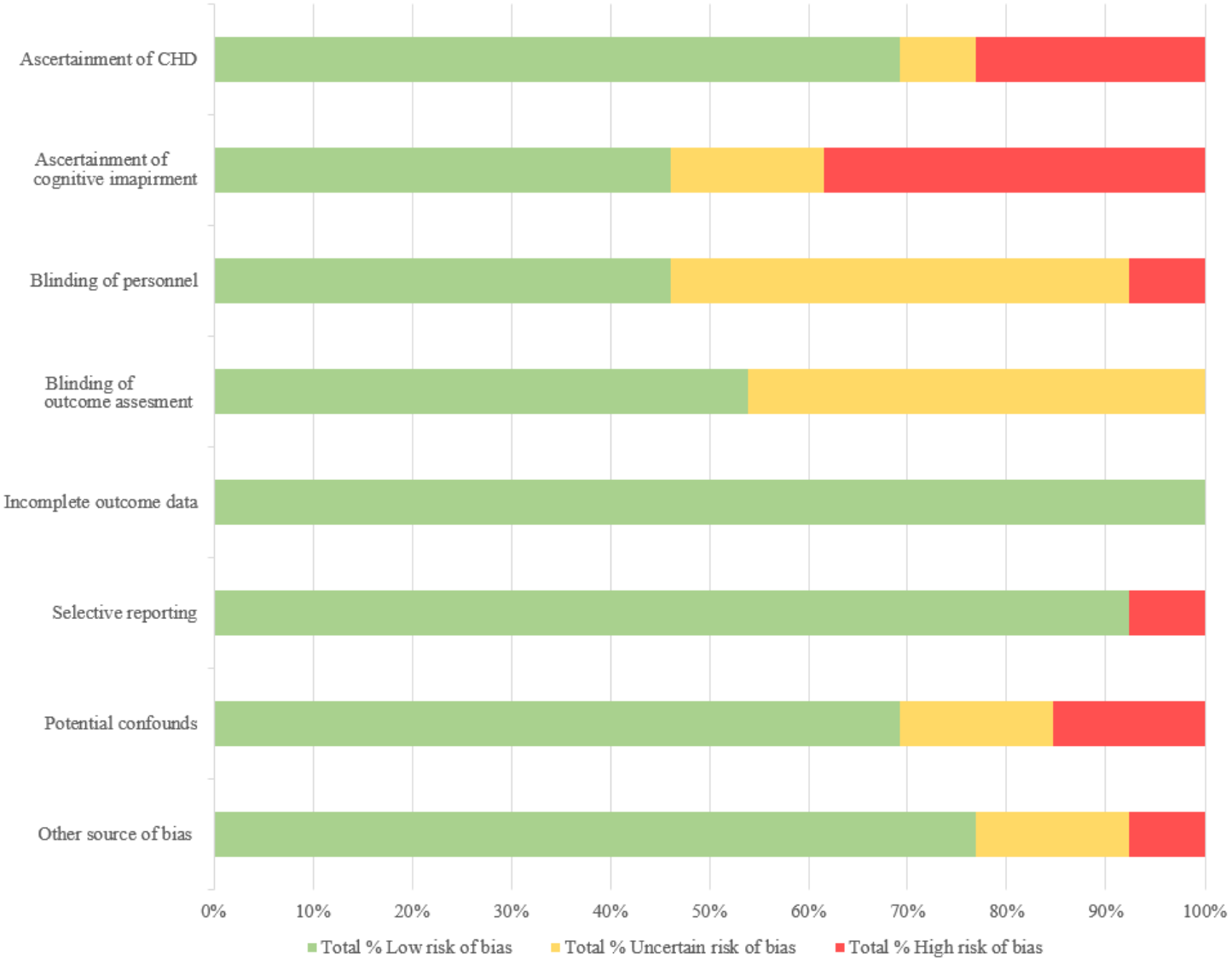
3.2.7 Data synthesis

Our results are described and summarised using descriptive statistics. More specifically, for all findings, we reported proportions, average $(\overline{x})$ and standard deviation (SD). For the exclusion criteria, the median and inter-quartile range (IQR) are reported while findings from the neuropsychological tests are presented in a table.

3.3.0 Results

From the database search, we identified a total of T_T = 45,855 publications of which T_T = 19,012 were duplicates, which left us with a final database of T_T = 26,843 publications. During the title and abstract screening, we identified T_T = 26,425 publications as not relevant. We then screened a total of T_T = 418 publications at the full-text screening phase. We kept T_T = 21 studies for data extraction. During extraction, we excluded an additional eight studies. These eight studies were excluded specifically because the number of participants reported was not consistent (e.g., text *vs.* tables) in three studies, the group of women was made of three

Figure 3 *(Figure 2 for Chapter III) Risk of Bias Assessment at the study level*



participants in one study, the same database was used in one study but the analysis was not as extensive, and we could not extract the information from the tables or the text for three studies because the information was amalgamated together. As a result, we included $T_T = 13$ articles in this systematic review. Articles included in this review are identified by an * in the reference list. See Appendix D for the full characteristics of the studies included.

3.3.1 Characteristics of the Sample

Of the 13 studies we kept for analysis, five compared participants with a type of CHD to a healthy control group, two studies had CHD participants only, three studies compared another type of CVD to a MI group (as a control group), and three studies did not study CHD as their primary objective. With the exception of Xie et al. (2019), none of the studies reported calculating the effect size required for their studies. Eight studies used a cohort sample while five recruited participants. The characteristics of the studies and samples can be found in Table 1.

3.3.1.1 Women Participants

Of the 418 articles we included during the full-text screening phase (Section 2.3.2), we excluded 185 articles because they did not specify the sex of their participants (T_T=12), the sample consisted only of men (T_T=12) or they did not separate analyses for men and women (T_T=161); this represents slightly more than two-fifths (46.60%) of the full-text screening phase sample. The thirteen studies included varied in the percentages of sampled women, and apart from one study exclusively including women (Haring et al., 2013), men largely outnumbered women in CHD groups. Specifically, the CHD groups (or its variants [e.g., MI]) had one study with less than 20 % of women, five between 20 to 25 %, three between 26 to 30 %, two between 31 and 36 %, and one study with an almost equal distribution of sexes. Of the 12 studies that had

both men and women participants, six consistently used the term 'sex', two consistently used the term 'gender', and four studies used both terms interchangeably.

3.3.1.2 Hormonal Status

As reported in Section 1.3, the average age of women at menopause is 50 years old. Therefore, we were interested to know if studies controlled for menstrual cycles, as it is known to affect cognitive abilities (Le et al., 2020; Sundström Poromaa & Gingnell, 2014).

Overall, twelve studies did not control for menstrual cycle and eleven of those studies had an age range or mean age of participants that overlapped with the mean age of menopause, suggesting that samples contained pre- and post- menopausal women, as well as perimenopausal women. One study did not control for the menstrual cycle but had a minimum age of 70 years old, making it likely that all women were postmenopausal, and one study controlled for the menstrual cycle by including only postmenopausal women.

3.3.1.3. Coronary Heart Disease Diagnosis and Definition

Of the thirteen studies included, three studies used self-administered questionnaires or interviews to determine CHD history, six studies used medical records, three performed a medical assessment to confirm the diagnosis, and one study did not clearly report how they determined CHD history. We were also interested to know how researchers defined the conditions in their respective samples. Four studies defined CHD as a previous MI and/or prevalent AP while three studies did not provide a definition for CHD. As for AP, six studies did not define it, and two studies used medical records, physiological tools (e.g., electrocardiogram), and self-reports from participants. Regarding MI, eight studies did not provide a definition, and five studies used medical records or physiological measures.

Table 4 *(Table 1 for Chapter III)* Study characteristics

Study	Groups for Comparison	N of the sample (% of women)	CHD type 1	n of CHD group 1 (% of women)	CHD type 2	n of CHD group 2 (% of women)
(Arntzen et al., 2011)	Population based study of cardiovascular risk factors	5033 (55.75)	CHD	102 (28.43)	-	-
(Burkauskas, et al., 2016)	CHD only	510 (28.63)	MI	358 (25.70)	Unstable AP[1]	152 (35.53)
(Burkauskas et al., 2017)	CHD only	827 (25.63)	MI	558 (22.94)	Unstable AP[1]	269 (31.23)
(Dijkstra et al., 2002)	Depressed MI *vs* Non-depressed MI *vs* healthy control	144 (27.08)	MI	96 (27.08)	-	-
(Evans et al., 1964)	Cerebral thrombosis *vs* MI	275 (27.27)	MI	136 (20.59)	-	-
(Haring et al., 2013)	CVD *vs* no CVD	6455 (100)	MI	209 (100)	AP	465 (100)
(Jaszke-Psonka et al., 2016)	Sudden cardiac arrest *vs* MI *vs* healthy control	91 (29.67)	MI	31 (35.48)	-	-
(Lipnicki et al., 2013)	Community based study of cognitive decline	889 (54.11)	CHD	166 (33.73)	-	-
(Morsund et al., 2019)	Non-ST Segment Elevation MI (NSTEMI) *vs* Ischemic stroke	468 (32.26)	NSTEMI	144 (28.51)	-	-
(Singh-Manoux, et al., 2008a)	CHD *vs* no CHD	5837 (28.39)	MI	228 (28.51)	AP[1]	392 (24.23)
(Singh-Manoux, et al., 2008b)	Population based study of socioeconomic gradient in health	3896 (27.93)	CHD	335 (24.18)	-	-
(Stetkiewicz-Lewandowicz et al., 2015)	CHD *vs* healthy controls	161 (19.88)	CHD	111 (19.82)	-	-
(Xie et al., 2019)	England Longitudinal Study of Ageing (ELSA)	7888 (58.65)	CHD	480 (50.42)	-	-

Note. [1] Authors combined CHD type 2 with CHD type 1 for statistical analyses

3.3.1.4 Time Between CHD Diagnosis and Neuropsychological Assessment

Nine studies did not report the mean time between CHD diagnosis and neuropsychological assessment. One study completed the assessment 3 months after the acute phase of the illness, one completed the assessment between one and 6 months after diagnosis and one completed the assessment 12 months after diagnosis. One study stratified results by time since occurrence, grouping events as having occurred less than 5, 5-10 or more than 10 years prior to evaluation.

3.3.2 Exclusion Criteria

We listed the number of exclusion criteria for each article and found thirteen exclusion criteria used by at least two articles and up to nine specific exclusion criteria per article. The median number of exclusion criteria was 4.0 for the IQR, Q1 and Q3 were 3.5 and 9.0, respectively. Eight studies, respectively, controlled for a minimum and/or maximum age, and for other types of CVD possibly present in participants (e.g., stroke). Five studies, respectively, excluded participants if they had a psychiatric/mental illness, and had dementia or Alzheimer's disease. Four studies excluded participants if they could not communicate in the language of the study, three studies if they had impaired motor functions, and finally, two studies, respectively, excluded participants if they had a communicative disability, impaired eyesight or hearing, an MMSE below a certain cut-off, a substance use disorder, or had undergone a specific surgical procedure.

3.3.3 Study Demographics

We extracted information concerning analysis of the following demographic variables depending on the participants' sex and conditions: a) age; b) body mass index (BMI); c) cholesterol; d) diabetes; e) education level; f) ethnicity; g) hypertension; h) marital status; i)

smoking; and j) social status. The number of demographic variables considered by the studies ranged from two to eight. All studies analysed age and education levels, while eight considered diabetes and hypertension, seven measured BMI and smoking, five considered cholesterol and marital status, two collected ethnicity data, and one study included social status.

3.3.3.1. Demographic Differences Between Sexes

For the twelve studies that had participants of both sexes, we noted if the authors reported differences between men and women for each demographic variable measured. As shown in Table 2, differences between the sexes were not consistently reported for any of the demographic variables. Oftentimes, variables were measured but comparisons between sexes were not made.

3.3.3.2. Demographic Differences Between Conditions

Similarly, we noted if the authors reported a difference in the occurrence of these demographic variables between participants with CHD and other study participants. Two studies exclusively enrolled CHD patients and consequently are not discussed in this section. Three studies were conducted using a sample recruited from the general population, not having CHD as a primary focus. Therefore, these studies did not present comparisons between participants with CHD and other participants, except for Singh-Manoux et al. (2008b), whose study found that women with a lower socioeconomic status had a significantly higher CHD prevalence.

Of the five studies that compared CHD participants to healthy controls, three found their CHD group to be significantly older than the healthy controls (Haring et al., 2013; Singh-Manoux et al., 2008a; Xie et al., 2019), Dijkstra et al. (2002) found no difference, and Stetkiewicz-Lewandowicz et al. (2015) did not provide that information. Education level was significantly lower for the CHD group in three studies (Haring et al., 2013; Singh-Manoux et al., 2008a; Xie et al., 2019), whereas Dijkstra et al. (2002) found no difference, and Stetkiewicz-Lewandowicz

et al. (2015) did not include that information. Two studies (Haring et al., 2013; Xie et al., 2019) found significantly higher BMI and an increased prevalence of diabetes, hypertension, and smoking in CHD participants compared to healthy controls. For marital status, neither Singh-Manoux et al. (2008a) or Xie et al. (2019) presented comparisons between conditions. With respect to cholesterol and ethnicity, Haring et al. (2013) found a significant difference in cholesterol levels, with more frequent treatment for hypercholesterolemia in CHD participants, but found no differences for ethnicity.

Regarding the three studies that compared MI to another CVD, two found a significant difference related to age (Evans & Marmorston, 1964; Morsund et al., 2019). For the rest of the variables – considering there is much variability – please consult Appendix D.

3.3.4 Neuropsychological Impact

Overall, we did not find consistency in the use of neuropsychological and psychological tests among the thirteen studies. More specifically, 30 different tests were used and more than half (n=18; 60.0%) were used exclusively in one study (see Table 3 for more details). Likewise, we did not find consistency among the studies in the use of psychological questionnaires to measure mood and anxiety levels in participants. Finally, we were interested to know if studies used similar statistics to analyze their findings. While we found some similarities, many different types of statistics were used. We encourage readers to review Appendix D for the details of the neuropsychological assessments performed in each study.

Table 5 *(Table 2 for Chapter III)* Differences found between sexes for the demographic variables

Study	Number of variables measured	Age	BMI	Cholesterol	Diabetes	Education level	Ethnicity	Hypertension	Marital status	Smoking	Social status
(Arntzen et al., 2011)	7	No	Yes	Yes	No	Yes	-	Yes	-	No	-
(Burkauskas, Brozaitiene, et al., 2016)	5	Yes	-	-	No	No	-	No	Yes	-	-
(Burkauskas et al., 2017)	6	Yes	No	-	No	No	-	No	-	Yes	-
(Dijkstra et al., 2002)	2	N/V	-	-	-	No	-	-	-	-	-
(Evans et al., 1964)	3	N/V	-	-	-	N/V	N/V	-	-	-	-
(Haring et al., 2013)	8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	-	N/A	-
(Jaszke-Psonka et al., 2016)	5	N/V	-	-	N/V	N/V	-	N/V	N/V	-	-
(Lipnicki et al., 2013)	8	No	Yes	Yes	Yes	Yes	-	Yes	Yes	Yes	-
(Morsund et al., 2019)	7	N/V	Yes	No	No	N/V	-	Yes	-	No	-
(Singh-Manoux, et al., 2008a)	3	N/V	-	-	-	N/V	-	-	N/V	-	-
(Singh-Manoux, et al., 2008b)	6	N/V	N/V	N/V	-	N/V	-	-	-	N/V	Yes
(Stetkiewicz-Lewandowicz et al., 2015)	2	N/V	-	-	-	N/V	-	-	-	-	-
(Xie et al., 2019)	7	N/V	N/V	-	N/V	N/V	-	N/V	N/V	N/V	-

Note. N/V = Differences between sexes were not available. N/A = Not applicable, study exclusively enrolled women.

3.3.4.1 Findings Based on Tests

We have divided the findings from studies by cognitive themes (e.g., language, executive functions). As a reminder, we extracted the findings for women, consequently, we are only presenting the results for this group, unless otherwise specified. See table 4 for summary of study results

We were also interested to know if other variables could potentially influence cognitive results. Please note that we are reporting tendencies that were either significant or not and only if the information was clearly stated. Overall, we found that: a) anxiety was associated with lower cognitive performance (Burkauskas, et al., 2016); b) cholesterol was not associated with cognitive performance (Arntzen et al., 2011); c) diabetes was associated with a lower cognitive performance (Arntzen et al., 2011; Haring et al., 2013); d) hypertension was associated with a lower cognitive performance in some studies (Arntzen et al., 2011; Haring et al., 2013) while Burkauskas et al. (2016) did not find an association; e) mental fatigue was associated with lower cognitive performance (Burkauskas et al., 2017); f) mood was either associated with a lower cognitive performance (Arntzen et al., 2011; Burkauskas, et al., 2016) or had mix findings (Dijkstra et al., 2002); g) physical activity was associated with a better cognitive performance (Arntzen et al., 2011); h) smoking showed an inverse association with cognitive performance (Arntzen et al., 2011); and i) systolic blood pressure showed an inverse association with cognitive performance (Arntzen et al., 2011).

Table 6 *(Table 3 for Chapter III)* Neuropsychological tests used across studies

Tests	Number of times used
Alice Heim 4 - part I (AH4-I)	2
Benton Visual Retention Test (BVRT)	2
Boston Naming Test (BNT)	1
Clock Drawing Test	1
Concept Shifting Test (CST)	1
Consortium to Establish a Registry for Alzheimer's Disease (CERAD)	2
Controlled Oral Word Association Test (COWA)	1
Delis–Kaplan Executive Function System (D-KEFS) - Color-Word interference test	1
Delis–Kaplan Executive Function System (D-KEFS) -Verbal Fluency Test	1
Lauretta Bender's Visual-Motor Gestalt Test	1
Letter-Digit Substitution Test (LDST)	1
Mill Hill Vocabulary test	2
MMSE	6
Rey Auditory Verbal Learning Test (RAVLT)	1
Rorschach	1
Stroop Color-Word Test (SCWT)	1
Tapping test	1
Temporal orientation (Origin not specified; assessed using four questions)	1
Trail-Making Test (TMT) - part A	4
Trail-Making Test (TMT) - part B	3
Twelve Word Memory Test	1
Verbal Fluency - phonemic ("S")	2
Verbal Fluency- Semantic (animals)	3
Visual Verbal Learning Test (VVLT)	1
WAIS (Digit Span; DS)	3
WAIS (Digit-Symbol coding; DSC)	4
WCST (Computer version)	1
WMS (Logical Memory Story A)	1
10-word free recall test (Origin not specified)	1
20-word free recall test (Origin not specified)	2

3.4.0 Discussion

Our systematic review aimed to assess the neuropsychological impact of CHD in women exclusively, in addition to identifying the most recurrent neuropsychological tests that would allow the assessment of cognitive deficits in women with CHD. Unfortunately, despite having retrieved more than 26,000 publications through a sensitive search conducted in eight databases, we were not able to identify a large group of publications studying the impact of CHD in women. As stated in the methodology and results sections, we excluded a significant number of articles primarily because authors provided a broader definition of CHD that encapsulated a wide array of diseases, but they did not separate the larger group of diseases into smaller subsections for analysis. This made it impossible for us to extract the impact of CHD itself. Moreover, several publications did not provide enough details for us to be able to separate their analysis in two groups – men and women – which made it impossible to analyze the impact of their findings in women. Additionally, several articles reported that they had a sample representative of the population or that they did not find differences between sexes during analyses. However, when we looked at the number of participants of each sex in their groups, they had samples with less than 20% of women, and did not calculate the power and precision relative to their sample size. We did not find a specific set of neuropsychological tests used to assess cognitive deficits in CHD in women. We found studies reporting significant results while others did not find any differences. The inconsistency in tests used by researchers could explain the contradictory results in the literature. More specifically, not all neuropsychological tests have strong validity and reliability, in such that when 13 articles use 30 different tests, it is unsurprising that there is important variability in the findings. Nonetheless, despite the wide range of results reported for the different cognitive areas assessed, overall, researchers are finding that CHD impacts

cognitive function in women. In general, researchers found that participants: a) had difficulties with word retrieval; b) needed more time to complete visuospatial/motor tests; c) struggled to recall previously learned verbal material; and d) had difficulties with reasoning and problem-solving. In addition, we noticed that studies with a higher percentage of women in their CHD, MI, and AP groups tended to have more significant results or trends, compared to studies with smaller samples of women. This could be due to the increased statistical power of the sample size.

In the next sections, we provide a series of guidelines based on the literature and this systematic review to increase the accuracy in reporting results, as well as to provide parameters for future research on the interaction between heart disease and cognitive deficits in women.

3.4.1 Characteristics of the Sample

Guideline 1. As stated by Sullivan & Feinn (2012), it is crucial that researchers calculate and report effect and sample size to plan, analyze, report, and report valuable statistical analyses. As we demonstrated in our systematic review, none of the studies provided this type of information except for one. Therefore, we encourage researchers to calculate and report the power, precision, and size of their sample, so that differences between sexes can be confidently stated. For example, G*Power is a free software that allows researchers to calculate a priori and post recruitment the power, precision, and size of their sample (Faul et al., 2007, 2009). Other statistical packages, such as the Statistical Package for the Social Sciences (SPSS) or SYSTAT, can also be used to calculate the power of a sample. The absence of such statistics in a study can compromise the validity of stating that there were no differences between sexes, especially when the sample of women was considerably smaller than that of men.

Table 7 *(Table 4 for Chapter III*) Study findings

Cognitive area	*Test*	*Study*	*Findings*
General functioning	MMSE	Singh-Manoux et al. (2008a)	Women with CHD had overall lower scores compared to women without CHD.
		Burkauskas, et al. (2016)	Did not find an association.
		Burkauskas et al. (2017)	Did not compare results on this test between sexes.
		Jaszke-Psonka et al. (2016)	Cognitive impairment was more frequent in their study group (sudden cardiac arrest) than in their control group (MI).
Language	Mill Hill Vocabulary Test (MHVT)	Singh-Manoux et al. (2008a)	Women with CHD had lower scores compared to women without CHD.
	Verbal Fluency – Phonemic ('S') & Semantic (animals)		

MHVT Verbal Fluency – Phonemic ('S') & Semantic (animals)	Singh-Manoux et al., (2008b)	Respectively 11.1, 5.8, and 1.0 % of the scores obtained on the Verbal Fluency – Phonemic ('S') & Semantic (animals) subscales could be explained by changes of the intima-media thickness in women with CHD.
Delis-Kaplan Executive Function System (D-KEFS) - Verbal Fluency Test	Morsund et al. (2019)	Did not find a difference between sexes or between their study group (stroke) and their control group (MI).
D-KEFS – Color Word Interference Test		MI participants had a score lower than the normative data in two subtests (color naming and inhibition/switching). However, no significant sex differences were observed.
Verbal Fluency Test – Semantic (animals)	Xie et al. (2019)	Participants with CHD showed an accelerated decline throughout the years. Although no

			significance difference between sexes were noted, researchers observed a faster decline post-CHD diagnosis compared to pre-CHD diagnosis.
Visuo-spatial & Visual-motor	Trail Making Test (TMT) – part A.	Burkauskas, et al. (2016)	Found differences between sexes in the time taken to complete the TMT- part A.
	TMT – part A	Burkauskas et al. (2017)	Found differences between sexes in the time taken to complete the TMT- part A.
	TMT – part B		Did not find a significant difference between sexes.
	TMT – part A & B	Morsund et al. (2019)	Did not find a difference between sexes or between their study group (stroke) and their control group (MI).

Clock Drawing Test		Did not find a difference between groups (score of 5 in both).
Cognitive Shifting Test (CST) – motor speed part (CST-0)	Dijkstra et al. (2002)	No difference between the MI and control groups were found although performance of MI participants diagnosed with depression was slower compared to the control group.
Bender Visual-Motor Gestalt Test version D	Jaszke-Psonka et al. (2016)	Reported more frequent cognitive problems specific to that scale in the sudden cardiac arrest and MI groups compared to a healthy control group.
Wechsler Adult Memory Scale (WAIS) – Digit-Symbol Coding (DSC)		No sex differences noted.

	WAIS – DSC	Burkauskas, et al. (2016)	No sex differences noted.
	WAIS – DSC	Burkauskas et al. (2017)	No sex differences noted.
Attention & Auditory Working Memory	WAIS – Digit Span (DS)	Burkauskas, et al. (2016)	No differences noted.
	WAIS – DS	Burkauskas et al. (2017)	No differences noted.
	WAIS – DS	Jaszke-Psonka et al. (2016)	No differences noted.
Learning & Memory	Visual Verbal Learning Test (VVLT)	Dijkstra et al. (2002)	Compared to a healthy control group, the MI group had a better performance on the total number of correct possible answers (VVLT-TOT). On the delayed recall (VVLTT-DelRec), no difference was noted between the MI and control groups. Surprisingly, participants in the MI group with a diagnosis of depression showed improved performance compared to non depressed MI

		participants.
Wechsler Memory Scale (WMS) – Logical memory story A Rey Auditory Verbal Learning Test (RAVLT)	Lipnicki et al. (2013)	CAD Participants showed more severe memory decline.
Twelve Word Memory Test	Arntzen et al. (2011)	No changes reported in CHD participants.
10-word immediate and delayed recall	Xie et al. (2019)	CHD participants showed accelerated decline in verbal memory throughout the years. Although no sex difference was noted, researchers observed a faster decline post-CHD diagnosis compared to pre-CHD diagnosis.

Perception	Rorschach Test	Evans et al., (1964)	Authors noted different answers on 14 different signs between men and women, although no sex differences in total scores were apparent. Older MI participants showed higher impairment scores compared to younger ones.
Executive Functions	Wisconsin Sorting Card Test (WSCT) – computerized version	(Stetkiewicz-Lewandowicz et al., 2015)	CHD participants obtained lower scores compared to the control group in every WSCT scales analyzed.
	Alice Heim 4 – part I (AH4-I)	Singh-Manoux et al. (2008a)	Women with CHD obtained lower scores on the reasoning scale compared to the control group.
	AH4-I	Singh-Manoux et al., (2008b)	6.3 % of the association between intima-media thickness and the AH4-I could be explained by a

			history of CHD.
	Stroop Color-Word Test	Dijkstra et al. (2002)	No differences observed between the MI and control groups.
Battery of Tests	Consortium to Establish a Registry for Alzheimer's Disease (CERAD)	Haring et al., (2013)	History of MI and AP had a strong association with cognitive decline. Notably, participants with a history of MI had double the risk of cognitive decline if participants were postmenopausal.

3.4.1.1 Women Participants and Hormonal Status

Guideline 2. The terminology selected in regard to 'sex' or 'gender' should be maintained throughout the article. Sex, which refers to the biological attributes of an individual, is mainly associated with physical and physiological features whereas gender refers to socially constructed roles, behaviors, expectations, expressions, and identities (Canadian Institutes of Health Research, 2014). Biologically, men and women differ in many aspects, such as diameter of the arteries (Krejza et al., 2006), morphology of the brain, and cellular function (Ventura-Clapier et al., 2017), all of which have an effect on the impact of CHD. However, gender has also been found to influence how CVD progresses, notably in a study by Pelletier et al. (2016) who found that young adults with female gender, independent of female sex, were at increased risk of having recurrent acute coronary syndrome within 12 months. Both sex and gender have unique influences on cardiovascular disease making it essential to use correct and consistent terminology so that findings can be appropriately interpreted and compared. Therefore, it appears crucial that researchers clearly specify in their methodology if they are studying the biology, the social construct, or both in their sample.

Guideline 3. According to a recent census, women account for 48.4 % of the total CHD prevalence in the USA (Virani, et al., 2020) but none of the reviewed studies that included both sexes reached this proportion in terms of women's inclusion, except one. Therefore, we recommend that the number of women included in CHD trials be representative of the distribution of CHD in the general population. While recruiting women for cardiovascular trials is more difficult (Ghare et al., 2019), the underrepresentation of women in CHD research is striking and there needs to be a continued effort for their inclusion in such trials. For example, multicenter research trials could allow researchers to achieve greater representation, not only in

the inclusion of more women but also in the inclusion of more diverse populations, by enrolling participants from different parts of the city or the country. If this is not possible, researchers should, as suggested in Guideline 1, calculate the power, precision, and size, and provide details about the specific type of statistics used. This will, in turn, still allow them to share meaningful results even if their sample includes a lower percentage of the larger population. Moreover, researchers have a responsibility to collect data from a diverse group of participants to provide a representative sample of the general population and not only majority White, considering that in general CVD are more fatal with People of Color (Virani et al., 2020).

Guideline 4. We recommend that researchers report and control for the menstrual cycle or menopausal state when performing neuropsychological assessments, as menstrual cycle and menopause have been found to influence the cognitive performance of women. In premenopausal women, the hormonal variations between the luteal and follicular phases have a significant impact on cognitive function, such as better performance on sustained attention tasks during the luteal phase (Pletzer et al., 2017; Solís-Ortiz & Corsi-Cabrera, 2008). There is also evidence indicating age-independent effects of the transition from pre- to post- menopausal stages on immediate and delayed recall (Berent-Spillson et al., 2012) and verbal fluency (Epperson et al., 2013).

3.4.1.2 Coronary Heart Disease Diagnosis and Definition

Guideline 5. When recruiting participants for cardiovascular trials, the use of medical records or medical assessments should be used to validate self-report whenever possible. A comparison between self-reported data and hospital records among middle-aged and older women found that self-reported heart disease tended to be higher than the data obtained from medical records (Navin Cristina et al., 2016). Some of these discrepancies could be due to the

participant's faulty interpretation of heart disease, leading them to include conditions that would not meet medical definitions. Erroneously including participants who do not have CHD might undermine studying the effects of CHD on neuropsychological performance.

Guideline 6. Discrepancies between self-reported data and medical records could be minimized by establishing a clear definition of CHD to use within a study, which would also allow for better comparisons across studies. If self-administered questionnaires must be used to ensure study feasibility, we recommend including all relevant terminology in the questionnaire such as indicating that CHD is also known as CAD or IHD. When using medical records to validate CHD, we encourage researchers to state what medical diagnosis was used for inclusion. The parameters used to diagnose CHD with a medical assessment should also be clearly reported.

Guideline 7. When performing analyses of neuropsychological performance, CHD participants should not be combined with other cardiovascular conditions. As previously mentioned, CVD such as stroke or cardiac surgical procedures (e.g., CABG), have been shown to influence cognitive function (Greaves et al., 2019; Sexton et al., 2019). If the sample size does not allow for separate groups, statistical analyses should control for other CVD conditions to avoid any confounding effects.

3.4.1.3 Time Between CHD Diagnosis and Neuropsychological Assessment

Guideline 8. Results from the Whitehall II study (Singh-Manoux et al., 2008a) show a trend for lower cognitive scores with increased time since the first CHD event. Similar results were found in the longitudinal study performed by Xie et al. (2019). Therefore, researchers should provide the mean time between CHD diagnosis and neuropsychological testing to promote better comparability between studies and a better understanding of performance on

neuropsychological tests.

3.4.2 Controlling for Confounds

Guideline 9. Each research design has a specific set of exclusion and inclusion criteria and different approaches to controlling for confounds, depending on the primary goal of the study. We encourage researchers working with an adult/older adult population and with medical conditions, to consult different guidelines and take into consideration relevant variables to avoid erroneous interpretation of their results. For example, research has shown that smoking, cholesterol levels, hypertension, and pharmacotherapy should be assessed (Brotman et al., 2005; Vasan et al., 2005) when studying a CHD population. When studying cognitive function, age and education are usually considered, but demographic variables such as BMI, cholesterol, diabetes, hypertension, and smoking are also linked with an increased risk of developing vascular dementia (Gorelick et al., 2016) and should be taken into account. Cognitive function is also affected by social (J. H. Zhao et al., 2005) and marital status (Håkansson et al., 2009), and researchers should keep in mind that some neuropsychological tests are sensitive to ethnicity (Byrd et al., 2006). Taking these variables into account would allow for a more representative picture of cognitive function in participants with CHD. Uneven distribution of these demographic variables, whether between sexes or between conditions, could have an influence on the interpretation of neuropsychological tests if not properly accounted for.

3.4.3 Reporting Results Separately for Sexes and Conditions

Guideline 10. While the recruitment of more women in cardiovascular trials will play an important role in bettering our understanding of the effects of CHD on cognition, these efforts are voided if results are presented in a way that prevents the information from being extracted and understood. Therefore, we urge researchers to report all results separately for men and

women for all conditions, to allow for a more in-depth understanding of results and to promote better knowledge synthesis. We encourage researchers to report the number of men and women in each condition and want to emphasize the importance of presenting the demographic characteristics separately in the tables and figures and performing statistical analyses to assess for differences in the distribution of these variables between sexes. For example, presenting the average age of men and women with CHD separately is essential, as the onset of CHD tends to be later in women than in men (Saeed et al., 2017). Furthermore, different demographic variables, such as cholesterol and BMI, are known to impact men and women differently (Peters et al., 2019). This separation of demographic characteristics would allow for a better understanding of the distribution of the potential confounds and comorbidities within the sample and could provide meaningful insight into the results obtained on cognitive tests.

3.4.4 Neuropsychological Assessment

Guideline 11. To allow for a more representative depiction of cognitive function after CHD, it is essential that the results of the neuropsychological assessment be presented separately by sex. This is particularly relevant as recent studies have shown that cardiovascular patients, and in some cases particularly women with CVD and/or CHD, are more likely to develop Alzheimer's disease and/or cognitive decline (Bleckwenn et al., 2017; Deckers et al., 2017; Haring et al., 2013; Johansen et al., 2020; R. Song et al., 2020; Volgman et al., 2019).

Guideline 12. It is well known and acknowledged that neuropsychological tests are biased towards a White population and that they lack sensitivity and validity for persons from different cultural backgrounds (Manly, 2008). However, there are several tests that have been translated and used in many languages that do not heavily rely on verbal cues and are culture-free, such as the TMT or the Stroop test. Therefore, researchers should consider using culture-free

neuropsychological tests to reduce the impact of cultural backgrounds on performance. This will allow for more representative scores, and enable comparison between different studies across the globe. As proposed by the NINDS, studies on North-American populations could use a standardized battery (Hachinski et al., 2006) composed of validated and reliable tests.

In addition, considering the guidelines in Section 4.1.1 regarding women, we also suggest that researchers be as accurate as possible when reporting testing conditions, with particular attention to the temperature of the room. Chang & Kajackaite (2019) found that women had a better performance in both mathematics and verbal tasks if the temperature of the room was at the higher end of a 16 to 33°C range. Therefore, to provide the best environment possible for their participants, researchers might want to consider increasing the room temperature where possible.

3.5.0 Limitations

One limitation worth noting is related to the type of studies that were selected. Considering a significant lack of research specifically assessing CVD and CHD in women, we also extracted information from studies where the neurocognitive impact of CHD in women was not indicated as the primary goal of the study. In such cases, the information that could be extracted was more limited. Another limitation is the fact that the total number of references presented at each phase of the review is artificially inflated because Covidence cannot effectively identify all possible duplicates (e.g., nine duplicates were identified during data extraction). Regardless, to be transparent, we believe that this information needs to be communicated and we want to reassure readers that despite this artificial inflation, duplicates do not represent a significant portion of the final totals.

3.6.0 Conclusion

Overall, we found that women and men groups are still disproportionate in studies assessing functional recovery following CHD, with women typically making up 36 % or less of CHD groups. Our review also revealed that researchers do not consistently define what diseases are encapsulated in CHD, which makes it harder to establish and understand the impact of CHD in men and women. Notably, researchers are not reporting results for both sexes, and are assuming that pooled results are representative of the recovery profile of both men and women. More importantly, we did find an association between CHD, MI, or AP conditions and lower cognitive performance in different cognitive domains, such as difficulty with word retrieval, longer time to completion for visuospatial/motor tests, difficulty recalling previously learned verbal material, and with reasoning and problem-solving. This finding is extremely important considering that researchers investigating the impact of CVD in either men or women have noticed that these individuals are more at risk of developing a neurodegenerative disorder (e.g., dementia). We cannot stress enough the role that governments, academic institutions, and hospitals can play by prioritizing research on women's heart health, enabling to further explore factors that may influence recovery, especially now that there is an increase in the CHD survival rate.

3.7.0 Acknowledgements

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including studies by J.B. in this review, J.B. was not part of the team analyzing the results or consulted in this regard. A doctoral scholarship from the FRQNT supported N.F.N.L.'s research. The National Sciences and Engineering Research Council (NSERC) - Undergraduate Student Research Award supported M.P.'s research. The European Social Fund under the No 09.3.3-LMT-K-712-19-0127 "Development of Competences of Scientists, other Researchers and Students through Practical Research Activities" funded J.B.'s research. A discovery grant to H.P. from NSERC (RG203596-13) supported this review.

Appendix A - Search Strategy

Search strategy - T_1: August 15, 2018; T_2 : July 23, 2020

Medline (Ovid)

1. exp myocardial ischemia/
2. heart diseases/
3. (myocard* adj3 (ischaemi* or ischemi*)).ti,ab
4. (myocard* adj3 infarct*).ti,ab
5. (heart adj3 (ischaemia or ischemi*)).ti,ab
6. (coronary adj3 (disease* or thrombo*)).ti,ab
7. (heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti,ab
8. angina*.ti,ab
9. (cardiac adj3 arrest*).ti,ab
10. or/1-9
11. cognition/
12. cognition disorders/
13. cognitive dysfunction/
14. exp neuropsychological tests/
15. exp memory/
16. exp neurobehavioral manifestations/
17. mental processes/
18. learning/
19. cognition.ti,ab

20. ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti,ab.
21. ((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti,ab
22. psychometric*.ti,ab
23. or/11-22
24. 10 and 23

APA PsycInfo (Ovid)

1. exp heart disorders/
2. (myocard* adj3 (ischaemi* or ischemi*)).ti,ab
3. (myocard* adj3 infarct*).ti,ab
4. (heart adj3 (ischaemia or ischemi*)).ti,ab
5. (coronary adj3 (disease* or thrombo*)).ti,ab
6. (heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti,ab
7. angina*.ti,ab
8. (cardiac adj3 arrest*).ti,ab
9. or/1-8
10. cognition/
11. cognitive impairment/
12. exp neuropsychological assessment/

13. exp memory/
14. cognitive processes/
15. learning/
16. cognition.ti,ab
17. ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti,ab.
18. ((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti,ab
19. psychometric*.ti,ab
20. or/10-19
21. 9 and 20

Embase (Ovid)

1. exp heart muscle ischemia/
2. heart disease/
3. (myocard* adj3 (ischaemi* or ischemi*)).ti,ab
4. (myocard* adj3 infarct*).ti,ab
5. (heart adj3 (ischaemia or ischemi*)).ti,ab
6. (coronary adj3 (disease* or thrombo*)).ti,ab
7. (heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti,ab
8. angina*.ti,ab

9. (cardiac adj3 arrest*).ti,ab
10. or/1-9
11. cognition/
12. cognitive defect/
13. exp neuropsychological test/
14. exp memory/
15. mental function/
16. learning/
17. cognition.ti,ab
18. ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti,ab.
19. ((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti,ab
20. psychometric*.ti,ab
21. or/11-20
22. 10 and 21

AMED (Ovid)

1. exp myocardial ischemia/
2. heart disease/
3. (myocard* adj3 (ischaemi* or ischemi*)).ti,ab

4. (myocard* adj3 infarct*).ti,ab
5. (heart adj3 (ischaemia or ischemi*)).ti,ab
6. (coronary adj3 (disease* or thrombo*)).ti,ab
7. (heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti,ab
8. angina*.ti,ab
9. (cardiac adj3 arrest*).ti,ab
10. or/1-9
11. cognition/
12. cognition disorders/
13. neuropsychological tests/
14. exp memory/
15. mental processes/
16. learning/
17. cognition.ti,ab
18. ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti,ab.
19. ((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti,ab
20. psychometric*.ti,ab
21. or/11-20

22. 10 and 21

Cochrane CENTRAL (Ovid)

1. exp myocardial ischemia/
2. heart diseases/
3. (myocard* adj3 (ischaemi* or ischemi*)).ti,ab
4. (myocard* adj3 infarct*).ti,ab
5. (heart adj3 (ischaemia or ischemi*)).ti,ab
6. (coronary adj3 (disease* or thrombo*)).ti,ab
7. (heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti,ab
8. angina*.ti,ab
9. (cardiac adj3 arrest*).ti,ab
10. or/1-9
11. cognition/
12. cognition disorders/
13. exp neuropsychological tests/
14. exp memory/
15. exp neurobehavioral manifestations/
16. mental processes/
17. learning/
18. cognition.ti,ab
19. ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or

degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti,ab.

20. ((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti,ab
21. psychometric*.ti,ab
22. or/11-21
23. 10 and 22

CINAHL (Ebsco)

1. (MH "Myocardial Ischemia+")
2. (MH "Heart Diseases")
3. TI (myocard* N3 (ischaemi* or ischemi*)) OR AB (myocard* N3 (ischaemi* or ischemi*))
4. TI (myocard* N3 infarct*) OR AB (myocard* N3 infarct*)
5. TI (heart N3 (ischaemia or ischemi*)) OR AB (heart N3 (ischaemia or ischemi*))
6. TI (coronary N3 (disease* or thrombo*)) OR AB (coronary N3 (disease* or thrombo*))
7. TI (heart N3 (infarct* or disease* or disorder* or attack* or failure*)) OR AB (heart N3 (infarct* or disease* or disorder* or attack* or failure*))
8. TI (angina*) OR AB (angina*)
9. TI (cardiac N3 arrest*) OR AB (cardiac N3 arrest*)
10. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
11. (MH "cognition")
12. (MH "cognition disorders")

13. (MH "neuropsychological tests")
14. (MH "memory+")
15. (MH "neurobehavioral manifestations+")
16. (MH "mental processes")
17. (MH "learning")
18. TI (cognition) OR AB (cognition)
19. TI ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) N3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)) OR AB ((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) N3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*))
20. TI ((neuropsycholog* or cognitive) N3 (test* or measure* or instrument* or assessment*)) OR AB ((neuropsycholog* or cognitive) N3 (test* or measure* or instrument* or assessment*))
21. TI (psychometric*) OR AB (psychometric*)
22. S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21
23. S10 AND S22

Web of Science

1. TS=(myocard* NEAR/3 (ischaemi* or ischemi*))

2. TS=(myocard* NEAR/3 infarct*)
3. TS=(heart NEAR/3 (ischaemia or ischemi*))
4. TS=(coronary NEAR/3 (disease* or thrombo*))
5. TS=(heart NEAR/3 (infarct* or disease* or disorder* or attack* or failure*))
6. TS=(angina*)
7. TS=(cardiac NEAR/3 arrest*)
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. TS=(cognition)
10. TS=((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) NEAR/3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).
11. TS=((neuropsycholog* or cognitive) NEAR/3 (test* or measure* or instrument* or assessment*))
12. TS=(psychometric*)
13. #9 OR #10 OR #11 OR #12
14. #8 AND #13

Scopus

1. TITLE-ABS(myocard* w/3 (ischaemi* or ischemi*))
2. TITLE-ABS(myocard* w/3 infarct*)
3. TITLE-ABS(heart w/3 (ischaemia or ischemi*))
4. TITLE-ABS(coronary w/3 (disease* or thrombo*))

5. TITLE-ABS(heart w/3 (infarct* or disease* or disorder* or attack* or failure*))
6. TITLE-ABS(angina*)
7. TITLE-ABS(cardiac w/3 arrest*)
8. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
9. TITLE-ABS(cognition)
10. TITLE-ABS((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) w/3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*))
11. TITLE-ABS((neuropsycholog* or cognitive) w/3 (test* or measure* or instrument* or assessment*))
12. TITLE-ABS(psychometric*)
13. #9 OR #10 OR #11 OR #12
14. #8 AND #13

Appendix B – Articles excluded during full-text screening (reason)

Table 1
Articles excluded during full-text screening

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
A Comparative Study of Life Events, life Style, Negative Emotion Between Acute Myocardial Infarction Patients and Normal Persons	Zhang, Hui; Zou, Wen-Hua; Wang, Min-Zhu	2006	Chinese Journal of Clinical Psychology	14	5	535-536		Exclusion reason: Publication was not available
A dynamic view of depressive symptoms and neurocognitive change among patients with coronary artery disease	Freiheit, Elizabeth A.; Hogan, David B.; Eliasziw, Misha; Patten, Scott B.; Demchuk, Andrew M.; Faris, Peter; Anderson, Todd; Galbraith, Diane; Parboosingh, Jillian S.; Ghali, William A.; Knudtson, Merril; Maxwell, Colleen J.	2012	Archives of general psychiatry	69	3	244-55	https://dx.doi.org/10.1001/archgenpsychiatry.2011.1361	Exclusion reason: No separate analysis for sexes
A follow-up investigation of patients with acute myocardial infarction and cardiac arrest	Garbol, J.; Olsen, P. P.; Tolstrup, N.	1979	Ugeskrift for Laeger	141	38	2594-2598		Exclusion reason: Publication was not available
A Lipidomics Approach to Assess the Association Between Plasma Sphingolipids and Verbal Memory Performance in Coronary Artery Disease Patients Undertaking Cardiac Rehabilitation: A C18:0 Signature for Cognitive Response to Exercise	Saleem, Mahwesh; Herrmann, Nathan; Dinoff, Adam; Mielke, Michelle M.; Oh, Paul I.; Shammi, Prathiba; Cao, Xingshan; Venkata, Swarajya Lakshmi Vattem; Haughey, Norman J.; Lanctot, Krista L.	2017	Journal of Alzheimer's disease : JAD	60	3	829-841	https://dx.doi.org/10.3233/JAD-161292	Exclusion reason: No separate analysis for sexes
A plasma phospholipid omega-3 fatty acid index > 4% prevents cognitive decline in cognitively	Vemuri B, Malik A, Asbeutah AAA, Welty FK	2019		140				Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
healthy subjects with coronary artery disease								
A population-based study of the association between coronary artery bypass graft surgery (CABG) and cognitive decline: the Cache County study	Lyketsos, C. G.; Toone, L.; Tschanz, J.; Corcoran, C.; Norton, M.; Zandi, P.; Munger, R.; Breitner, J. C.; Welsh-Bohmer, K.	2006	International Journal of Geriatric Psychiatry	21	6	509-518		Exclusion reason: No separate analysis for sexes
A preliminary study of the effects of cardiac procedures on cognitive performance	Blumenthal, James A.; Madden, David J.; Burker, Eileen J.; Croughwell, Narda; Schniebolk, S.; Smith, R.; White, W. D.; Hlatky, M.; Reves, J. G.	1991	International Journal of Psychosomatics	38	04-Jan	13-16		Exclusion reason: Publication was not available
A prospective study of pravastatin in the elderly at risk: new hope for older persons	Shepherd, James	2004	The American journal of geriatric cardiology	13	3 Suppl 1	17-24		Exclusion reason: Publication was not available
A prospective, randomized study of the effects of prostacyclin on neuropsychologic dysfunction after coronary artery operation	Fish, K. J.; Helms, K. N.; Sarnquist, F. H.; van Steennis, C.; Linet, O. I.; Hilberman, M.; Mitchell, R. S.; Jamieson, S. W.; Miller, D. C.; Tinklenberg, J. S.	1987	The Journal of thoracic and cardiovascular surgery	93	4	609-15		Exclusion reason: Men only
A trial of B vitamins and cognitive function among women at high risk of cardiovascular disease	Kang, J. H.; Cook, N.; Manson, J.; Buring, J. E.; Albert, C. M.; Grodstein, F.	2008	Am. J. Clin. Nutr.	88	6	1602-1610	10.3945/ajcn.2008.26404	Exclusion reason: No separate analysis for conditions
Ability to Regulate Emotion Is Predicted by Depressive	Spitznagel, M. B.; Potter, V.; Miller, L. A.; Miller, A. N.; Hughes, J.; Rosneck, J.; Gunstad, J.	2013	Journal of Cardiovascular Nursing	28	5	453-459	10.1097/JCN.0b013e318256be99	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Symptoms and Cognitive Function in a Cardiac Sample								
Accounting for differences in cognitive health between older adults in New Zealand and the USA	Stephens, Christine; Spicer, John; Budge, Claire; Stevenson, Brendan; Alpass, Fiona	2015	International psychogeriatrics	27	4	591-600	https://dx.doi.org/10.1017/S1041610214002579	Exclusion reason: No separate analysis for conditions
Aging, stress, and sudden cardiac death	Kennedy, G. J.; Fisher, J. D.	1987	Mount Sinai Journal of Medicine	54	1	56-62		Exclusion reason: Publication (title or abstract) not found
Analysis of post-operative cognitive dysfunction after different methods of aortocoronary bypass surgery.	Alekseevich, G. Yu; Rodikov, M. V; Marchenko, A. V; Myalyuk, P. A; Alekseevich, G. V	2019	Neuroscience and Behavioral Physiology	49	3	347-351	http://dx.doi.org/10.1007/s11055-019-00738-8http://dx.doi.org/10.1007/s11055-019-00738-8	Exclusion reason: No separate analysis for sexes
Angina pectoris severity among coronary heart disease patients is associated with subsequent cognitive impairment	Weinstein, Galit; Goldbourt, Uri; Tanne, David	2015	Alzheimer disease and associated disorders	29	1	11-Jun	https://dx.doi.org/10.1097/WAD.0000000000000038	Exclusion reason: No separate analysis for sexes
Angina-like chest pain: a joint medical and psychiatric investigation	Colgan, S. M.; Schofield, P. M.; Whorwell, P. J.; Bennett, D. H.; Brooks, N. H.; Jones, P. E.	1988	Postgraduate medical journal	64	756	743-6		Exclusion reason: No cognitive assessment performed
Aortic atherosclerosis and postoperative neurological dysfunction in elderly coronary surgical patients	Goto, Tomoko; Baba, Tomoko; Matsuyama, Kumi; Honma, Keiko; Ura, Masashi; Koshiji, Takaaki	2003	The Annals of thoracic surgery	75	6	12-Aug		Exclusion reason: Does not mention any CHD in methods or analysis

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Apathy and cognitive test performance in patients undergoing cardiac testing	Kakos, Lynn Reese; Alosco, Michael L.; Spitznagel, Mary Beth; Hughes, Joel; Rosneck, Jim; Gunstad, John	2013	Cardiovascular psychiatry and neurology	2013		659589	https://dx.doi.org/10.1155/2013/659589	Exclusion reason: No separate analysis for sexes
Apolipoprotein E genotypes and cognitive functions in healthy elderly persons	Staehelin, H. B.; Perrig-Chiello, P.; Mitrache, C.; Miserez, A. R.; Perrig, W. J.	1999	Acta Neurol. Scand.	100	1	53-60	10.1111/j.1600-0404.1999.tb00723.x	Exclusion reason: Does not mention any CHD in methods or analysis
Apolipoprotein epsilon 4 genotype is associated with less improvement in cognitive function five years after cardiac surgery: a retrospective cohort study	Bartels, Karsten; Li, Yi-Ju; Li, Yen-Wei; White, William D.; Laskowitz, Daniel T.; Kertai, Miklos D.; Stafford-Smith, Mark; Podgoreanu, Mihai V.; Newman, Mark F.; Mathew, Joseph P.	2015	Canadian journal of anaesthesia = Journal canadien d'anesthesie	62	6	618-26	https://dx.doi.org/10.1007/s12630-015-0337-8	Exclusion reason: No separate analysis for sexes
Are different vascular risk scores calculated at midlife uniformly associated with subsequent poor cognitive performance?	Kesse-Guyot, Emmanuelle; Lassale, Camille; Assmann, Karen E.; Andreeva, Valentina A.; Julia, Chantal; Blacher, Jacques; Fezeu, Leopold; Hercberg, Serge; Galan, Pilar	2015	Atherosclerosis	243	1	286-92	https://dx.doi.org/10.1016/j.atherosclerosis.2015.09.023	Exclusion reason: No separate analysis for sexes
Arterial stiffness, cognitive decline, and risk of dementia: the Rotterdam study	Poels, Marielle M. F.; van Oijen, Marieke; Mattace-Raso, Francesco U. S.; Hofman, Albert; Koudstaal, Peter J.; Witteman, Jacqueline C. M.; Breteler, Monique M. B.	2007	Stroke	38	3	888-92		Exclusion reason: Does not mention any CHD in methods or analysis
Assessement of vascular event prevention and cognitive function among older adults with preexisting vascular disease or diabetes: a secondary	Offer A, Arnold M, Clarke R, Bennett D, Bowman L, Bulbulia R, Haynes R, Li J, Hopewell JC, Landray M, Armitage J, Collins R, Parish S	2019		2	3	e190223		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
analysis of 3 randomized clinical trials								
Assessing cognitive effects of anticholinergic medications in patients with coronary artery disease	Lanctot, Krista L.; O'Regan, Jordana; Schwartz, Yael; Swardfager, Walter; Saleem, Mahwesh; Oh, Paul I.; Herrmann, Nathan	2014	Psychosomatics	55	1	Aug-61	https://dx.doi.org/10.1016/j.psym.2013.04.004	Exclusion reason: No separate analysis for sexes
Asset of creatine phosphate for cardiocerebral syndrome treatment in acute myocardial infarction in old age. PRINOS UZITI KREATINFOSFATU V TERAPII KARDIOCEREBRALNIHO SYNDROMU U AKUTNIHO INFARKTU MYOKARDU VE STARI	Weber P, Vlasicova Y. Labrova R. Semrad B.	1995	Casopis lekaru ceskych	134	2	53		Exclusion reason: Not available in English
Association between cognitive function and parameters of echocardiography and coronary artery angiography	Hashemi, Mohammad; Jervekani, Zahra Teimouri; Mortazavi, Shahrzad; Maracy, Mohammad Reza; Barekatain, Majid	2018	Arquivos de neuro-psiquiatria	76	4	225-230	https://dx.doi.org/10.1590/0004-282x20180026	Exclusion reason: Does not mention any CHD in methods or analysis
Association between Cognitive Impairment, Vascular Disease and All-Cause Mortality.	Kim, J-H; Chon, D	2018	The journal of nutrition, health & aging	22	7	790-795	https://dx.doi.org/10.1007/s12603-018-1011-y	Exclusion reason: No separate analysis for sexes
Association between dialysis treatment and cognitive decline: A study from the Project in Sado for Total Health (PROST), Japan	Watanabe, Yumi; Kitamura, Kaori; Nakamura, Kazutoshi; Sanpei, Kazuhiro; Wakasugi, Minako; Yokoseki, Akio; Kabasawa, Keiko; Onodera, Osamu; Ikeuchi, Takeshi;	2017	Geriatrics & gerontology international	17	10	1584-1587	https://dx.doi.org/10.1111/ggi.12937	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Kuwano, Ryozo; Momotsu, Takeshi; Narita, Ichiei; Endo, Naoto							
Association Between Endothelial Function and Cognitive Performance in Patients With Coronary Artery Disease During Cardiac Rehabilitation.	Saleem, Mahwesh; Herrmann, Nathan; Dinoff, Adam; Mazereeuw, Graham; Oh, Paul I; Goldstein, Benjamin I; Kiss, Alex; Shammi, Prathiba; Lanctot, Krista L	2019	Psychosomatic medicine	81	2	184-191	https://dx.doi.org/10.1097/PSY.0000000000000651	Exclusion reason: No separate analysis for sexes
Association between functional status and use and effectiveness of beta-blocker prophylaxis in elderly survivors of acute myocardial infarction	Vitagliano, Gail; Curtis, Jeptha P.; Concato, John; Feinstein, Alvan R.; Radford, Martha J.; Krumholz, Harlan M.	2004	Journal of the American Geriatrics Society	52	4	495-501		Exclusion reason: No separate analysis for sexes
Association between hypotension, low ejection fraction and cognitive performance in cardiac patients	Gottesman, R. F.; Grega, M. A.; Bailey, M. M.; Zeger, S. L.; Baumgartner, W. A.; McKhann, G. M.; Selnes, O. A.	2009	Behav. Neurol.	22	02-Jan	63-71	10.3233/ben-2009-0261	Exclusion reason: No separate analysis for sexes
Association between hypotension, low ejection fraction and cognitive performance in cardiac patients	Gottesman, Rebecca F.; Grega, Maura A.; Bailey, Maryanne M.; Zeger, Scott L.; Baumgartner, William A.; McKhann, Guy M.; Selnes, Ola A.	2010	Behavioural neurology	22	02-Jan	63-71	https://dx.doi.org/10.3233/BEN-2009-0261	Exclusion reason: Duplicate
Association between mortality and cognitive change over 7 years in a large representative sample of UK residents	Shipley, Beverly A.; Der, Geoff; Taylor, Michelle D.; Deary, Ian J.	2007	Psychosomatic medicine	69	7	640-50		Exclusion reason: No separate analysis for sexes
Association between serum long-chain omega-3 polyunsaturated fatty acids and cognitive performance in elderly	D'Ascoli, T. A.; Mursu, J.; Voutilainen, S.; Kauhanen, J.; Tuomainen, T. P.; Virtanen, J. K.	2016	European journal of	70	8	970-5	https://dx.doi.org/10.1038/ejcn.2016.59	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
men and women: The Kuopio Ischaemic Heart Disease Risk Factor Study			clinical nutrition					
Association of cognitive dysfunction with cardiovascular disease events in elderly hypertensive patients	Yano, Yuichiro; Bakris, George L.; Inokuchi, Takashi; Ohba, Yusuke; Tamaki, Noboru; Nagata, Masahiko; Kuwabara, Masachika; Yokota, Naoto; Eto, Takuma; Kuroki, Munetoshi; Shimada, Kazuyuki; Kario, Kazuomi	2014	Journal of hypertension	32	2	423-31	https://dx.doi.org/10.1097/HJH.0000000000000025	Exclusion reason: Not pertinent research (e.g., protocol registration)
Association of Cognitive Impairment With Treatment and Outcomes inÂ Older Myocardial Infarction Patients: A Report From the NCDRÂ Chest Pain-MI Registry.	Bagai, Akshay; Chen, Anita Y.; Udell, Jacob A.; Dodson, John A.; McManus, David D.; Maurer, Mathew S.; Enriquez, Jonathan R.; Hochman, Judith; Goyal, Abhinav; Henry, Timothy D.; Gulati, Martha; Garratt, Kirk N.; Roe, Matthew T.; Alexander, Karen P.	2019	Journal of the American Heart Association	8	17	09-Jan	10.1161/JAHA.119.012929	Exclusion reason: No separate analysis for sexes
Association of diagnosis of ischaemic heart disease, diabetes mellitus and heart failure with cognitive function in the elderly population	Halling, Anders; Berglund, Johan	2006	The European journal of general practice	12	3	114-9		Exclusion reason: No separate analysis for conditions
Association of Exercise Capacity with Physical Functionality and Various Aspects of Fatigue in Patients with Coronary Artery Disease	Nagy, Alexandra; Szabados, Eszter; Simon, Attila; Mezey, Bela; Sandor, Barbara; Tiringer, Istvan; Toth, Kalman; Bencsik, Krisztina; Csatho, Arpad	2018	Behavioral medicine (Washington, D.C.)	44	1	28-35	https://dx.doi.org/10.1080/08964289.2016.1189395	Exclusion reason: No cognitive assessment performed
Association of geriatric conditions and cardiovascular diseases with disability in older	Li, Chia-Lin; Chiu, Yi-Chen; Chang, Hsing-Yi; Hsu, Kuang-Hung; Bai, Yuh-Bin; Wang, Hui-Hsuan	2013	Geriatrics & gerontology international	13	3	563-70	https://dx.doi.org/10.1111/j.1447-	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
adults with diabetes: findings from a nationally representative survey							0594.2012.00935.x	
Association of locomotive activity with sleep latency and cognitive function of elderly patients with cardiovascular disease in the maintenance phase of cardiac rehabilitation.	Kurose, Satoshi; Miyauchi, Takumi; Yamashita, Ryo; Tamaki, Shohei; Imai, Masaru; Nakashima, Yuri; Umeda, Yoko; Sato, Shinji; Kimura, Yutaka; Masuda, Izuru	2019	Journal of cardiology	73	6	530-535	https://dx.doi.org/10.1016/j.jjcc.2018.12.015	Exclusion reason: No separate analysis for sexes
Associations Between Midlife (but Not Late-Life) Elevated Coronary Heart Disease Risk and Lower Cognitive Performance: Results From the Framingham Offspring Study.	Armstrong, Nicole M; Bangen, Katherine J; Au, Rhoda; Gross, Alden L	2019	American Journal of Epidemiology	188	12	2175-2187	10.1093/aje/kwz210	Exclusion reason: No separate analysis for sexes
Associations between single and multiple cardiometabolic diseases and cognitive abilities in 474 129 UK Biobank participants	Lyall, Donald M.; Celis-Morales, Carlos A.; Anderson, Jana; Gill, Jason M. R.; Mackay, Daniel F.; McIntosh, Andrew M.; Smith, Daniel J.; Deary, Ian J.; Sattar, Naveed; Pell, Jill P.	2017	European heart journal	38	8	577-583	https://dx.doi.org/10.1093/eurheartj/ehw528	Exclusion reason: No separate analysis for sexes
Asymptomatic cerebral infarctions: Risk factors and cognitive impairment	Zhetishchev, R. R.; Mikhailova, N. A.; Ivashchenko, R. A.; Kamchatnov, P. R.	2014	Zhurnal Nevrologii i Psihiatrii imeni S.S. Korsakova	2014	3	06-Mar		Exclusion reason: Not available in English
Attention in Older Adults: A Normative Study of the Integrated Visual and Auditory Continuous Performance Test for Persons Aged 70 Years	Berginstrom, Nils; Johansson, Jonas; Nordstrom, Peter; Nordstrom, Anna	2015	The Clinical neuropsychologist	29	5	595-610	https://dx.doi.org/10.1080/13854046.2015.1063695	Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Attentional bias and anxiety in individuals with coronary heart disease	Ginting, Henndy; Naring, Gerard; Becker, Eni S.	2013	Psychology & health	28	11	1306-22	https://dx.doi.org/10.1080/08870446.2013.803554	Exclusion reason: No separate analysis for sexes
Attentional Capacity and Working Memory in Coronary Artery Disease Patients: impact of the Presence of a Sleep Apnea Syndrome and Chronic Effects of Treatment With CPAP	Nct	2015						Exclusion reason: Not pertinent research (e.g., protocol registration)
Attentional reactions to an MI: the impact of mood state, worry, and coping style	Constans, J. I.; Mathews, A.; Brantley, P. J.; James, T.	1999	Journal of psychosomatic research	46	5	415-23		Exclusion reason: No separate analysis for sexes
Beta-Blocker Use in U.S. Nursing Home Residents After Myocardial Infarction: A National Study	Zullo, Andrew R.; Lee, Yoojin; Daiello, Lori A.; Mor, Vincent; John Boscardin, W.; Dore, David D.; Miao, Yinghui; Fung, Kathy Z.; Komaiko, Kiya D. R.; Steinman, Michael A.	2017	Journal of the American Geriatrics Society	65	4	754-762	https://dx.doi.org/10.1111/jgs.14671	Exclusion reason: No cognitive assessment performed
Beyond sociodemographics: factors influencing the decision to seek treatment for symptoms of acute myocardial infarction	Dracup, K.; Moser, D. K.	1997	Heart & lung : the journal of critical care	26	4	253-62		Exclusion reason: No cognitive assessment performed
BLOOD PRESSURE AND COGNITIVE FUNCTION IN OLDER ADULTS WITH CARDIOVASCULAR DISEASE	Gunstad, J.; Keary, T. A.; Spitznagel, M. B.	2009	Int. J. Neurosci.	119	12	2228-2242	10.3109/00207450903139713	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Body height and late-life cognition among patients with atherothrombotic disease	Weinstein, Galit; Goldbourt, Uri; Tanne, David	2013	Alzheimer disease and associated disorders	27	2	145-52	https://dx.doi.org/10.1097/WAD.0b013e31825ca9ef	Exclusion reason: No separate analysis for sexes
Brain and mood changes over 2 years in healthy controls and adults with heart failure and ischaemic heart disease	Almeida, Osvaldo P.; Garrido, Griselda J.; Etherton-Beer, Christopher; Lautenschlager, Nicola T.; Arnolda, Leonard; Alfonso, Helman; Flicker, Leon	2013	European journal of heart failure	15	8	850-8	https://dx.doi.org/10.1093/eurjhf/hft029	Exclusion reason: No separate analysis for sexes
Brain derived neurotrophic factor, cardiopulmonary fitness and cognition in patients with coronary artery disease	Swardfager, W.; Herrmann, N.; Marzolini, S.; Saleem, M.; Shammi, P.; Oh, P. I.; Albert, P. R.; Daigle, M.; Kiss, A.; Lanctot, K. L.	2011	Brain, behavior, and immunity	25	6	1264-71	https://dx.doi.org/10.1016/j.bbi.2011.04.017	Exclusion reason: No separate analysis for conditions
Brain volume and cognitive function in patients with revascularized coronary artery disease	Ottens, Thomas H.; Hendrikse, Jeroen; Nathoe, Hendrik M.; Biessels, Geert Jan; van Dijk, Diederik	2017	International journal of cardiology	230		80-84	https://dx.doi.org/10.1016/j.ijcard.2016.12.079	Exclusion reason: No separate analysis for conditions
Brain-derived neurotrophic factor Val66Met polymorphism and cognitive function in persons with cardiovascular disease	Szabo, A. J.; Alosco, M. L.; Miller, L. A.; McGeary, J. E.; Poppas, A.; Cohen, R. A.; Gunstad, J.	2013	Psychogeriatrics	13	4	206-212	10.1111/psyg.12013	Exclusion reason: No separate analysis for conditions
CAMTA1 T polymorphism is associated with neuropsychological test performance in older adults with cardiovascular disease	Miller, L. A.; Gunstad, J.; Spitznagel, M. B.; McCaffery, J.; McGeary, J.; Poppas, A.; Paul, R. H.; Sweet, L. H.; Cohen, R. A.	2011	Psychogeriatrics	11	3	135-140	10.1111/j.1479-8301.2011.00357.x	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Capacity for direct attention in patients undergoing percutaneous coronary intervention: the effects of psychological distress	Carroll, D. L.	2005	Progress in Cardiovascular Nursing	20	1	16-Nov		Exclusion reason: No separate analysis for sexes
Cardiac arrest: prognostic factors and outcome at one year	Beuret, P.; Feihl, F.; Vogt, P.; Perret, A.; Romand, J. A.; Perret, C.	1993	Resuscitation	25	2	171-9		Exclusion reason: Does not mention any CHD in methods or analysis
Cardiac disease associated with increased risk of nonamnestic cognitive impairment: stronger effect on women	Roberts, Rosebud O.; Geda, Yonas E.; Knopman, David S.; Cha, Ruth H.; Pankratz, V. Shane; Boeve, Bradley F.; Tangalos, Eric G.; Ivnik, Robert J.; Mielke, Michelle M.; Petersen, Ronald C.	2013	JAMA neurology	70	3	374-82	https://dx.doi.org/10.1001/jamaneurol.2013.607	Exclusion reason: No separate analysis for conditions
Cardiac function and cognition in older community-dwelling cardiac patients	Eggermont, L. H. P.; Aly, M. F. A.; Vuijk, P. J.; de Boer, K.; Kamp, O.; van Rossum, A. C.; Scherder, E. J. A.	2017	Psychogeriatrics	17	6	356-363	10.1111/psyg.12245	Exclusion reason: No separate analysis for conditions
Cardiac Output, Blood Pressure Variability, and Cognitive Decline in Geriatric Cardiac Patients	Okonkwo, O. C.; Cohen, R. A.; Gunstad, J.; Poppas, A.	2011	J. Cardiopulm. Rehabil. Prev.	31	5	290-297	10.1097/HCR.0b013e318220a817	Exclusion reason: No separate analysis for sexes
Cardiac rehabilitation in the elderly: patient selection and outcomes	Ferrara, Nicola; Corbi, Graziamaria; Bosimini, Enzo; Cobelli, Franco; Furgi, Giuseppe; Giannuzzi, Pantaleo; Giordano, Amerigo; Pedretti, Roberto; Scrutinio, Domenico; Rengo, Franco	2006	The American journal of geriatric cardiology	15	1	22-Jul		Exclusion reason: Not pertinent research (e.g., protocol registration)
Cardiopulmonary fitness is associated with cognitive	Swardfager, Walter; Herrmann, Nathan; Marzolini, Susan; Saleem, Mahwesh; Kiss, Alexander; Shammi,	2010	Journal of the American	58	8	1519-25	https://dx.doi.org/10.1111/j.1532-	Exclusion reason: Duplicate

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
performance in patients with coronary artery disease	Prathiba; Oh, Paul I.; Lanctot, Krista L.		Geriatrics Society				5415.2010.02966.x	
Cardiopulmonary Fitness is Associated with Cognitive Performance in Patients with Coronary Artery Disease (vol 74, pg 9, 2010)	Swardfager, W.; Herrmann, N.; Marzolini, S.; Sherman, M.; Kiss, A.; Shammi, P.; Oh, P.; Lanctot, K.	2010	Neurology	75	9	839-839		Exclusion reason: No separate analysis for conditions
Cardiovascular and lifestyle risk factors and cognitive function in patients with stable coronary heart disease	Stewart RAH, Held C, Krug-Gourley S, Waterworth D, Stebbins A, Chiswell K, Hagstrom E, Armstrong PW, Wallentin L, White H	2019		8	7	e010641		Exclusion reason: No separate analysis for conditions
Cardiovascular diseases and related risk factors accelerated cognitive deterioration in patients with late-life depression: a one-year prospective study.	Zhong, Xiaomei; Wu, Zhangying; Ouyang, Cong; Liang, Wanyuan; Chen, Ben; Peng, Qi; Mai, Naikeng; Wu, Yuejie; Chen, Xinru; Zhang, Min; Ning, Yuping	2019	International Psychogeriatrics	31	10	1483-1489	10.1017/S1041610218002041	Exclusion reason: No separate analysis for sexes
Cardiovascular Fitness and Neurocognitive Performance among Older Adults in the Maintenance Stage of Cardiac Rehabilitation	Netz, Y.; Dwolatzky, T.; Khaskia, A.; Dunsky, A.	2015	Isr. J. Psychiatr. Relat. Sci.	52	3	55-64		Exclusion reason: No separate analysis for conditions
Cardiovascular risk factors and cognitive function in middle aged and elderly Lithuanian urban population: results from the HAPIEE study	Tamosiunas, Abdonas; Baceviciene, Migle; Reklaitiene, Regina; Radisauskas, Ricardas; Jureniene, Kristina; Azaraviciene, Adelina; Luksiene, Dalia; Malinauskiene, Vilija; Daugeliene, Evelina; Sapranaviciute-Zabazlajeva, Laura	2012	BMC neurology	12		149	https://dx.doi.org/10.1186/1471-2377-12-149	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Carotid artery intima-media thickness and cognition in cardiovascular disease	Haley, Andreana P.; Forman, Daniel E.; Poppas, Athena; Hoth, Karin F.; Gunstad, John; Jefferson, Angela L.; Paul, Robert H.; Ler, Albert S. H.; Sweet, Lawrence H.; Cohen, Ronald A.	2007	International journal of cardiology	121	2	148-54		Exclusion reason: No separate analysis for conditions
Ceramide Accumulation Is Associated with Declining Verbal Memory in Coronary Artery Disease Patients: An Observational Study	Chan, Parco; Saleem, Mahwesh; Herrmann, Nathan; Mielke, Michelle M.; Haughey, Norman J.; Oh, Paul I.; Kiss, Alexander; Lanctot, Krista L.	2018	Journal of Alzheimer's disease : JAD				https://dx.doi.org/10.3233/JAD-180030	Exclusion reason: No separate analysis for sexes
Ceramides predict verbal memory performance in coronary artery disease patients undertaking exercise: a prospective cohort pilot study	Saleem, Mahwesh; Bandaru, Veera V. Ratnam; Herrmann, Nathan; Swardfager, Walter; Mielke, Michelle M.; Oh, Paul I.; Shammi, Prathiba; Kiss, Alexander; Haughey, Norman J.; Rovinski, Randal; Lanctot, Krista L.	2013	BMC geriatrics	13		135	https://dx.doi.org/10.1186/1471-2318-13-135	Exclusion reason: No separate analysis for sexes
Cerebral changes and cognitive impairment after an ischemic heart disease: a multimodal MRI study	Bernard, Charlotte; Catheline, Gwenaelle; Dilharreguy, Bixente; Couffinhal, Thierry; Ledure, Sylvain; Lassalle-Lagadec, Saioa; Callaert, Dorothee; Allard, Michele; Sibon, Igor	2016	Brain imaging and behavior	10	3	893-900	https://dx.doi.org/10.1007/s11682-015-9483-4	Exclusion reason: No separate analysis for sexes
Cerebral circulation and cognitive status of coronary heart disease patients after bypass surgery	Petrova, M. M.; Prokopenko, S. V.; Eremina, O. V.; Mozheiko, E. Y.; Kaskaeva, D. S.; Gankin, M. I.	2017	Russian Journal of Cardiology	149	9	34-41	10.15829/1560-4071-2017-9-34-41	Exclusion reason: Not available in English

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cerebral functional changes following cardiac surgery: Neuropsychological and EEG assessment	Toner, I.; Taylor, K. M.; Newman, S.; Smith, P. L.	1998	European journal of cardio-thoracic surgery	13	1	13-20		Exclusion reason: No separate analysis for sexes
Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery	Lund, Christian; Sundet, Kjetil; Tennoe, Bjorn; Hol, Per K.; Rein, Kjell A.; Fosse, Erik; Russell, David	2005	The Annals of thoracic surgery	80	6	2126-31		Exclusion reason: No separate analysis for sexes
Changes in emerging cardiac biomarkers after an intensive lifestyle intervention	Chainani-Wu, Nita; Weidner, Gerdi; Purnell, Daniel M.; Frenda, Steven; Merritt-Worden, Terri; Pischke, Claudia; Campo, Rebecca; Kemp, Colleen; Kersh, Edward S.; Ornish, Dean	2011	The American journal of cardiology	108	4	498-507	https://dx.doi.org/10.1016/j.amjcard.2011.03.077	Exclusion reason: No cognitive assessment performed
Characteristics of neuropsychological functions in inpatients with poorly-controlled type 2 diabetes mellitus	Takeuchi, Ai; Matsushima, Eisuke; Kato, Motoichiro; Konishi, Mika; Izumiyama, Hajime; Murata, Yuji; Hirata, Yukio	2012	Journal of diabetes investigation	3	3	325-30	https://dx.doi.org/10.1111/j.2040-1124.2011.00170.x	Exclusion reason: No separate analysis for conditions
Characterization of Vascular Disease Risk in Postmenopausal Women and Its Association with Cognitive Performance	Dowling, N. M.; Gleason, C. E.; Manson, J. E.; Hodis, H. N.; Miller, V. M.; Brinton, E. A.; Neal-Perry, G.; Santoro, M. N.; Cedars, M.; Lobo, R.; Merriam, G. R.; Wharton, W.; Naftolin, F.; Taylor, H.; Harman, S. M.; Asthana, S.	2013	Plos One	8	7		10.1371/journal.pone.0068741	Exclusion reason: No separate analysis for conditions
Choice reaction time and grip strength as predictors of cardiovascular mortality in middle-aged and elderly	Shimizu, Masaki; Misumi, Munechika; Yamada, Michiko;	2018	Internal medicine journal				https://dx.doi.org/10.1111/imj.14002	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Japanese: From the Radiation Effects Research Foundation Adult Health Study	Ohishi, Waka; Yamamoto, Hideya; Kihara, Yasuki							
Chronic memory impairment after cardiac arrest outside hospital	Grubb, N. R.; O'Carroll, R.; Cobbe, S. M.; Sirel, J.; Fox, K. A.	1996	BMJ (Clinical research ed.)	313	7050	143-6		Exclusion reason: No separate analysis for conditions
Chronicity of memory impairment in long-term out-of-hospital cardiac arrest survivors	Drysdale, E. E.; Grubb, N. R.; Fox, K. A.; O'Carroll, R. E.	2000	Resuscitation	47	1	27-32		Exclusion reason: Sex of participants was not specified
Circulating Progenitor Cells and Cognitive Impairment in Men and Women with Coronary Artery Disease.	Moazzami, Kasra; Wittbrodt, Matthew T; Lima, Bruno B; Kim, Jeong Hwan; Hammadah, Muhammad; Ko, Yi-An; Obideen, Malik; Abdelhadi, Naser; Kaseer, Belal; Gafeer, M Mazen; Nye, Jonathon A; Shah, Amit J; Ward, Laura; Raggi, Paolo; Waller, Edmund K; Bremner, J Douglas; Quyyumi, Arshed A; Vaccarino, Viola	2020	Journal of Alzheimer's disease : JAD	74	2	659-668	https://dx.doi.org/10.3233/JAD-191063	Exclusion reason: No separate analysis for sexes
Clinical comparison of the General Electric-Peirce membrane lung and bubble oxygenator for prolonged cardiopulmonary bypass	Chopra, P. S.; Dufek, J. H.; Kroncke, G. M.; Dacumos, G. C.; Celesia, G. G.; Troner, S. P.; Marshall, J. R.; Jefferson, J. W.; Loring, L. L.; Kahn, D. R.	1973	Surgery	74	6	874-879		Exclusion reason: Publication was not available
Clinical features, intelligence, and memory of subcortical arteriosclerotic encephalopathy	Cui, Cheng; Zhang, Tianling; Kang, Minglan; Tao, Hong	1998	Chinese Journal of Clinical Psychology	6	1	47-48		Exclusion reason: Publication was not available

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Clinical manifestations of geriatric depression in a memory clinic: toward a proposed subtyping of geriatric depression	Dillon, Carol; Machnicki, Gerardo; Serrano, Cecilia M.; Rojas, Galeno; Vazquez, Gustavo; Allegri, Ricardo F.	2011	Journal of affective disorders	134	03-Jan	177-87	https://dx.doi.org/10.1016/j.jad.2011.05.036	Exclusion reason: No separate analysis for sexes
Cognition 6 years after surgical or medical therapy for coronary artery disease	Selnes, Ola A.; Grega, Maura A.; Bailey, Maryanne M.; Pham, Luu D.; Zeger, Scott L.; Baumgartner, William A.; McKhann, Guy M.	2008	Annals of neurology	63	5	581-90	https://dx.doi.org/10.1002/ana.21382	Exclusion reason: No separate analysis for sexes
Cognition and Exercise Training	Nct	2013						Exclusion reason: Not pertinent research (e.g., protocol registration)
Cognition and incident coronary heart disease in late midlife: The Whitehall II study	Singh-Manoux, Archana; Sabia, Severine; Kivimaki, Mika; Shipley, Martin J.; Ferrie, Jane E.; Marmot, Michael G.	2009	Intelligence	37	6	529-534		Exclusion reason: No separate analysis for sexes
Cognition of risk factors of coronary heart disease among patients at the First People's Hospital of Kashi Prefecture	Zhang, Guangwei; Wang, Zhangli; Maimaitituxun, Reyilanmuhan; Maihesuti, Ajiguli; Nizamu, Zulihuma; Yiming, Haierguli; Luo, Xianyu; Liu, Lijuan; Guo, Ziwei; Wang, Chen; Liu, Enqi; Men, Ke	2018	International Journal of Clinical and Experimental Medicine	11	10	10802-10808		Exclusion reason: No cognitive assessment performed
Cognitive ability and physical health: a Mendelian randomization study.	Hagenaars, Saskia P; Gale, Catharine R; Deary, Ian J; Harris, Sarah E	2017	Scientific reports	7	1	2651	https://dx.doi.org/10.1038/s41598-017-02837-3	Exclusion reason: No separate analysis for sexes
Cognitive and cardiovascular benefits of docosahexaenoic	Yurko-Mauro, K.	2010	Current Alzheimer research	7	3	190-6		Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
acid in aging and cognitive decline								
Cognitive and functional impairment in an older community population from Brazil: The intriguing association with frequent pain	Lopes, Marcos Antonio; Xavier, Andre Junqueira; D'Orsi, Eleonora	2016	Archives of gerontology and geriatrics	66		134-9	https://dx.doi.org/10.1016/j.archger.2016.05.010	Exclusion reason: No separate analysis for conditions
Cognitive and Physical Function by Statin Exposure in Elderly Individuals Following Acute Myocardial Infarction	Swiger, Kristopher J.; Martin, Seth S.; Tang, Fengming; Blaha, Michael J.; Blumenthal, Roger S.; Alexander, Karen P.; Arnold, Suzanne V.; Spertus, John A.	2015	Clinical cardiology	38	8	455-61	https://dx.doi.org/10.1002/clc.22423	Exclusion reason: No separate analysis for sexes
Cognitive changes in prevalent and incident cardiovascular disease: a 12-year follow-up in the Maastricht Aging Study (MAAS)	Schievink, Syenna H. J.; van Boxtel, Martin P. J.; Deckers, Kay; van Oostenbrugge, Robert J.; Verhey, Frans R. J.; Kohler, Sebastian	2017	European heart journal				https://dx.doi.org/10.1093/eurheartj/ehx365	Exclusion reason: No separate analysis for sexes
Cognitive changes with coronary artery disease: a prospective study of coronary artery bypass graft patients and nonsurgical controls	Selnes, Ola A.; Grega, Maura A.; Borowicz, Louis M., Jr.; Royall, Richard M.; McKhann, Guy M.; Baumgartner, William A.	2003	The Annals of thoracic surgery	75	5	1377-6		Exclusion reason: No separate analysis for sexes
Cognitive Decline in Older Patients With Non- ST Elevation Acute Coronary Syndrome.	Gu, Sophie Z; Beska, Benjamin; Chan, Danny; Neely, Dermot; Batty, Jonathan A; Adams-Hall, Jennifer; Mossop, Helen; Qiu, Weiliang; Kunadian, Vijay	2019	Journal of the American Heart Association	8	4	e011218-e011218	10.1161/JAHA.118.011218	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cognitive decline, cardiovascular risk factors, and neuroimaging abnormalities	De Toledo, T. C.; Alves, F.; Wajngarten, M.; Busatto Filho, G.	2005	Revista de Psiquiatria Clinica	32	3	160-169		Exclusion reason: Not available in English
Cognitive deficits and changes in neurometabolites after a lacunar infarct	van Zandvoort, M. J. E.; van der Grond, J.; Kappelle, L. J.; de Haan, E. H. F.	2005	Journal of neurology	252	2	183-90		Exclusion reason: No separate analysis for sexes
Cognitive deficits in peripheral vascular disease. A comparison of mild stroke patients and normal control subjects	Phillips, N. A.; Mate-Kole, C. C.	1997	Stroke	28	4	777-84		Exclusion reason: No separate analysis for sexes
Cognitive disorders, Depressive status and chronic complications of type 2 diabetes mellitus	Tache, M.; Tocut, S. M.; Dobjanschi, C.	2014	Romanian Journal of Diabetes, Nutrition and Metabolic Diseases	21	4	313-318	10.2478/rjdnmd-2014-0038	Exclusion reason: No separate analysis for sexes
Cognitive function after cardiac arrest and temperature management; rationale and description of a sub-study in the Target Temperature Management trial	Lilja, Gisela; Nielsen, Niklas; Friberg, Hans; Horn, Janneke; Kjaergaard, Jesper; Pellis, Tommaso; Rundgren, Malin; Wetterslev, Jorn; Wise, Matt P.; Nilsson, Fredrik; Cronberg, Tobias	2013	BMC cardiovascular disorders	13		85	https://dx.doi.org/10.1186/1471-2261-13-85	Exclusion reason: Sex of participants was not specified
Cognitive function after on or off pump coronary artery bypass grafting	Vedin, Jenny; Nyman, Hakan; Ericsson, Anders; Hylander, Susanne; Vaage, Jarle	2006	European journal of cardio-thoracic	30	2	305-10		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cognitive function after supplementation with B vitamins and long-chain omega-3 fatty acids: ancillary findings from the SU.FOL.OM3 randomized trial	Andreeva, Valentina A.; Kesse-Guyot, Emmanuelle; Barberger-Gateau, Pascale; Fezeu, Leopold; Hercberg, Serge; Galan, Pilar	2011	The American journal of clinical nutrition	94	1	278-86	https://dx.doi.org/10.3945/ajcn.110.006320	Exclusion reason: No separate analysis for sexes
Cognitive Function and Changes in Cognitive Function as Predictors of Incident Cardiovascular Disease: The Women's Health Initiative Memory Study	Leng, Xiaoyan; Espeland, Mark A.; Manson, JoAnn E.; Stefanick, Marcia L.; Gower, Emily W.; Hayden, Kathleen M.; Limacher, Marian C.; Vaughan, Leslie; Robinson, Jennifer; Wallace, Robert; Wassertheil-Smoller, Sylvia; Yaffe, Kristine; Shumaker, Sally A.	2018	The journals of gerontology. Series A, Biological sciences and medical sciences	73	6	779-785	https://dx.doi.org/10.1093/gerona/glx138	Exclusion reason: Not pertinent research (e.g., protocol registration)
COGNITIVE FUNCTION AND CORONARY HEART-DISEASE	Barry, A.; Daly, J.; Kelly, J.	1972	Med. Sci. Sports Exerc.	4	1	57-&		Exclusion reason: Publication (title or abstract) not found
Cognitive function and risks of cardiovascular disease and hypoglycaemia in patients with type 2 diabetes: the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial	de Galan, B. E.; Zoungas, S.; Chalmers, J.; Anderson, C.; Dufouil, C.; Pillai, A.; Cooper, M.; Grobbee, D. E.; Hackett, M.; Hamet, P.; Heller, S. R.; Lisheng, L.; MacMahon, S.; Mancia, G.; Neal, B.; Pan, C. Y.; Patel, A.; Poulter, N.; Travert, F.; Woodward, M.; group, Advance Collaborative	2009	Diabetologia	52	11	2328-2336	https://dx.doi.org/10.1007/s00125-009-1484-7	Exclusion reason: No separate analysis for sexes
Cognitive function in a middle aged cohort is related to higher quality dietary pattern 5 and 25 years earlier: the CARDIA study	Zhu, N.; Jacobs, D. R.; Meyer, K. A.; He, K.; Launer, L.; Reis, J. P.; Yaffe, K.; Sidney, S.; Whitmer, R. A.; Steffen, L. M.	2015	The journal of nutrition, health & aging	19	1	Aug-33	https://dx.doi.org/10.1007/s12603-014-0491-7	Exclusion reason: Does not mention any CHD in methods or analysis

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cognitive function in patients with peripheral artery disease: a prospective single-center cohort study	Hutter, I.; Kovacicova, L.; Jacomella, V.; Husmann, M.; Clemens, R.; Amann-Vesti, B.	2015	International angiology : a journal of the International Union of Angiology	34	5	459-66		Exclusion reason: Publication was not available
Cognitive function in patients with stable coronary heart disease: Related cerebrovascular and cardiovascular responses	Gayda, Mathieu; Gremeaux, Vincent; Bherer, Louis; Juneau, Martin; Drigny, Joffrey; Dupuy, Olivier; Lapierre, Gabriel; Labelle, Veronique; Fortier, Annik; Nigam, Anil	2017	PloS one	12	9	e0183791	https://dx.doi.org/10.1371/journal.pone.0183791	Exclusion reason: No separate analysis for conditions
Cognitive function in post-cardiac intensive care: patient characteristics and impact of multidisciplinary cardiac rehabilitation	Sumida, Hitoshi; Yasunaga, Yuichi; Takasawa, Kensei; Tanaka, Aya; Ida, Seiko; Saito, Tadaoki; Sugiyama, Seigo; Matsui, Kunihiko; Nakao, Koichi; Tsujita, Kenichi; Tohya, Yuji	2020	Heart and Vessels	35	7	946-956	10.1007/s00380-020-01566-4	Exclusion reason: No separate analysis for sexes
Cognitive function in survivors of out-of-hospital cardiac arrest after target temperature management at 33[degrees]C versus 36[degrees]C	Lilja G, Nielsen N. Friberg H. Horn J. Kjaergaard J. Nilsson F. Pellis T. Wetterslev J. Wise M. P. Bosch F. Bro-Jeppesen J. Brunetti I. Buratti A. F. Hassager C. Hofgren C. Insorsi A. Kuiper M. Martini A. Palmer N. Rundgren M. Rylander C. van der Veen A. Wanscher M. Watkins H. Cronberg T.	2015	Circulation	131	15	1340		Exclusion reason: Duplicate
Cognitive Function in Survivors of Out-of-Hospital Cardiac Arrest After Target Temperature	Lilja, Gisela; Nielsen, Niklas; Friberg, Hans; Horn, Janneke; Kjaergaard, Jesper; Nilsson, Fredrik; Pellis, Tommaso; Wetterslev, JÃ¸rn; Wise, Matt P.; Bosch, Frank; Bro-	2015	Circulation	131	15	1340-1349	10.1161/CIRCULATIONAHA.114.014414	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Management at 33Â°C Versus 36Â°C	Jeppesen, John; Brunetti, Iole; Buratti, Azul Forti; Hassager, Christian; Hofgren, Caisa; Insorsi, Angelo; Kuiper, Michael; Martini, Alice; Palmer, Nicki; Rundgren, Malin							
COGNITIVE FUNCTIONING AND DEPRESSIVE SYMPTOMS IN PATIENTS WITH ISCHEMIC HEART DISEASE UNDERGOING COMPREHENSIVE CARDIOLOGICAL REHABILITATION	Guzinska, K.; Bidzan, M.; Kupc, A.	2009	Acta Neuropsychol.	7	1	33-44		Exclusion reason: No separate analysis for sexes
Cognitive Functioning in Coronary Artery Disease Patients: Associations with Thyroid Hormones, N-Terminal Pro-B-Type Natriuretic Peptide and High-Sensitivity C-Reactive Protein	Burkauskas, Julius; Bunevicius, Adomas; Brozaitiene, Julija; Neverauskas, Julius; Lang, Peter; Duwors, Robert; Mickuviene, Narseta; Bunevicius, Robertas	2017	Archives of clinical neuropsychology	32	2	245-251	https://dx.doi.org/10.1093/arclin/acx004	Exclusion reason: No separate analysis for sexes
Cognitive Functioning is Associated with Triiodothyronine Concentrations in Patients with Coronary Artery Disease	Burkauskas, J.; Brozaitiene, J.; Mickuviene, N.	2015	Clin. Neuropsychol.	29	3	363-363		Exclusion reason: Not pertinent research (e.g., protocol registration)
Cognitive functions and psychological states among clinical and non-clinical subjects	Latha; Priya, R. P. Jaya	2010	Journal of the Indian Academy of Applied Psychology	36	1	123-131		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cognitive impairment among elderly coronary heart disease patients	Ahto, M.; Isoaho, R.; Puolijoki, H.; Laippala, P.; Sulkava, R.; Kivela, S. L.	1999	Gerontology	45	2	87-95		Exclusion reason: No separate analysis for conditions
Cognitive impairment and outcomes in older adult survivors of acute myocardial infarction: findings from the translational research investigating underlying disparities in acute myocardial infarction patients' health status registry	Gharacholou, S. Michael; Reid, Kimberly J.; Arnold, Suzanne V.; Spertus, John; Rich, Michael W.; Pellikka, Patricia A.; Singh, Mandeep; Holsinger, Tracey; Krumholz, Harlan M.; Peterson, Eric D.; Alexander, Karen P.	2011	American heart journal	162	5	860-869.e1	https://dx.doi.org/10.1016/j.ahj.2011.08.005	Exclusion reason: No separate analysis for sexes
Cognitive impairment before and six months after cardiac surgery increase mortality risk at median 11 year follow-up: a cohort study	Tully, P. J.; Baune, B. T.; Baker, R. A.	2013	International Journal of Cardiology	168	3	2796-2802	10.1016/j.ijcard.2013.03.123	Exclusion reason: No separate analysis for sexes
Cognitive impairment in diabetes mellitus and hypertension, a possibility of correction	Khairullin, I. Kh; Esin, R. G.; Esin, O. R.	2016	Nevrologiya, Neiropsikhiatriya, Psikhosomatika	8	3	48-52	10.14412/2074-2711-2016-3-48-52	Exclusion reason: Not available in English
Cognitive impairment in patients with coronary artery disease; comparison of montreal cognitive assessment (MoCA) and mini mental state examination (MMSE)	Eftekhari, S.S.; Hejazi, S.A.; Sharifipour, E.; Hejazi, S.F.; Talebizadeh, M.; Mostafavi, H.; Yoosefee, S.	2018	Journal of Zanjan University of Medical Sciences and Health Services	26	119	16-Dec		Exclusion reason: Does not mention any CHD in methods or analysis

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Cognitive impairment without dementia in older people: prevalence, vascular risk factors, impact on disability. The Italian Longitudinal Study on Aging	Di Carlo, A.; Baldereschi, M.; Amaducci, L.; Maggi, S.; Grigoletto, F.; Scarlato, G.; Inzitari, D.	2000	Journal of the American Geriatrics Society	48	7	775-82		Exclusion reason: No separate analysis for sexes
Cognitive impairment, chronic medical illness, and risk of mortality in an elderly cohort	Feil, Denise; Marmon, Tonya; Unutzer, Jurgen	2003	The American journal of geriatric psychiatry	11	5	551-60		Exclusion reason: No cognitive assessment performed
Cognitive outcome and quality of life one year after subarachnoid haemorrhage	McKenna, P.; Willison, J. R.; Phil, B.; Lowe, D.; Neil-Dwyer, G.	1989	Neurosurgery	24	3	361-7		Exclusion reason: No separate analysis for sexes
Cognitive outcomes five years after not undergoing coronary artery bypass graft surgery	van Dijk, Diederik; Moons, Karel G. M.; Nathoe, Hendrik M.; van Aarnhem, Egidius H. L.; Borst, Cornelius; Keizer, Annemieke M. A.; Kalkman, Cor J.; Hijman, Ron; Octopus Study, Group	2008	The Annals of thoracic surgery	85	1	Apr-60		Exclusion reason: No separate analysis for sexes
Cognitive outcomes three years after coronary artery bypass surgery: a comparison of on-pump coronary artery bypass graft surgery and nonsurgical controls	Selnes, Ola A.; Grega, Maura A.; Borowicz, Louis M., Jr.; Barry, Sarah; Zeger, Scott; Baumgartner, William A.; McKhann, Guy M.	2005	The Annals of thoracic surgery	79	4	1201-9		Exclusion reason: Sex of participants was not specified
Cognitive performance following fluoxetine treatment in depressed patients post myocardial infarction	Strik, Jacqueline J. M. H.; Honig, Adriaan; Klinkenberg, Edwin; Dijkstra, Jeanette; Jolles, Jelle	2006	Acta neuropsychiatrica	18	1	06-Jan	https://dx.doi.org/10.1111/j.0924-	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
							2708.2006.00110.x	
Cognitive Processing Speed Mediates the Effects of Cardiovascular Disease on Executive Functioning	Liebel, S. W.; Jones, E. C.; Oshri, A.; Hallowell, E. S.; Jerskey, B. A.; Gunstad, J.; Sweet, L. H.	2017	Neuropsychology	31	1	44-51	10.1037/neu0000324	Exclusion reason: Does not mention any CHD in methods or analysis
Cognitive status and future risk of frailty in older Mexican Americans	Raji, Mukaila A.; Al Snih, Soham; Ostir, Glenn V.; Markides, Kyriakos S.; Ottenbacher, Kenneth J.	2010	Journals of Gerontology Series A: Biological Sciences & Medical Sciences	65A	11	1228-1234	10.1093/gerona/glq121	Exclusion reason: Duplicate
Cognitive status and future risk of frailty in older Mexican Americans	Raji, M. A.; Al Snih, S.; Ostir, G. V.; Markides, K. S.; Ottenbacher, K. J.	2010	Journals of Gerontology - Series A Biological Sciences and Medical Sciences	65 A	11	1228-1234	10.1093/gerona/glq121	Exclusion reason: No separate analysis for sexes
Cognitive status, muscle strength, and subsequent disability in older Mexican Americans	Raji, Mukaila A.; Kuo, Yong-Fang; Snih, Soham Al; Markides, Kyriakos S.; Peek, M. Kristen; Ottenbacher, Kenneth J.	2005	Journal of the American Geriatrics Society	53	9	1462-8		Exclusion reason: No separate analysis for conditions
Community-Dwelling People Screened Positive for Dementia in Primary Care: A Comprehensive, Multivariate	Thyrian, Jochen Rene; Eichler, Tilly; Michalowsky, Bernhard; Wucherer, Diana; Reimann, Melanie; Hertel, Johannes; Richter, Steffen; Dreier, Adina; Hoffmann, Wolfgang	2016	Journal of Alzheimer's disease : JAD	52	2	609-17	https://dx.doi.org/10.3233/JAD-151076	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Descriptive Analysis Using Data from the DelpHi-Study								
Comparing cognitive and somatic symptoms of depression in myocardial infarction patients and depressed patients in primary and mental health care	Groenewold, Nynke A.; Doornbos, Bennard; Zuidersma, Marij; Vogelzangs, Nicole; Penninx, Brenda W. J. H.; Aleman, Andre; de Jonge, Peter	2013	PloS one	8	1	e53859	https://dx.doi.org/10.1371/journal.pone.0053859	Exclusion reason: No cognitive assessment performed
Comparison of Pueraria lobata with hormone replacement therapy in treating the adverse health consequences of menopause	Woo, Jean; Lau, Edith; Ho, Suzanne C.; Cheng, Francis; Chan, Cynthia; Chan, Agnes S. Y.; Haines, Christopher J.; Chan, Thomas Y. K.; Li, Martin; Sham, Aprille	2003	Menopause (New York, N.Y.)	10	4	352-61		Exclusion reason: Does not mention any CHD in methods or analysis
Contribution of vascular risk factors to the progression in Alzheimer disease	Helzner, Elizabeth P.; Luchsinger, Jose A.; Scarmeas, Nikolaos; Cosentino, Stephanie; Brickman, Adam M.; Glymour, M. Maria; Stern, Yaakov	2009	Archives of neurology	66	3	343-8	https://dx.doi.org/10.1001/archneur.66.3.343	Exclusion reason: No separate analysis for conditions
Coronary artery disease and plasma apolipoprotein E4 in mild cognitive impairment	Barekatain, Majid; Zahedian, Faezeh; Askarpour, Hedyeh; Maracy, Mohammad Reza; Hashemi-Jazi, Mohammad; Aghaye-Ghazvini, Mohammad Reza	2014	ARYA atherosclerosis	10	5	244-51		Exclusion reason: No separate analysis for sexes
Coronary artery disease is associated with cognitive decline independent of changes on magnetic resonance imaging in cognitively normal elderly adults	Zheng, Ling; Mack, Wendy J.; Chui, Helena C.; Heflin, Lara; Mungas, Dan; Reed, Bruce; DeCarli, Charles; Weiner, Michael W.; Kramer, Joel H.	2012	Journal of the American Geriatrics Society	60	3	499-504	https://dx.doi.org/10.1111/j.1532-5415.2011.03839.x	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Coronary heart disease is associated with non-amnestic mild cognitive impairment	Roberts, Rosebud O.; Knopman, David S.; Geda, Yonas E.; Cha, Ruth H.; Roger, Veronique L.; Petersen, Ronald C.	2010	Neurobiology of aging	31	11	1894-902	https://dx.doi.org/10.1016/j.neurobiolaging.2008.10.018	Exclusion reason: No separate analysis for conditions
Coronary heart disease is associated with regional grey matter volume loss: implications for cognitive function and behaviour	Almeida, O. P.; Garrido, G. J.; Beer, C.; Lautenschlager, N. T.; Arnolda, L.; Lenzo, N. P.; Campbell, A.; Flicker, L.	2008	Internal medicine journal	38	7	599-606	https://dx.doi.org/10.1111/j.1445-5994.2008.01713.x	Exclusion reason: Brief report
Cost-effectiveness and population impact of statins for primary prevention in adults aged 75 years or older in the United States	Odden, Michelle C.; Pletcher, Mark J.; Coxson, Pamela G.; Thekkethala, Divya; Guzman, David; Heller, David; Goldman, Lee; Bibbins-Domingo, Kirsten	2015	Annals of internal medicine	162	8	533-41	https://dx.doi.org/10.7326/M14-1430	Exclusion reason: No cognitive assessment performed
Dementia and Depression with Ischemic Heart Disease: A Population-Based Longitudinal Study Comparing Interventional Approaches to Medical Management	Mutch, W. A. C.; Fransoo, R. R.; Campbell, B. I.; Chateau, D. G.; Sirski, M.; Warrian, R. K.	2011	PLoS One	6	2	7	10.1371/journal.pone.0017457	Exclusion reason: No cognitive assessment performed
Dementia and other chronic diseases in older adults in Havana and Matanzas: the 10/66 study in Cuba	Llibre, Juan de Jesus; Valhuerdi, Adolfo; Calvo, Marina; Garcia, Rosa M.; Guerra, Milagros; Laucerique, Tania; Lopez, Ana M.; Llibre, Juan Carlos; Noriega, Lisseth; Sanchez, Isis Y.; Porto, Rudbeskia; Arencibia, Francis; Marcheco, Beatriz; Moreno, Carmen	2011	MEDICC review	13	4	30-Jul		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Depression increases mortality and morbidity in acute life-threatening medical illness	Silverstone, P. H.	1990	Journal of psychosomatic research	34	6	651-7		Exclusion reason: No cognitive assessment performed
Depressive symptoms and associated factors in a cognitively normal elderly population: the Tajiri Project	Ambo, H.; Meguro, K.; Ishizaki, J.; Shimada, M.; Yamaguchi, S.; Sekita, Y.; Yamadori, A.	2001	International journal of geriatric psychiatry	16	8	780-8		Exclusion reason: No cognitive assessment performed
Depressive Symptoms and Longitudinal Changes in Cognition: Women's Health Initiative Study of Cognitive Aging	Goveas, Joseph S.; Espeland, Mark A.; Hogan, Patricia E.; Tindle, Hilary A.; Shih, Regina A.; Kotchen, Jane M.; Robinson, Jennifer G.; Barnes, Deborah E.; Resnick, Susan M.	2014	Journal of geriatric psychiatry and neurology	27	2	94-102	https://dx.doi.org/10.1177/0891988714522697	Exclusion reason: No separate analysis for conditions
Deriving a model of the necessity to hospitalize nursing home residents	O'Malley, A. J.; Marcantonio, E. R.; Murkofsky, R. L.; Caudry, D. J.; Buchanan, J. L.	2007	Research on Aging	29	6	606-625		Exclusion reason: Not pertinent research (e.g., protocol registration)
Design and rationale of the EBBINGHAUS trial: A phase 3, double-blind, placebo-controlled, multicenter study to assess the effect of evolocumab on cognitive function in patients with clinically evident cardiovascular disease and receiving statin background lipid-lowering therapyA cognitive study of patients enrolled in the FOURIER trial	Giugliano, R. P.; Mach, F.; Zavitz, K.; Kurtz, C.; Schneider, J.; Wang, H.; Keech, A.; Pedersen, T. R.; Sabatine, M. S.; Sever, P. S.; Honarpour, N.; Wasserman, S. M.; Ott, B. R.; Investigators, Ebbinghaus	2017	Clin. Cardiol.	40	2	59-65	10.1002/clc.22678	Exclusion reason: No separate analysis for sexes
Development of a cerebrovascular magnetic	Vemuri, Prashanthi; Lesnick, Timothy G.; Przybelski, Scott A.; Graffâ€• Radford, Jonathan; Reid, Robert I.; Lowe, Val J.; Zuk,	2018	Annals of Neurology	84	5	705-716	10.1002/ana.25346	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
resonance imaging biomarker for cognitive aging.	Samantha M.; Senjem, Matthew L.; Schwarz, Christopher G.; Gunter, Jeffrey L.; Kantarci, Kejal; Machulda, Mary M.; Mielke, Michelle M.; Petersen, Ronald C.; Knopman, David S.; Jack, Clifford R.; Graff-Radford, Jonathan; Jack, Clifford R Jr							
Dietary fat intake in relation to cognitive change in high-risk women with cardiovascular disease or vascular factors	Vercambre, M. N.; Grodstein, F.; Kang, J. H.	2010	European journal of clinical nutrition	64	10	1134-40	https://dx.doi.org/10.1038/ejcn.2010.113	Exclusion reason: No separate analysis for conditions
Disturbed cerebral function in menopause and its prevention	Altieri, M.; Bogousslavsky, J.	1997	Praxis	86	36	1378-1382		Exclusion reason: Publication (title or abstract) not found
Do management strategies for coronary artery disease influence 6-year cognitive outcomes?	Selnes, Ola A.; Grega, Maura A.; Bailey, Maryanne M.; Pham, Luu D.; Zeger, Scott L.; Baumgartner, William A.; McKhann, Guy M.	2009	The Annals of thoracic surgery	88	2	445-454	https://dx.doi.org/10.1016/j.athoracsur.2009.04.061	Exclusion reason: No separate analysis for sexes
Do patients with acute medical conditions have the capacity to give informed consent for emergency medicine research?	Smithline, H. A.; Mader, T. J.; Crenshaw, B. J.	1999	Academic emergency medicine	6	8	776-80		Exclusion reason: No separate analysis for sexes
Does 8-Foot Walk Time Predict Cognitive Decline in Older Mexican Americans?	Alfaro-Acha, Ana; Al Snih, Soham; Raji, Mukaila A.; Markides, Kyriakos S.; Ottenbacher, Kenneth J.	2007	Journal of the American Geriatrics Society	55	2	245-251	http://dx.doi.org/10.1111/j.1532-5415.2007.01039.x	Exclusion reason: Duplicate

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Does 8-foot walk time predict cognitive decline in older Mexicans Americans?	Alfaro-Acha, Ana; Al Snih, Soham; Raji, Mukaila A.; Markides, Kyriakos S.; Ottenbacher, Kenneth J.	2007	Journal of the American Geriatrics Society	55	2	245-51		Exclusion reason: No separate analysis for sexes
Does caregiving stress affect cognitive function in older women?	Lee, Sunmin; Kawachi, Ichiro; Grodstein, Francine	2004	The Journal of nervous and mental disease	192	1	Jul-51		Exclusion reason: Not pertinent research (e.g., protocol registration)
Does IQ explain socioeconomic inequalities in health? Evidence from a population based cohort study in the west of Scotland	Batty, G. D.; Der, G.; Macintyre, S.; Deary, L.	2006	Br. Med. J.	332	7541	580-583	10.1136/bmj.38723.660637.AE	Exclusion reason: No separate analysis for sexes
Driving-Related Cognitive Performance in Older Adults with Pharmacologically Treated Cardiovascular Disease	Viamonte, Sarah; Vance, David; Wadley, Virginia; Roenker, Dan; Ball, Karlene	2010	Clinical gerontologist	33	2	109-123		Exclusion reason: No separate analysis for sexes
Early neurological outcomes after simultaneous coronary artery bypass surgery and carotid endarterectomy	Maleva, O.V.; Trubnikova, O.A.; Syrova, I.D.; Golovin, A.A.; Barbarash, O.L.; Barbarash, L.S.	2019	Kardiologiya i Serdechno-Sosudistaya Khirurgiya	12	5	386-394	10.17116/kardio201912051386	Exclusion reason: Not available in English
Early versus late extubation after coronary artery bypass grafting: effects on cognitive function	Dumas, A.; Dupuis, G. H.; Searle, N.; Cartier, R.	1999	Journal of cardiothoracic and vascular anesthesia	13	2	130-5		Exclusion reason: No separate analysis for sexes
EEG and clinical factors associated with mild cognitive	Tarasova, I.V.; Trubnikova, O.A.; Barbarash, O.L.	2019	Dementia and Geriatric	46	06-May	275-284	10.1159/000493787	Exclusion reason: Duplicate

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
impairment in coronary artery disease patients			Cognitive Disorders					
EEG and Clinical Factors Associated with Mild Cognitive Impairment in Coronary Artery Disease Patients.	Tarasova, IrinaÂ V.; Trubnikova, OlgaÂ A.; Barbarash, OlgaÂ L.	2018	Dementia & Geriatric Cognitive Disorders	46	06-May	275-284	10.1159/000493787	Exclusion reason: Men only
Effect of Cardiac Function on Cognition and Brain Structural Changes in Dementia	Oh, J. E.; Shin, J. W.; Sohn, E. H.; Jung, J. O.; Jeong, S. H.; Song, H. J.; Kim, J. M.; Lee, A. Y.	2012	J. Clin. Neurol.	8	2	123-129	10.3988/jcn.2012.8.2.123	Exclusion reason: Does not mention any CHD in methods or analysis
Effect of cardiac rehabilitation on cognitive function in elderly patients with cardiovascular diseases	Fujiyoshi, Kazuhiro; Minami, Yoshiyasu; Yamaoka-Tojo, Minako; Kutsuna, Toshiki; Obara, Shinichi; Aoyama, Akihiro; Ako, Junya	2020	Plos One	15	5	e0233688	10.1371/journal.pone.0233688	Exclusion reason: No separate analysis for conditions
Effect of Cilostazol on Incident Dementia in Elderly Men and Women with Ischemic Heart Disease	Kim, Mi-Young; Noh, Yoojin; Son, Sang Joon; Shin, Sooyoung; Paik, Hee-Young; Lee, Sukhyang; Jung, Yi-Sook	2018	Journal of Alzheimer's disease : JAD	63	2	635-644	https://dx.doi.org/10.3233/JAD-170895	Exclusion reason: No cognitive assessment performed
Effect of cognitive status on exercise performance and quality of life in patients with symptomatic peripheral artery disease	Gardner, Andrew W.; Waldstein, Shari R.; Montgomery, Polly S.; Zhao, Yan D.	2016	Journal of vascular surgery	63	1	98-104	https://dx.doi.org/10.1016/j.jvs.2015.08.064	Exclusion reason: No separate analysis for sexes
Effect of Different Anesthetics on Cognitive Function After Off-Pump Coronary Artery Bypass Grafting	Yi, L.; Yao, S.; Chen, X.; Wu, Q.; Huang, M.; Wang, T.; Shi, Q.; Guo, C.	2018	Medical Journal of Wuhan University	39	4	627-631	10.14188/j.1671-8852.2018.0068	Exclusion reason: Publication was not available

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Effect of solifenacin on cognition in geriatric patients: Results of the non-interventional study "vesicare in geriatric application: Vega"	Hampel C, Burger M. Buerger K. Nowak C. Betz D. Vogel M.	2012	Urology	80	3 SUPPL. 1	S10		Exclusion reason: Publication (title or abstract) not found
Effects of Anthocyanin Supplementation on Serum Lipids, Glucose, Markers of Inflammation and Cognition in Adults With Increased Risk of Dementia - A Pilot Study.	Bergland, Anne Katrine; Soennesyn, Hogne; Dalen, Ingvild; Rodriguez-Mateos, Ana; Berge, Rolf Kristian; Giil, Lasse Melvaer; Rajendran, Lawrence; Siow, Richard; Tassotti, Michele; Larsen, Alf Inge; Aarsland, Dag	2019	Frontiers in genetics	10	1015606 21	536	https://dx.doi.org/10.3389/fgene.2019.00536	Exclusion reason: No separate analysis for sexes
Effects of cognitive training on change in accuracy in inductive reasoning ability	Boron, J. B.; Turiano, N. A.; Willis, S. L.; Schaie, K. W.	2007	Journals of Gerontology Series B: Psychological Sciences & Social Sciences	62	3	P179-86		Exclusion reason: No separate analysis for conditions
Effects of death within 11 years on cognitive performance in old age	Rabbitt, Patrick; Watson, Peter; Donlan, Chris; Mc Innes, Lynn; Horan, Michael; Pendleton, Neil; Clague, John	2002	Psychology and aging	17	3	468-81		Exclusion reason: No separate analysis for conditions
Electrocardiogram Changes of Donepezil Administration in Elderly Patients with Ischemic Heart Disease	Wang, Deguo; Wu, Yong; Wang, Ancai; Chen, Yueyun; Zhang, Ting; Hu, Nengwei	2018	Cardiology research and practice	2018		9141320	https://dx.doi.org/10.1155/2018/9141320	Exclusion reason: No cognitive assessment performed
Elevated biochemical markers of myocardial injury are not associated with postoperative	Hudetz, J. A.; Amole, O.; Riley, A. V.; Patterson, K. M.; Pagel, P. S.	2011	Journal of Anesthesia	2	5	134	10.4172/2155-6148.1000134	Exclusion reason: Men only

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
cognitive dysfunction after coronary artery surgery			and Clinical Research					
Elevated natriuretic peptide levels and cognitive function in community-dwelling older adults	Daniels, Lori B.; Laughlin, Gail A.; Kritz-Silverstein, Donna; Clopton, Paul; Chen, Wei-Chung; Maisel, Alan S.; Barrett-Connor, Elizabeth	2011	The American journal of medicine	124	7	670.e1-8	https://dx.doi.org/10.1016/j.amjmed.2011.02.027	Exclusion reason: No separate analysis for sexes
Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery	Hudetz, Judith A.; Gandhi, Sweeta D.; Iqbal, Zafar; Patterson, Kathleen M.; Pagel, Paul S.	2011	Journal of anesthesia	25	1	09-Jan	https://dx.doi.org/10.1007/s00540-010-1042-y	Exclusion reason: Men only
Endostatin as a Mediator Between Endothelial Function and Cognitive Performance in Those at Risk for Vascular Cognitive Impairment.	Isaacs-Trepanier, Cameron; Saleem, Mahwesh; Herrmann, Nathan; Swardfager, Walter; Oh, Paul I; Goldstein, Benjamin I; Mitchell, Jane; Sugamori, Kim S; Lanctot, Krista L	2020	Journal of Alzheimer's disease : JAD		9814863		https://dx.doi.org/10.3233/JAD-200058	Exclusion reason: No separate analysis for sexes
Ethnogeriatric issues in neuropsychologic assessment and rehabilitation	Banks, M. E.; Ackerman, R. J.	1997	Topics in Geriatric Rehabilitation	12	3	47-61		Exclusion reason: Not pertinent research (e.g., protocol registration)
Evaluation of coated oxygenators in cardiopulmonary-bypass systems and their impact on neurocognitive function	Khosravi, Amir; Skrabal, Christian A.; Westphal, Bernd; Kundt, Guenther; Greim, Brigitte; Kunesch, Erwin; Liebold, Andreas; Steinhoff, Gustav	2005	Perfusion	20	5	249-54		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Event-Related Desynchronization/Synchronization of Electrical Brain Activity during Modified Odd-Ball Tasks in Patients with Coronary Artery Disease and Mild Cognitive Impairment	Tarasova, I.V.; Volf, N.V.; Akbirov, R.M.; Kukhareva, I.N.; Barbarash, O.L.	2020	Human Physiology	46	1	58-65	10.1134/S0362119719060136	Exclusion reason: Men only
Everyday cognitive functioning in cardiac patients: relationships between self-report, report of a significant other and cognitive test performance	Elliott, Peter C.; Smith, Geoff; Ernest, Christine S.; Murphy, Barbara M.; Worcester, Marian U. C.; Higgins, Rosemary O.; Le Grande, Michael R.; Goble, Alan J.; Andrewes, David; Tatoulis, James	2010	Neuropsychology, development, and cognition. Section B, Aging, neuropsychology and cognition	17	1	71-88	https://dx.doi.org/10.1080/13825580903009089	Exclusion reason: No separate analysis for conditions
Executive dysfunction, heart disease burden, and remission of geriatric depression	Alexopoulos, George S.; Kiosses, Dimitris N.; Murphy, Christopher; Heo, Moonseong	2004	Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology	29	12	2278-84		Exclusion reason: No separate analysis for sexes
Executive function, but not memory, associates with incident coronary heart disease and stroke	Rostamian, Somayeh; van Buchem, Mark A.; Westendorp, Rudi G. J.; Jukema, J. Wouter; Mooijaart, Simon P.; Sabayan, Behnam; de Craen, Anton J. M.	2015	Neurology	85	9	783-9	https://dx.doi.org/10.1212/WNL.0000000000001895	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Exercise self-efficacy, habitual physical activity, and fear of falling in patients with coronary heart disease	Lapier, Tanya Kinney; Cleary, Kimberly; Kidd, Joshua	2009	Cardiopulmonary physical therapy journal	20	4	11-May		Exclusion reason: No separate analysis for sexes
Exploratory Analyses of Cerebral Gray Matter Volumes After Out-of-Hospital Cardiac Arrest in Good Outcome Survivors.	Byron-Alhassan, Aziza; Tulloch, Heather E; Collins, Barbara; Quinlan, Bonnie; Fang, Zhuo; Chakraborty, Santanu; Le May, Michel; Duchesne, Lloyd; Smith, Andra M	2020	Frontiers in psychology	11	10155090 2	856	https://dx.doi.org/10.3389/fpsyg.2020.00856	Exclusion reason: No separate analysis for sexes
Exploring Cognitive Concomitants of Mental Fatigue in Patients with Coronary Artery Disease	Burkauskas, Julius; Bunevicius, Adomas; Brozaitiene, Julija; Neverauskas, Julius; Fineberg, Naomi A.; Wellsted, David; Bunevicius, Robertas; Mickuviene, Narseta	2018	Neuropsychobiology			10-Jan	https://dx.doi.org/10.1159/000489713	Exclusion reason: Duplicate
Factors influencing employment after minor stroke and NSTEMI	Morsund, Ã….H.; EllekjÃ¦r, H.; Gramstad, A.; Reiestad, M.T.; Midgard, R.; Sando, S.B.; Jonsbu, E.; NÃ¸ss, H.	2020	Journal of Stroke and Cerebrovascular Diseases	29	9		10.1016/j.jstrokecerebrovasdis.2020.105036	Exclusion reason: No separate analysis for sexes
Falls and cognitive decline in Mexican Americans 75 years and older	Padubidri, Anokha; Al Snih, Soham; Samper-Ternent, Rafael; Markides, Kyriakos S.; Ottenbacher, Kenneth J.; Raji, Mukaila A.	2014	Clinical interventions in aging	9		719-26	https://dx.doi.org/10.2147/CIA.S59448	Exclusion reason: No separate analysis for conditions
Features of piribedil use in the treatment of mild cognitive impairments in patients with chronic heart failure	Akimova Ns, Martinovich T. V. Persashvili D. G. Shvarts Y. G.	2014		10	4	406		Exclusion reason: Not available in English

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Female Gender Is Associated With Impaired Quality of Life 1 Year After Coronary Artery Bypass Surgery	Bute, Barbara Phillips; Mathew, Joseph; Blumenthal, James A.; Welsh-Bohmer, Kathleen; White, William D.; Mark, Daniel; Landolfo, Kevin; Newman, Mark F.	2003	Psychosomatic Medicine	65	6	944-951	http://dx.doi.org/10.1097/01.PSY.0000097342.24933.A2	Exclusion reason: Does not mention any CHD in methods or analysis
Frailty in patients with acute coronary syndrome: comparison between tools for comprehensive geriatric assessment and the Tilburg Frailty Indicator	Uchmanowicz, Izabella; Lisiak, Magdalena; Wontor, Radoslaw; Loboz-Grudzien, Krystyna	2015	Clinical interventions in aging	10		521-9	https://dx.doi.org/10.2147/CIA.S78365	Exclusion reason: No separate analysis for sexes
Frequency and predictors of cognitive decline in patients undergoing coronary artery bypass graft surgery	Habib, Sultana; Khan, Arif ur Rehman; Afridi, M. Iqbal; Saeed, Anum; Jan, Agha Fahad; Amjad, Najma	2014	Journal of the College of Physicians and Surgeons--Pakistan : JCPSP	24	8	543-8	https://dx.doi.org/08.2014/JCPSP.543548	Exclusion reason: No separate analysis for sexes
Functional disability and cognitive impairment after hospitalization for myocardial infarction and stroke	Levine, Deborah A.; Davydow, Dimitry S.; Hough, Catherine L.; Langa, Kenneth M.; Rogers, Mary A. M.; Iwashyna, Theodore J.	2014	Circulation. Cardiovascular quality and outcomes	7	6	863-71	https://dx.doi.org/10.1161/HCQ.000000000000008	Exclusion reason: Sex of participants was not specified
Functional disability, cognitive impairment, and depression after hospitalization for pneumonia	Davydow, Dimitry S.; Hough, Catherine L.; Levine, Deborah A.; Langa, Kenneth M.; Iwashyna, Theodore J.	2013	The American journal of medicine	126	7	615-24.e5	https://dx.doi.org/10.1016/j.amjmed.2012.12.006	Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Functional health and white matter hyperintensities as effect modifiers of blood pressure-lowering on cognitive function and vascular events in older Secondary Prevention of Small Subcortical Strokes trial participants	Blum MR, Scherzer R, Ikeme JC, Benavente OR, McClure LA, Peralta CA, Odden MC	2020						Exclusion reason: No separate analysis for conditions
Gait Speed Test and Cognitive Decline in Frail Women With Acute Myocardial Infarction.	Mone, Pasquale; Pansini, Antonella	2020	The American journal of the medical sciences		3l2, 0370 506		https://dx.doi.org/10.1016/j.amjms.2020.03.021	Exclusion reason: Not pertinent research (e.g., protocol registration)
Gender-specific secondary prevention? Differential psychosocial risk factors for major cardiovascular events	Kure, Christina E.; Chan, Yih-Kai; Ski, Chantal F.; Thompson, David R.; Carrington, Melinda J.; Stewart, Simon	2016	Open heart	3	1	e00035 6	https://dx.doi.org/10.1136/openhrt-2015-000356	Exclusion reason: No separate analysis for conditions
Generalized atherosclerosis, cognitive decline, and depressive symptoms in old age	Vinkers, D. J.; Stek, M. L.; van der Mast, R. C.; de Craen, A. J. M.; Le Cessie, S.; Jolles, J.; Westendorp, R. G. J.; Gussekloo, J.	2005	Neurology	65	1	107-12		Exclusion reason: No separate analysis for sexes
Health related quality of life after conservative or invasive treatment of inducible postinfarction ischaemia	Mortensen Os, Madsen J. K. Haghfelt T. Grande P. Saunamaki K. Haunso S. Hjelms E. Arendrup H.	2000	Heart (british cardiac society)	84	5	535		Exclusion reason: No cognitive assessment performed
Health related quality of life after conservative or invasive treatment of inducible postinfarction ischaemia. DANAMI study group	Mortensen, O. S.; Madsen, J. K.; Haghfelt, T.; Grande, P.; Saunamaki, K.; Haunso, S.; Hjelms, E.; Arendrup, H.	2000	Heart (British Cardiac Society)	84	5	535-40		Exclusion reason: Duplicate

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Health status of the older population in Estonia	Saks, K.; Kolk, H.; Allev, R.; Soots, A.; Koiv, K.; Paju, I.; Jaanson, K.; Schneider, G.	2001	Croatian medical journal	42	6	663-8		Exclusion reason: No separate analysis for conditions
Heart diseases and long-term risk of dementia and Alzheimer's disease: a population-based CAIDE study	Rusanen, Minna; Kivipelto, Miia; Levalahti, Esko; Laatikainen, Tiina; Tuomilehto, Jaakko; Soininen, Hilkka; Ngandu, Tiia	2014	Journal of Alzheimer's disease : JAD	42	1	183-91	https://dx.doi.org/10.3233/JAD-132363	Exclusion reason: No separate analysis for sexes
High Postoperative Serum Cortisol Level Is Associated with Increased Risk of Cognitive Dysfunction Early after Coronary Artery Bypass Graft Surgery: A Prospective Cohort Study	Mu, D. L.; Li, L. H.; Wang, D. X.; Li, N.; Shan, G. J.; Li, J.; Yu, Q. J.; Shi, C. X.	2013	Plos One	8	10		10.1371/journal.pone.0077637	Exclusion reason: No separate analysis for sexes
High Sensitivity Cardiac Troponin T and Cognitive Function in the Oldest Old: The Leiden 85-Plus Study	Bertens, A. S.; Sabayan, B.; de Craen, A. J. M.; Van der Mast, R. C.; Gussekloo, J.	2017	J. Alzheimers Dis.	60	1	235-242	10.3233/jad-170171	Exclusion reason: No separate analysis for sexes
High-sensitivity cardiac troponin T is associated with cognitive decline in older adults at high cardiovascular risk	Wijsman, Liselotte W.; de Craen, Anton Jm; Trompet, Stella; Sabayan, Behnam; Muller, Majon; Stott, David J.; Ford, Ian; Welsh, Paul; Westendorp, Rudi Gj; Jukema, J. Wouter; Sattar, Naveed; Mooijaart, Simon P.	2016	European journal of preventive cardiology	23	13	1383-92	https://dx.doi.org/10.1177/2047487316632364	Exclusion reason: No separate analysis for sexes
Homocysteine and C-reactive protein are not markers of cognitive impairment in patients with major cardiovascular disease	Silbert, Brendan; Evered, Lisbeth; Scott, David A.; McCutcheon, Craig; Jamrozik, Konrad	2008	Dementia and geriatric cognitive disorders	25	4	309-16	https://dx.doi.org/10.1159/000119105	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Homocysteine, Grey Matter and Cognitive Function in Adults with Cardiovascular Disease	Ford, A. H.; Garrido, G. J.; Beer, C.; Lautenschlager, N. T.; Arnolda, L.; Flicker, L.; Almeida, O. P.	2012	PLoS One	7	3	7	10.1371/journal.pone.0033345	Exclusion reason: No separate analysis for sexes
Hormone replacement therapy and cognitive performance: The role of homocysteine	Whitmer, R. A.; Haan, M. N.; Miller, J. W.; Yaffe, K.	2003	J. Gerontol. Ser. A-Biol. Sci. Med. Sci.	58	4	324-330		Exclusion reason: No separate analysis for conditions
Hostility disturbs learning	Shimojima, Yumi; Tujii, Takeo; Yanagisawa, Atsuo; Tajino, Kazuhiro; Kanda, Hiroko; Yamagami, Masako	2003	Perceptual and motor skills	96	2	616-22		Exclusion reason: Not pertinent research (e.g., protocol registration)
Impact of cardiovascular risk factors on cognitive function: the Tromso study	Arntzen, K. A.; Schirmer, H.; Wilsgaard, T.; Mathiesen, E. B.	2011	European journal of neurology	18	5	737-43	https://dx.doi.org/10.1111/j.1468-1331.2010.03263.x	Exclusion reason: Duplicate
Impaired Cerebral Hemodynamics and Cognitive Performance in Patients with Atherothrombotic Disease	Haratz, Salo; Weinstein, Galit; Molshazki, Noa; Beeri, Michal Schnaider; Ravona-Springer, Ramit; Marzeliak, Oleg; Goldbourt, Uri; Tanne, David	2015	Journal of Alzheimer's disease : JAD	46	1	137-44	https://dx.doi.org/10.3233/JAD-150052	Exclusion reason: Men only
Impaired Cerebrovascular Function in Coronary Artery Disease Patients and Recovery Following Cardiac Rehabilitation	Anazodo, U. C.; Shoemaker, J. K.; Suskin, N.; Ssali, T.; Wang, D. J. J.; St Lawrence, K. S.	2016	Front. Aging Neurosci.	7		13	10.3389/fnagi.2015.00224	Exclusion reason: No separate analysis for sexes
Improved mental functioning with Premarin therapy in atherosclerosis	Evans, Ray B.; Marmorston, Jessie	1963	Proceedings of the Society for Experimenta	113		698-703	http://dx.doi.org/10.3181/003	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
			l Biology & Medicine				79727-113-28466	
Improvements in Cognitive Function Following Cardiac Rehabilitation for Older Adults With Cardiovascular Disease	Stanek, K. M.; Gunstad, J.; Spitznagel, M. B.; Waechter, D.; Hughes, J. W.; Luyster, F.; Josephson, R.; Rosneck, J.	2011	Int. J. Neurosci.	121	2	86-93	10.3109/00207454.2010.531893	Exclusion reason: No separate analysis for sexes
Incidence and severity of cognitive deficits in cardiac arrest survivors	Sauve, M. J.	1992	Heart & Lung	21	3	293-293		Exclusion reason: Publication (title or abstract) not found
Independent vascular and cognitive risk factors for postoperative delirium	Rudolph, James L.; Jones, Richard N.; Rasmussen, Lars S.; Silverstein, Jeffrey H.; Inouye, Sharon K.; Marcantonio, Edward R.	2007	The American journal of medicine	120	9	807-13		Exclusion reason: No separate analysis for conditions
Inferential processing of context: studies of cognitively impaired subjects	LeDoux, J. F.; Blum, C.; Hirst, W.	1983	Brain and language	19	2	216-24		Exclusion reason: Sex of participants was not specified
Influence of cardiopulmonary bypass on the state of cognitive functions in patients with ischemic heart disease	Buziashvili, Yu I.; Ambat'ello, S. G.; Aleksakhina, Yu A.; Pashchenkov, M. V.	2006	Neuroscienc e and behavioral physiology	36	2	107-13		Exclusion reason: Men only
Influence of cerebral white matter hyperintensities on cognitive impairment in elderly medical patients	Shibata, Koichi; Nishimura, Yoshiko; Otsuka, Kuniaki; Sakura, Hiroshi	2017	Geriatrics & gerontology international	17	10	1488-1493	https://dx.doi.org/10.1111/ggi.12900	Exclusion reason: No separate analysis for sexes
Influence of mild cognitive impairment on activities of daily living in patients with cardiovascular disease	Ishihara, Kodai; Izawa, Kazuhiro P.; Kitamura, Masahiro; Shimogai, Takayuki; Kanejima, Yuji; Morisawa, Tomoyuki; Shimizu, Ikki	2019	Heart and Vessels	34	12	1944-1951	10.1007/s00380-019-01437-7	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
In-hospital cardiac arrest leads to chronic memory impairment	O'Reilly, Samantha M.; Grubb, Neil R.; O'Carroll, Ronan E.	2003	Resuscitation	58	1	Sep-73		Exclusion reason: No separate analysis for sexes
Insulin Resistance and Future Cognitive Performance and Cognitive Decline in Elderly Patients with Cardiovascular Disease	Lutski, Miri; Weinstein, Galit; Goldbourt, Uri; Tanne, David	2017	Journal of Alzheimer's disease : JAD	57	2	633-643	https://dx.doi.org/10.3233/JAD-161016	Exclusion reason: No separate analysis for sexes
Integrated treatment approach improves cognitive function in demented and clinically depressed patients	Bragin, V.; Chemodanova, M.; Dzhafarova, N.; Bragin, I.; Czerniawski, J. L.; Aliev, G.	2005	American Journal of Alzheimer's Disease and other Dementias	20	1	21-26	10.1177/1533317505020001 03	Exclusion reason: No separate analysis for sexes
Interleukin-6 and C-reactive protein as predictors of cognitive decline in late midlife	Singh-Manoux, Archana; Dugravot, Aline; Brunner, Eric; Kumari, Meena; Shipley, Martin; Elbaz, Alexis; Kivimaki, Mika	2014	Neurology	83	6	486-93	https://dx.doi.org/10.1212/WNL.0000000000000665	Exclusion reason: Does not mention any CHD in methods or analysis
Is there cognitive decline 1 year after CABG? Comparison with surgical and nonsurgical controls	McKhann, G. M.; Grega, M. A.; Borowicz, L. M., Jr.; Bailey, M. M.; Barry, S. J. E.; Zeger, S. L.; Baumgartner, W. A.; Selnes, O. A.	2005	Neurology	65	7	991-9		Exclusion reason: No separate analysis for sexes
Lack of associations between modifiable risk factors and dementia in the very old: findings from the Cambridge City over-75s cohort study	Deckers, Kay; Kohler, Sebastian; van Boxtel, Martin; Verhey, Frans; Brayne, Carol; Fleming, Jane; collaboration, Cc C. study	2017	Aging & mental health			07-Jan	https://dx.doi.org/10.1080/13607863.2017.1280767	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Lipid Peroxidation Markers in Coronary Artery Disease Patients with Possible Vascular Mild Cognitive Impairment	Suridjan, Ivonne; Herrmann, Nathan; Adibfar, Alex; Saleem, Mahwesh; Andreazza, Ana; Oh, Paul I.; Lanctot, Krista L.	2017	Journal of Alzheimer's disease : JAD	58	3	885-896	https://dx.doi.org/10.3233/JAD-161248	Exclusion reason: No separate analysis for conditions
Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery	Newman, Mark F.; Kirchner, Jerry L.; Phillips-Bute, Barbara; Gaver, Vincent; Grocott, Hilary; Jones, Robert H.; Mark, Daniel B.; Reves, Joseph G.; Blumenthal, James A.	2001	The New England Journal of Medicine	344	6	395-402	http://dx.doi.org/10.1056/NEJM200102083440601	Exclusion reason: Does not mention any CHD in methods or analysis
Longitudinal Changes in Regional Cerebral Perfusion and Cognition After Cardiac Operation.	Smith, Patrick J; Browndyke, Jeffrey N; Monge, Zachary A; Harshbarger, Todd B; James, Michael L; Gaca, Jeffrey G; Alexander, John H; Berger, Miles M; Newman, Mark F; Milano, Carmelo A; Mathew, Joseph P; Neurologic Outcomes Research Group (NORG)	2019	The Annals of thoracic surgery	107	1	112-118	https://dx.doi.org/10.1016/j.athoracsur.2018.07.056	Exclusion reason: No separate analysis for sexes
Longitudinal cognitive performance in older adults with cardiovascular disease: evidence for improvement in heart failure	Stanek, Kelly M.; Gunstad, John; Paul, Robert H.; Poppas, Athena; Jefferson, Angela L.; Sweet, Lawrence H.; Hoth, Karin F.; Haley, Andreana P.; Forman, Daniel E.; Cohen, Ronald A.	2009	The Journal of cardiovascular nursing	24	3	192-7	https://dx.doi.org/10.1097/JCN.0b013e31819b54de	Exclusion reason: No separate analysis for sexes
Longitudinal Cognitive Trajectories of Women Veterans from the Women's Health Initiative Memory Study	Padula, Claudia B.; Weitlauf, Julie C.; Rosen, Allyson C.; Reiber, Gayle; Cochrane, Barbara B.; Naughton, Michelle J.; Li, Wenjun; Rissling, Michelle; Yaffe, Kristine; Hunt, Julie R.; Stefanick, Marcia L.; Goldstein, Mary K.; Espeland, Mark A.	2016	The Gerontologist	56	1	115-25	https://dx.doi.org/10.1093/geront/gnv663	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease	Okonkwo, Ozioma C.; Cohen, Ronald A.; Gunstad, John; Tremont, Geoffrey; Alosco, Michael L.; Poppas, Athena	2010	Cerebrovascular diseases (Basel, Switzerland)	30	4	362-73	https://dx.doi.org/10.1159/000319564	Exclusion reason: No separate analysis for sexes
Long-term effects of brief hypoxia due to cardiac arrest: Hippocampal reductions and memory deficits	Stamenova, Vess; Nicola, Raneen; Aharon-Peretz, Judith; Goldsher, Dorith; Kapeliovich, Michael; Gilboa, Asaf	2018	Resuscitation	126		65-71	https://dx.doi.org/10.1016/j.resuscitation.2018.02.016	Exclusion reason: No separate analysis for sexes
Long-term neurological outcome of out-of-hospital cardiac arrest survivors	Lilja G, Nielsen N. Friberg H. Horn J. Kjaergaard J. Pellis T. Rundgren M. Wetterslev J. Wise M. P. Nilsson F. Cronberg T.	2015	Neurocritical care	23	1 SUPPL. 1	S12		Exclusion reason: Not pertinent research (e.g., protocol registration)
Long-term physical functioning and psychosocial adjustment in survivors of sudden cardiac death	Sauve, M. J.	1995	Heart & lung : the journal of critical care	24	2	133-44		Exclusion reason: No cognitive assessment performed
Low incidence of neurologic events during long-term support with the HeartMate (R) XVE left ventricular assist device	Slaughter, M. S.; Sobieski, M. A.; Gallagher, C.; Dia, M.; Silver, M. A.	2008	Tex. Heart Inst. J.	35	3	245-249		Exclusion reason: Does not mention any CHD in methods or analysis
Low mini-mental status predicts mortality in asymptomatic carotid arterial stenosis	Pettigrew, L. Creed; Thomas, N.; Howard, V. J.; Veltkamp, R.; Toole, J. F.	2000	Neurology	55	1	30-34	http://dx.doi.org/10.1159/000023529	Exclusion reason: Sex of participants was not specified
Low mini-mental status predicts mortality in asymptomatic carotid arterial stenosis. Asymptomatic Carotid Atherosclerosis Study investigators	Pettigrew, L. C.; Thomas, N.; Howard, V. J.; Veltkamp, R.; Toole, J. F.	2000	Neurology	55	1	30-Apr		Exclusion reason: Sex of participants was not specified

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Lower Performance in Orientation to Time and Place Associates with Greater Risk of Cardiovascular Events and Mortality in the Oldest Old: Leiden 85-Plus Study	Rostamian, S.; van Buchem, M. A.; Jukema, J. W.; Gussekloo, J.; Poortvliet, R. K. E.; de Cren, A. J. M.; Sabayan, B.	2017	Front. Aging Neurosci.	9		7	10.3389/fnagi.2017.00307	Exclusion reason: No separate analysis for conditions
Lower Plasma Klotho Concentrations Are Associated with Vascular Dementia but Not Late-Onset Alzheimer's Disease	Brombo, Gloria; Bonetti, Francesco; Ortolani, Beatrice; Morieri, Mario Luca; Bosi, Cristina; Passaro, Angelina; Vigna, Giovanni B.; Borgna, Caterina; Arcidicono, Maria Vittoria; Tisato, Veronica; Zuliani, Giovanni	2018	Gerontology			08-Jan	https://dx.doi.org/10.1159/000488318	Exclusion reason: No separate analysis for sexes
Medical burden and cognition in older patients in primary care: Selective deficits in attention	Duff, K.; Mold, J. W.; Roberts, M. M.; McKay, S. L.	2007	Arch. Clin. Neuropsychol.	22	5	569-575	10.1016/j.acn.2007.03.007	Exclusion reason: No separate analysis for conditions
Mediterranean diet and cognitive decline in women with cardiovascular disease or risk factors	Vercambre, Marie-Noel; Grodstein, Francine; Berr, Claudine; Kang, Jae H.	2012	Journal of the Academy of Nutrition and Dietetics	112	6	816-23	https://dx.doi.org/10.1016/j.jand.2012.02.023	Exclusion reason: No separate analysis for conditions
Memory function in patients with stable, moderate to severe cardiac failure	Grubb, N. R.; Simpson, C.; Fox, K. A.	2000	American heart journal	140	1	E1-5		Exclusion reason: Sex of participants was not specified
Mental state and presentation of myocardial infarction in the elderly	Black, D. A.	1987	Age and ageing	16	2	125-7		Exclusion reason: Sex of participants was not specified

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Mental stress and the induction of silent myocardial ischemia in patients with coronary artery disease	Rozanski, A.; Bairey, C. N.; Krantz, D. S.; Friedman, J.; Resser, K. J.; Morell, M.; Hilton-Chalfen, S.; Hestrin, L.; Bietendorf, J.; Berman, D. S.	1988	The New England journal of medicine	318	16	1005-12		Exclusion reason: No separate analysis for sexes
Mental stress in the functional evaluation of recent myocardial infarct: hemodynamic aspects	Mazzuero, G.; Zotti, A. M.; Tavazzi, L.	1983	Giornale Italiano di Cardiologia	13	9	172-182		Exclusion reason: Not available in English
Mental stress, panic disorder and the heart	Esler, M. D.	1998	Stress Med.	14	4	237-243	10.1002/(sici)1099-1700(199810014:4<237::aid-smi803>3.0.co;2-c	Exclusion reason: No cognitive assessment performed
Mid-term mortality of very elderly patients with acute myocardial infarction with or without coronary intervention	Kashima, Katsuro; Ikeda, Daisuke; Tanaka, Hideki; Yamashita, Erika; Nagayoshi, Shinya; Yoshishige, Yusuke; Tanoue, Kazuyuki; Nagano, Shinjirou; Nuruki, Norihito; Yoshinaga, Masao; Sonoda, Masahiro	2010	Journal of cardiology	55	3	397-403	https://dx.doi.org/10.1016/j.jjcc.2010.01.004	Exclusion reason: No cognitive assessment performed
Mild Cognitive Impairment and Receipt of Treatments for Acute Myocardial Infarction in Older Adults.	Levine, Deborah A; Langa, Kenneth M; Galecki, Andrzej; Kabeto, Mohammed; Morgenstern, Lewis B; Zahuranec, Darin B; Giordani, Bruno; Lisabeth, Lynda D; Nallamothu, Brahmajee K	2020	Journal of general internal medicine	35	1	28-35	https://dx.doi.org/10.1007/s11606-019-05155-8	Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Mild cognitive impairment: vascular risk factors in community elderly in four cities of Hebei Province, China	Wang, Yumei; Song, Mei; Yu, Lulu; Wang, Lan; An, Cuixia; Xun, Shunjiang; Zhao, Xiaochuan; Gao, Yuanyuan; Wang, Xueyi	2015	PloS one	10	5	e0124566	https://dx.doi.org/10.1371/journal.pone.0124566	Exclusion reason: No separate analysis for sexes
Modifiable risk factors associated with mild cognitive impairment in patients with stable coronary heart disease in the STABILITY trial	Stewart Rah, Armstrong P. W. Chiswell K. Hagstrom E. Held C. Krug-Gourley S. Ryan C. M. Stebbins A. Wallentin L. White H. D.	2015	European heart journal	36		1088		Exclusion reason: Not pertinent research (e.g., protocol registration)
Morbidity patterns in aged population in southern Italy. A survey sampling	Cacciatore, F.; Gallo, C.; Ferrara, N.; Abete, P.; Paolisso, G.; Canonico, S.; Signoriello, G.; Terracciano, C.; Napoli, C.; Varricchio, M.; Rengo, F.	1998	Archives of gerontology and geriatrics	26	3	201-13		Exclusion reason: No separate analysis for conditions
Mortality after a diagnosis of dementia in a population aged 75 and over in Spain	Llinas-Regla, Jordi; Lopez-Pousa, Secundino; Vilalta-Franch, Joan; Garre-Olmo, Josep; Roman, Gustavo C.	2008	Neuroepidemiology	31	2	Aug-80	https://dx.doi.org/10.1159/000144088	Exclusion reason: No separate analysis for conditions
Mortality in mild cognitive impairment varies by subtype, sex, and lifestyle factors: the Mayo Clinic Study of Aging	Vassilaki, Maria; Cha, Ruth H.; Aakre, Jeremiah A.; Therneau, Terry M.; Geda, Yonas E.; Mielke, Michelle M.; Knopman, David S.; Petersen, Ronald C.; Roberts, Rosebud O.	2015	Journal of Alzheimer's disease : JAD	45	4	1237-45	https://dx.doi.org/10.3233/JAD-143078	Exclusion reason: No separate analysis for conditions
Near vision impairment predicts cognitive decline: data from the Hispanic Established Populations for Epidemiologic Studies of the Elderly	Reyes-Ortiz, Carlos A.; Kuo, Yong-Fang; DiNuzzo, Anthony R.; Ray, Laura A.; Raji, Mukaila A.; Markides, Kyriakos S.	2005	Journal of the American Geriatrics Society	53	4	681-6		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Neurocognitive functioning in patients undergoing coronary artery bypass graft surgery or percutaneous coronary intervention: evidence of impairment before intervention compared with normal controls	Rosengart, Todd K.; Sweet, Jerry; Finnin, Eileen B.; Wolfe, Penny; Cashy, John; Hahn, Elizabeth; Marymont, Jesse; Sanborn, Timothy	2005	The Annals of thoracic surgery	80	4	1327-5		Exclusion reason: Does not mention any CHD in methods or analysis
Neurocognitive outcomes 3 years after coronary artery bypass graft surgery: a controlled study	Selnes, Ola A.; Grega, Maura A.; Bailey, Maryanne M.; Pham, Luu; Zeger, Scott; Baumgartner, William A.; McKhann, Guy M.	2007	The Annals of thoracic surgery	84	6	1885-96		Exclusion reason: No separate analysis for sexes
Neuroimaging and cardiac correlates of cognitive function among patients with cardiac disease	Paul, Robert H.; Gunstad, John; Poppas, Athena; Tate, David F.; Foreman, Dan; Brickman, Adam M.; Jefferson, Angela L.; Hoth, Karin; Cohen, Ronald A.	2005	Cerebrovascular diseases (Basel, Switzerland)	20	2	129-33		Exclusion reason: Sex of participants was not specified
Neurological outcome in coronary artery surgery with and without cardiopulmonary bypass	Malheiros, S. M.; Brucki, S. M.; Gabbai, A. A.; Bertolucci, P. H.; Juliano, Y.; Carvalho, A. C.; Buffolo, E.	1995	Acta neurologica Scandinavica	92	3	256-60		Exclusion reason: No separate analysis for sexes
Neuron loss after coronary artery bypass detected by SPECT estimation of benzodiazepine receptors	Rasmussen, Lars S.; Sperling, Bjorn; Abildstrom, Hanne H.; Moller, Jakob T.	2002	The Annals of thoracic surgery	74	5	1576-80		Exclusion reason: Does not mention any CHD in methods or analysis
Neuroprotection of the brain during cardiopulmonary bypass: a randomized trial of remacemide during coronary artery bypass in 171 patients	Arrowsmith, J. E.; Harrison, M. J.; Newman, S. P.; Stygall, J.; Timberlake, N.; Pugsley, W. B.	1998	Stroke	29	11	2357-62		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Neuropsychological alterations after coronary artery bypass graft surgery	Suksompong, Sirilak; Prakanratrana, Ungkab; Chumpathong, Saowapark; Sriyoschati, Somchai; Pornvilawan, Samphant	2002	Journal of the Medical Association of Thailand = Chotmaihet thangphaet	85 Suppl 3		S910-6		Exclusion reason: Duplicate
Neuropsychological alterations after coronary artery bypass graft surgery	Suksompong, S.; Prakanrattana, U.; Chumpathong, S.; Sriyoschati, S.; Pornvilawan, S.	2002	Journal of the Medical Association of Thailand	85	SUPPL. 3	S910-S916		Exclusion reason: Publication was not available
Neuropsychological deficits in patients with myocardial infarction	Antony, S. P.; Jamuna, R.; Kini, S. M.; Chakravarthy, M.	2010	Neuropsychol. Trends		7	37-50	10.7358/neur-2010-007-anto	Exclusion reason: No separate analysis for sexes
Neuropsychological functioning among cardiac rehabilitation patients	Moser, D. J.; Cohen, R. A.; Clark, M. M.; Aloia, M. S.; Tate, B. A.; Stefanik, S.; Forman, D. E.; Tilkemeier, P. L.	1999	Journal of cardiopulmonary rehabilitation	19	2	Jul-91		Exclusion reason: No separate analysis for sexes
Neuropsychological outcome of survivors of out-of-hospital cardiac arrest	Bertini, G.; Giglioli, C.; Giovannini, F.; Bartoletti, A.; Cricelli, F.; Margheri, M.; Russo, L.; Taddei, T.; Taiti, A.	1990	The Journal of emergency medicine	8	4	407-12		Exclusion reason: No separate analysis for sexes
Neuropsychological outcomes of coronary artery bypass grafting	Cassimjee, N.; Couzens, C. L.; Smith, F. J.; Wagner, C.	2004	Health SA Gesondheid	9	3	14-Mar		Exclusion reason: No separate analysis for sexes
Neuropsychological profiles of vascular disease and risk of dementia: implications for defining vascular cognitive	Stephan, Blossom Christa Maree; Minett, Thais; Muniz-Terrera,	2017	Age and ageing	46	5	755-760	https://dx.doi.org/10.1093/ageing/afx016	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
impairment no dementia (VCI-ND)	Graciela; Harrison, Stephanie L.; Matthews, Fiona E.; Brayne, Carol							
Not as transient: patients with transient ischaemic attack or minor stroke experience cognitive and communication problems; an exploratory study	Fens, Manon; van Heugten, Caroline M.; Beusmans, George H. M. I.; Limburg, Martien; Haeren, Roel; Kaemingk, Anita; Metsemakers, Job F. M.	2013	The European journal of general practice	19	1	06-Nov	https://dx.doi.org/10.3109/13814788.2012.715147	Exclusion reason: No cognitive assessment performed
N-Terminal Pro-Brain Natriuretic Peptide and Cognitive Decline in Older Adults at High Cardiovascular Risk	Wijsman, L. W.; Sabayan, B.; van Vliet, P.; Trompet, S.; de Ruijter, W.; Poortvliet, R. K. E.; van Peet, P. G.; Gussekloo, J.; Jukema, J. W.; Stott, D. J.; Sattar, N.; Ford, I.; Westendorp, R. G. J.; de Craen, A. J. M.; Mooijaart, S. P.	2014	Ann. Neurol.	76	2	213-222	10.1002/ana.24203	Exclusion reason: No separate analysis for sexes
Occurrence and risk factors of mild cognitive impairment in the older Chinese population: a 3-year follow-up study	Hai, Shan; Dong, Birong; Liu, Yixin; Zou, Yupei	2012	International journal of geriatric psychiatry	27	7	703-8	https://dx.doi.org/10.1002/gps.2768	Exclusion reason: Not pertinent research (e.g., protocol registration)
Off-Pump versus on-pump coronary artery bypass: can OPCAB reduce neurologic injury?	Schmitz, C.; Weinreich, S.; Schneider, R.; Schneider, D.; Speth, I.; Schulze-Rauschenbach, C.; Pohl, C.; Welz, A.	2003	The heart surgery forum	6	3	127-30		Exclusion reason: Publication was not available
Omega-3 fatty acids, depressive symptoms, and cognitive performance in patients with coronary artery disease	Mazereeuw G, Herrmann N. Oh P. I. Ma D. W. L. Wang C. T. Kiss A. Lanctot K. L.	2016	Journal of clinical psychopharmacology	36	5	436		Exclusion reason: No separate analysis for conditions
Omega-3 Fatty Acids, Depressive Symptoms, and Cognitive Performance in Patients With Coronary Artery	Mazereeuw, Graham; Herrmann, Nathan; Oh, Paul I.; Ma, David W.	2016	Journal of clinical	36	5	436-44	https://dx.doi.org/10.1097/J	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Disease: Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial	L.; Wang, Cheng Tao; Kiss, Alexander; Lanctot, Krista L.		psychopharmacology				CP.0000000000000565	
One-year follow-up evaluation of cognitive function in patients with coronary artery disease and over 65 years of age in Isfahan city, Iran	Barekatain, M.; Mortazavi, S.; Teimouri, Z.; Hashemi, S. M.; Maracy, M.	2017	Journal of Isfahan Medical School	35	444	1094-1100		Exclusion reason: Publication was not available
Oral function as an indexing parameter for mild cognitive impairment in older adults	Watanabe, Yutaka; Arai, Hidenori; Hirano, Hirohiko; Morishita, Shiho; Ohara, Yuki; Edahiro, Ayako; Murakami, Masaharu; Shimada, Hiroyuki; Kikutani, Takeshi; Suzuki, Takao	2018	Geriatrics & gerontology international	18	5	790-798	https://dx.doi.org/10.1111/ggi.13259	Exclusion reason: Does not mention any CHD in methods or analysis
Perceived cognitive function in coronary artery disease--an unrecognised predictor of unemployment	Kiessling, Anna; Henriksson, Peter	2005	Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation	14	6	1481-8		Exclusion reason: No separate analysis for sexes
Periodization of Exercise Training in Patients With Coronary Heart Disease	Nct	2018						Exclusion reason: Not pertinent research (e.g., protocol registration)
Perioperative hyperglycemia is associated with postoperative	Zhang, Xiaopeng; Yan, Xiaowei; Gorman, Jennifer; Hoffman, Stuart N.; Zhang, Li; Boscarino, Joseph A.	2014	Neuropsychiatric disease	10		361-70	https://dx.doi.org/10.2147/NDT.S57761	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
neurocognitive disorders after cardiac surgery			and treatment					
Physical activity and executive function in aging: the MOBILIZE Boston Study	Eggermont, Laura H. P.; Milberg, William P.; Lipsitz, Lewis A.; Scherder, Erik J. A.; Leveille, Suzanne G.	2009	Journal of the American Geriatrics Society	57	10	1750-6	https://dx.doi.org/10.1111/j.1532-5415.2009.02441.x	Exclusion reason: No separate analysis for sexes
Physical activity and risk of cognitive impairment among oldest-old women	Wang, Sophia; Luo, Xiaodong; Barnes, Deborah; Sano, Mary; Yaffe, Kristine	2014	The American journal of geriatric	22	11	1149-57	https://dx.doi.org/10.1016/j.jagp.2013.03.002	Exclusion reason: No separate analysis for conditions
Pilot study results of the influence of citicoline and piribedil on cognitive function in patients with ischemic heart disease after coronary artery bypass surgery	Petrova, M. M.; Prokopenko, S. V.; Eremina, O. V.; Matjushin, G. V.; Sakovich, V. A.; Drobot, D. B.; Mozhejko, E. Y.; Kaskaeva, D. S.	2015	Ration. Pharmacother. Cardiol.	11	4	391-397	10.20996/1819-6446-2015-11-4-391-397	Exclusion reason: Not available in English
Plasma Sphingolipids Mediate a Relationship Between Type 2 Diabetes and Memory Outcomes in Patients with Coronary Artery Disease Undertaking Exercise.	Eakin, Kelsey A; Saleem, Mahwesh; Herrmann, Nathan; Cogo-Moreira, Hugo; Mielke, Michelle M; Oh, Paul I; Haughey, Norman J; Venkata, Swarajya L V; Lanctot, Krista L; Swardfager, Walter	2019	Journal of Alzheimer's disease : JAD	69	3	717-727	https://dx.doi.org/10.3233/JAD-181203	Exclusion reason: No separate analysis for sexes
Platelet-activating factors are associated with cognitive deficits in depressed coronary artery disease patients: a hypothesis-generating study	Mazereeuw, Graham; Herrmann, Nathan; Xu, Hongbin; Figeys, Daniel; Oh, Paul I.; Bennett, Steffany A. L.; Lanctot, Krista L.	2014	Journal of neuroinflammation	11		119	https://dx.doi.org/10.1186/1742-2094-11-119	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Posthypoxic encephalopathy in patients undergoing coronary artery bypass surgery: Clinical, neuropsychological, and neuroimaging aspects	Portik, O.A.; Tsarevskaya, Yu.N.; Efimtsev, A.Yu.; Alekseeva, T.M.; Trufanov, G.E.	2019	Nevrologiya, Neiropsikhiatriya, Psikhosomatika	11	3	35-42	10.14412/2074-2711-2019-3-35-42	Exclusion reason: Not available in English
Potential effect of screening for subtle cognitive deficits on hospital readmission	Buslovich, Steven; Kennedy, Gary J.	2012	Journal of the American Geriatrics Society	60	10	1980-1981	http://dx.doi.org/10.1111/j.1532-5415.2012.04135.x	Exclusion reason: Brief report
Predicting 6-month mortality for older adults hospitalized with acute myocardial infarction	Dodson, J.A.; Hajduk, A.M.; Geda, M.; Krumholz, H.M.; Murphy, T.E.; Tsang, S.; Tinetti, M.E.; Nanna, M.G.; McNamara, R.; Gill, T.M.; Chaudhry, S.I.	2020	Annals of Internal Medicine	172	1	21-Dec	10.7326/M19-0974	Exclusion reason: No separate analysis for sexes
Prediction of Cognitive Status and 5-Year Survival Rate for Elderly with Cardiovascular Diseases: A Canadian Study of Health and Aging Secondary Data Analysis	Pakzad, S.; Bourque, P.; Fallah, N.		Journal of Frailty & Aging				10.14283/jfa.2020.21	Exclusion reason: No separate analysis for sexes
Predictors of functional change: a longitudinal study of nondemented people aged 65 and older	Wang, Li; van Belle, Gerald; Kukull, Walter B.; Larson, Eric B.	2002	Journal of the American Geriatrics Society	50	9	1525-34		Exclusion reason: No separate analysis for conditions
Predictors of health-promoting behaviors in Taiwanese patients with coronary artery disease	Ai-Fu, Chiou; Shu-Pen, Hsu; Huei-Fong, Hung	2016	Applied Nursing Research	30		06-Jan	10.1016/j.apnr.2015.08.008	Exclusion reason: No cognitive assessment performed

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Predictors of mortality in home-dwelling patients with cardiovascular disease aged 75 and older	Strandberg, Timo E.; Pitkala, Kaisu H.; Tilvis, Reijo S.	2009	Journal of the American Geriatrics Society	57	2	279-84	https://dx.doi.org/10.1111/j.1532-5415.2008.02112.x	Exclusion reason: No separate analysis for conditions
Predictors of neuropsychological status in cardiac patients	Kamper, Joel E.	2014	Dissertation Abstracts International: Section B: The Sciences and Engineering	74	12-B(E)	No-Specified		Exclusion reason: Not pertinent research (e.g., protocol registration)
Preexisting cognitive impairment in patients scheduled for elective coronary artery bypass graft surgery	Silbert, Brendan S.; Scott, David A.; Evered, Lisbeth A.; Lewis, Matthew S.; Maruff, Paul T.	2007	Anesthesia and analgesia	104	5	1023-contents		Exclusion reason: Does not mention any CHD in methods or analysis
Preexisting cognitive impairment in women before cardiac surgery and its relationship with C-reactive protein concentrations	Hogue, Charles W., Jr.; Hershey, Tamara; Dixon, David; Fucetola, Robert; Nassief, Abdullah; Freedland, Kenneth E.; Thomas, Betsy; Schechtman, Kenneth	2006	Anesthesia and analgesia	102	6	1602-contents		Exclusion reason: No separate analysis for conditions
Preexisting depressive symptoms are associated with long-term cognitive decline in patients after cardiac surgery	Patron, Elisabetta; Benvenuti, Simone Messerotti; Zanatta, Paolo; Polesel, Elvio; Palomba, Daniela	2013	General Hospital Psychiatry	35	5	472-479	http://dx.doi.org/10.1016/j.genhosppsych.2013.05.004	Exclusion reason: No separate analysis for conditions
Present clinical status of postoperative cognitive dysfunction in cardiovascular surgery	Ishida, K.; Yamashita, A.; Yamashita, S.; Matsumoto, M.	2017	Anesthesia and Neurotoxicity			59-94	10.1007/978-4-431-55624-4_5	Exclusion reason: Not pertinent research (e.g., protocol registration)

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Presurgical cognitive deficits in patients receiving coronary artery bypass graft surgery	Rankin, Katherine P.; Kochamba, Gary S.; Boone, Kyle B.; Petitti, Diana B.; Buckwalter, J. Galen	2003	Journal of the International Neuropsychological Society : JINS	9	6	913-24		Exclusion reason: Does not mention any CHD in methods or analysis
Prevalence and Correlates of Statin Underuse for Secondary Prevention of Cardiovascular Disease in Older Adults 65-79 Years of Age: The Italian Health Examination Survey 2008-2012.	Viscogliosi, Giovanni; Donfrancesco, Chiara; Lo Noce, Cinzia; Vanuzzo, Diego; Carle, Flavia; Giampaoli, Simona; Palmieri, Luigi	2020	Rejuvenation research		10121338 1		https://dx.doi.org/10.1089/rej.2019.2268	Exclusion reason: Publication was not available
Prevalence and effect factors of dementia among the community elderly in Chongqing, China.	Deng, Jing; Cao, Cheng; Jiang, Yi; Peng, Bin; Wang, Tingting; Yan, Ke; Lian, Jingxi; Wang, Zengzi	2018	Psychogeriatrics : the official journal of the Japanese Psychogeriatric Society	18	5	412-420	https://dx.doi.org/10.1111/psyg.12343	Exclusion reason: No separate analysis for sexes
Prevalence of functional cognitive impairment and associated factors in Brazilian community-dwelling older adults	Gondim, Andrea Silva; Coelho Filho, Joao Macedo; Cavalcanti, Alexandre de Andrade; Roriz Filho, Jarbas de Sa; Nogueira, Charlys Barbosa; Peixoto Junior, Arnaldo Aires; Lima, Jose Wellington de Oliveira	2017	Dementia & neuropsychologia	11	1	32-39	https://dx.doi.org/10.1590/1980-57642016dn11-010006	Exclusion reason: No separate analysis for sexes
Prevalence of mild cognitive impairment among older adults living in Mansoura city, Egypt	Amer, M.; Mousa, S.; Khater, M.; Wahab, W. A.	2012	Middle East Current Psychiatry	19	1	07-Mar	10.1097/01.XME.0000407821.18381.3c	Exclusion reason: Brief report

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Prevalence of Mild Cognitive Impairment and Its Subtypes among Chinese Older Adults: Role of Vascular Risk Factors	Ma, Fei; Wu, Tianfeng; Zhao, Jiangang; Ji, Lu; Song, Aili; Zhang, Meilin; Huang, Guowei	2016	Dementia and geriatric cognitive disorders	41	06-May	261-72	https://dx.doi.org/10.1159/000446507	Exclusion reason: No separate analysis for conditions
Prevalence of mild cognitive impairment and its subtypes in the Mexican population	Juarez-Cedillo, Teresa; Sanchez-Arenas, Rosalinda; Sanchez-Garcia, Sergio; Garcia-Pena, Carmen; Hsiung, Ging-Yuek R.; Sepehry, Amir A.; Beattie, B. Lynn; Jacova, Claudia	2012	Dementia and geriatric cognitive disorders	34	06-May	271-81	https://dx.doi.org/10.1159/000345251	Exclusion reason: No separate analysis for conditions
Prevalence of mild cognitive impairment in employable patients after acute coronary event in cardiac rehabilitation	Salzwedel, Annett; Heidler, Maria-Dorothea; Haubold, Kathrin; Schikora, Martin; Reibis, Rona; Wegscheider, Karl; Jobges, Michael; Voller, Heinz	2017	Vascular health and risk management	13		55-60	https://dx.doi.org/10.2147/VHRM.S121086	Exclusion reason: No separate analysis for conditions
Prognostic value of cardiovascular disease status: the Leiden 85-plus study	van Peet, Petra G.; Drewes, Yvonne M.; de Craen, Anton J. M.; Westendorp, Rudi G. J.; Gussekloo, Jacobijn; de Ruijter, Wouter	2013	Age (Dordrecht, Netherlands)	35	4	1433-44	https://dx.doi.org/10.1007/s11357-012-9443-5	Exclusion reason: No separate analysis for sexes
Prognostic Value of Geriatric Conditions Beyond Age After Acute Coronary Syndrome	Sanchis, Juan; Ruiz, Vicente; Bonanad, Clara; Valero, Ernesto; Ruescas-Nicolau, Maria Arantzazu; Ezzatvar, Yasmin; Sastre, Clara; Garcia-Blas, Sergio; Mollar, Anna; Bertomeu-Gonzalez, Vicente; Minana, Gema; Nunez, Julio	2017	Mayo Clinic proceedings	92	6	934-939	https://dx.doi.org/10.1016/j.mayocp.2017.01.018	Exclusion reason: Not pertinent research (e.g., protocol registration)
Prospective Disability in Different Combinations of Somatic and Mental Multimorbidity	Quinones, Ana R.; Markwardt, Sheila; Thielke, Stephen; Rostant, Ola; Vasquez, Elizabeth; Botoseneanu, Anda	2018	The journals of gerontology. Series A, Biological	73	2	204-210	https://dx.doi.org/10.1093/gerona/glx100	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
			sciences and medical sciences					
Prospective randomized trial of single clamp technique versus intermittent ischaemic arrest: myocardial and neurological outcome	Musumeci, F.; Feccia, M.; MacCarthy, P. A.; Ellis, G. R.; Mammana, L.; Brinn, F.; Penny, W. J.	1998	European journal of cardio-thoracic surgery	13	6	702-9		Exclusion reason: No separate analysis for sexes
Protein S-100B: A neurobiochemical marker for neuropsychological and neuropsychiatric disorders following heart surgery	Herrmann, M.; Steup, A. D.; Ansorge, I.; Kunz, W. S.; Huth, C.; Wallesch, C. W.	1997	Ann. Neurol.	42	3	M1-M1		Exclusion reason: No separate analysis for sexes
P-Selectin 1087G/A Polymorphism Is Associated With Neuropsychological Test Performance in Older Adults With Cardiovascular Disease	Gunstad, J.; Benitez, A.; Hoth, K. F.; Spitznagel, M. B.; McCaffery, J.; McGeary, J.; Kakos, L. S.; Poppas, A.; Paul, R. H.; Jefferson, A. L.; Sweet, L. H.; Cohen, R. A.	2009	Stroke	40	9	2969-2972	10.1161/strokeaha.109.553339	Exclusion reason: No separate analysis for conditions
Psychiatric morbidity during the early phase of coronary artery care for myocardial infarction: Association with cardiac diagnosis and outcome	Legault, S. E.; Joffe, R. T.; Armstrong, P. W.	1992	Canadian Journal of Psychiatry	37	5	316-325	10.1177/070674379203700505	Exclusion reason: Duplicate
Psychiatric morbidity during the early phase of coronary care for myocardial infarction: association with cardiac diagnosis and outcome	Legault, S. E.; Joffe, R. T.; Armstrong, P. W.	1992	Canadian journal of psychiatry. Revue canadienne de psychiatrie	37	5	316-25		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Psychologic assessment in cardiac rehabilitation	Blumenthal, J. A.	1985	Journal of Cardiac Rehabilitation	5	5	208-215		Exclusion reason: Not pertinent research (e.g., protocol registration)
Psychological stress and changes in blood pressure, heart rate, and EKG parameters in a group of heart patients without evidence of organic heart disease: A controlled study	delle Chiaie, R.; Carmenini, G.; Seripa, G.; Picardi, A.; et al.	1992		37	1	29-49		Exclusion reason: Not available in English
Psychoneuroimmunological aspects of cardiovascular diseases: a preliminary report	Bartczak, Dagmara; Szymanski, Lukasz; Bodera, Pawel; Stankiewicz, Wanda	2016	Central-European journal of immunology	41	2	209-16	https://dx.doi.org/10.5114/ceji.2016.60996	Exclusion reason: No cognitive assessment performed
Randomised controlled trial in women with coronary artery disease investigating the effects of aerobic interval training versus moderate intensity continuous exercise in cardiac rehabilitation: CAT versus MICE study.	Lee, Leanna S; Tsai, Ming-Chang; Brooks, Dina; Oh, Paul I	2019	BMJ open sport & exercise medicine	5	1	e000589	https://dx.doi.org/10.1136/bmjsem-2019-000589	Exclusion reason: No separate analysis for conditions
Rationale, design, and baseline participant characteristics in the MRI and cognitive substudy of the cardiovascular outcomes for people using anticoagulation strategies trial	Sharma, Mukul; Hart, Robert G.; Smith, Eric E.; Bosch, Jackie; Yuan, Fei; Casanova, Amparo; Eikelboom, John W.; Connolly, Stuart J.; Wong, Gloria; Diaz, Rafael; Lopez-Jaramillo, Patricio; Ertl, Georg; Stork, Stefan; Dagenais, Gilles R.; Lonn, Eva M.; Ryden, Lars; Tonkin, Andrew M.; Varigos, John D.; Bhatt, Deepak L.; Branch, Kelley Rh;	2018	International journal of stroke : official journal of the International Stroke Society			1.75E+15	https://dx.doi.org/10.1177/1747493018784478	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Probstfield, Jeffrey L.; Kim, Jae-Hyung; Ha, Jong-Won; O'Donnell, Martin; Vinereanu, Dragos; Fox, Keith Aa; Liang, Yan; Liu, Lisheng; Zhu, Jun; Pogosova, Nana; Maggioni, Aldo P.; Avezum, Alvaro; Piegas, Leopoldo S.; Keltai, Katalin; Keltai, Matyas; Cook Bruns, Nancy; Berkowitz, Scott; Yusuf, Salim							
RECURRENT MYOCARDIAL INFARCTION IS AN INDEPENDENT PREDICTOR OF COGNITIVE DECLINE IN OLDER PATIENTS WITH NON-ST ELEVATION ACUTE CORONARY SYNDROME: A PROSPECTIVE COHORT STUDY	Gu, Sophie Zhaotao; Batty, Jonathan; Veerasamy, Murugapathy; Sinclair, Hannah; Edwards, Richard; Das, Rajiv; Zaman, Azfar; Egred, Mohaned; Ahmed, Javed; Purcell, Ian; Bagnall, Alan; Spyridopoulos, Ioakim; Neely, Dermot; Qiu, Weiliang; Kunadian, Vijay	2018	Heart	104		A18-A19	10.1136/heartjnl-2018-BCS.19	Exclusion reason: Not pertinent research (e.g., protocol registration)
Reduced executive functioning is associated with poorer outcome in cardiac rehabilitation	Kakos, Lynn S.; Szabo, Ashley J.; Gunstad, John; Stanek, Kelly M.; Waechter, Donna; Hughes, Joel; Luyster, Faith; Josephson, Richard; Rosneck, Jim	2010	Preventive cardiology	13	3	100-3	https://dx.doi.org/10.1111/j.1751-7141.2009.00065.x	Exclusion reason: Does not mention any CHD in methods or analysis
Regional decline of cerebral blood flow with age in cognitively intact subjects	Zemcov, A.; Barclay, L.; Blass, J. P.	1984	Neurobiology of aging	5	1	06-Jan		Exclusion reason: No cognitive assessment performed
Relation between cardiovascular and metabolic disease and cognition in very old age: cross-sectional and longitudinal	Verhaegen, Paul; Borchelt, Markus; Smith, Jacqui	2003	Health psychology : official journal of the Division	22	6	559-69		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
findings from the berlin aging study			of Health Psychology					
Relation of Poor Nutritional Status to Mild Cognitive Impairment in Patients with Coronary Artery Disease	Ishihara, K.; Izawa, K. P.; Kitamura, M.; Ogawa, M.; Shimogai, T.; Kanejima, Y.; Morisawa, T.; Shimizu, I.		Journal of Nutrition Health & Aging				10.1007/s12603-020-1428-y	Exclusion reason: No separate analysis for sexes
Relationship between cerebral and heart blood flow and cognitive function in the elderly with ischemic cerebrovascular and cardiovascular diseases	Lu, H. H.; Jin, X.; Chen, Q. Z.; Huang, G.; Shi, Y. P.; Qui, J.	2004	Chinese Journal of Clinical Rehabilitation	8	10	1801-1803		Exclusion reason: Publication was not available
Relationship between emotional variables and cognitive test performance before and after open-heart surgery	Vingerhoets, Guy; De Soete, Geert; Jannes, Constantin	1995	Clinical Neuropsychologist	9	2	198-202	http://dx.doi.org/10.1080/13854049508401603	Exclusion reason: Does not mention any CHD in methods or analysis
Relationship between frailty and cognitive decline in older Mexican Americans	Samper-Ternent, Rafael; Al Snih, Soham; Raji, Mukaila A.; Markides, Kyriakos S.; Ottenbacher, Kenneth J.	2008	Journal of the American Geriatrics Society	56	10	1845-52	https://dx.doi.org/10.1111/j.1532-5415.2008.01947.x	Exclusion reason: No separate analysis for sexes
Relationship between plasma lipids and all-cause mortality in nondemented elderly	Schupf, Nicole; Costa, Rosann; Luchsinger, Jose; Tang, Ming-Xin; Lee, Joseph H.; Mayeux, Richard	2005	Journal of the American Geriatrics Society	53	2	219-26		Exclusion reason: No cognitive assessment performed
Relationship between Systemic and Cerebral Vascular Disease and Brain Structure Integrity in Normal Elderly Individuals	Riverol, Mario; Becker, James T.; Lopez, Oscar L.; Raji, Cyrus A.; Thompson, Paul M.; Carmichael, Owen T.; Gach, H. Michael; Longstreth, William T., Jr.; Fried,	2015	Journal of Alzheimer's disease : JAD	44	1	319-28	https://dx.doi.org/10.3233/JAD-141077	Exclusion reason: Does not mention any CHD in methods or analysis

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Linda; Tracy, Russell P.; Kuller, Lewis H.							
Relationship between the self-assessment and clinical assessment of health status and work ability	Eskelinen, Leena; Kohvakka, Antti; Merisalo, Tuula; Hurri, Heikki; et al.	1991	Scandinavian Journal of Work, Environment & Health	17	Suppl 1	40-47		Exclusion reason: Men only
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) intraindividual variability in older adults: Associations with disease and mortality	Thaler, Nicholas S.; Hill, Benjamin D.; Duff, Kevin; Mold, James; Scott, James G.	2015	Journal of clinical and experimental neuropsychology	37	6	622-9	https://dx.doi.org/10.1080/13803395.2015.1039962	Exclusion reason: No separate analysis for conditions
Resilience to health related adversity in older people	Gallacher, John; Mitchell, Clive; Heslop, Luke; Christopher, Gary	2012	Quality in Ageing & Older Adults	13	3	197-204	10.1108/14717791211264188	Exclusion reason: No separate analysis for sexes
Resting-State Functional Connectivity and Cognition After Major Cardiac Surgery in Older Adults without Preoperative Cognitive Impairment: Preliminary Findings	Browndyke, Jeffrey N.; Berger, Miles; Harshbarger, Todd B.; Smith, Patrick J.; White, William; Bisanar, Tiffany L.; Alexander, John H.; Gaca, Jeffrey G.; Welsh-Bohmer, Kathleen; Newman, Mark F.; Mathew, Joseph P.	2017	Journal of the American Geriatrics Society	65	1	e6-e12	https://dx.doi.org/10.1111/jgs.14534	Exclusion reason: No separate analysis for sexes
Return to Work and Participation in Society After Out-of-Hospital Cardiac Arrest	Lilja, Gisela; Nielsen, Niklas; Bro-Jeppesen, John; Dunford, Hannah; Friberg, Hans; Hofgren, Caisa; Horn, Janneke; Insorsi, Angelo; Kjaergaard, Jesper; Nilsson, Fredrik; Pelosi,	2018	Circulation. Cardiovascular quality and outcomes	11	1	e003566	https://dx.doi.org/10.1161/CIRCOUTCOMES.117.003566	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Paolo; Winters, Tineke; Wise, Matt P.; Cronberg, Tobias							
Risk factors for cerebrovascular and cardiovascular diseases beyond age 75 years	Mostafaie, N.; Huber, K. R.; Sebesta, C.; Krampla, W.; Jungwirth, S.; Zehetmayer, S.; Hinterberger, M.; Krugluger, W.; Tragl, K. H.; Fischer, P.	2010	Journal of neural transmission (Vienna, Austria : 1996)	117	11	1247-52	https://dx.doi.org/10.1007/s00702-010-0466-8	Exclusion reason: No cognitive assessment performed
Risk factors for cerebrovascular disease as correlates of cognitive function in a stroke-free cohort	Desmond, D. W.; Tatemichi, T. K.; Paik, M.; Stern, Y.	1993	Archives of neurology	50	2	162-6		Exclusion reason: No separate analysis for sexes
Risk factors for dementia diagnosis in German primary care practices	Booker, Anke; Jacob, Louis Ec; Rapp, Michael; Bohlken, Jens; Kostev, Karel	2016	International psychogeriatrics	28	7	1059-65	https://dx.doi.org/10.1017/S1041610215002082	Exclusion reason: No cognitive assessment performed
Risk Factors for Mild Cognitive Impairment in German Primary Care Practices	Jacob, Louis; Bohlken, Jens; Kostev, Karel	2017	Journal of Alzheimer's disease : JAD	56	1	379-384	https://dx.doi.org/10.3233/JAD-160875	Exclusion reason: No separate analysis for sexes
Risk factors for mild cognitive impairment in the cardiovascular health study cognition study	Lopez, O. L.; Jagust, W. J.; Dulberg, C.; Becker, J. T.; DeKosky, S. T.; Fitzpatrick, A.; Breitner, J.; Lyketsos, C.; Jones, B.; Kawas, C.; Carlson, M.; Kuller, L. H.	2003	Archives of Neurology	60	10	1394-1399	10.1001/archneur.60.10.1394	Exclusion reason: Duplicate
Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2	Lopez, Oscar L.; Jagust, William J.; Dulberg, Corinne; Becker, James T.; DeKosky, Steven T.; Fitzpatrick, Annette; Breitner, John; Lyketsos, Constantine; Jones, Beverly; Kawas,	2003	Archives of neurology	60	10	1394-9		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Claudia; Carlson, Michelle; Kuller, Lewis H.							
Role of behavioral and psychological factors in mental stress-induced silent left ventricular dysfunction in coronary artery disease	Burg, M. M.; Jain, D.; Soufer, R.; Kerns, R. D.; Zaret, B. L.	1993	Journal of the American College of Cardiology	22	2	440-8		Exclusion reason: Men only
Screening for mental disorders in cardiology outpatients	Birket-Smith, Morten; Rasmussen, Alice	2008	Nordic journal of psychiatry	62	2	147-50	https://dx.doi.org/10.1080/08039480801983562	Exclusion reason: No separate analysis for sexes
Secondary Prevention Medication Use After Myocardial Infarction in U.S. Nursing Home Residents	Zullo, Andrew R.; Sharmin, Sadia; Lee, Yoojin; Daiello, Lori A.; Shah, Nishant R.; John Boscardin, W.; Dore, David D.; Lee, Sei J.; Steinman, Michael A.	2017	Journal of the American Geriatrics Society	65	11	2397-2404	https://dx.doi.org/10.1111/jgs.15144	Exclusion reason: No cognitive assessment performed
Selective impairment of frontal-executive cognitive function in African Americans with cardiovascular risk factors	Pugh, K. G.; Kiely, D. K.; Milberg, W. P.; Lipsitz, L. A.	2003	Journal of the American Geriatrics Society	51	10	1439-1444	10.1046/j.1532-5415.2003.51463.x	Exclusion reason: No separate analysis for conditions
Serum concentration of dihomo-gamma-linolenic acid is associated with cognitive function and mild cognitive impairment in coronary artery disease patients.	Ishihara, Kodai; Izawa, Kazuhiro P; Kitamura, Masahiro; Shimogai, Takayuki; Kanejima, Yuji; Morisawa, Tomoyuki; Shimizu, Ikki	2020	Prostaglandins, leukotrienes, and essential fatty acids	158	p04, 8802730	102038	https://dx.doi.org/10.1016/j.plefa.2019.102038	Exclusion reason: Duplicate

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Serum concentration of dihomo-Î³-linolenic acid is associated with cognitive function and mild cognitive impairment in coronary artery disease patients	Ishihara, K.; Izawa, K.P.; Kitamura, M.; Shimogai, T.; Kanejima, Y.; Morisawa, T.; Shimizu, I.	2019	Prostaglandins Leukotrienes and Essential Fatty Acids				10.1016/j.plefa.2019.102038	Exclusion reason: No separate analysis for sexes
Serum concentration of eicosapentaenoic acid is associated with cognitive function in patients with coronary artery disease	Yagi, Shusuke; Hara, Tomoya; Ueno, Rie; Aihara, Ken-ichi; Fukuda, Daiju; Takashima, Akira; Hotchi, Junko; Ise, Takayuki; Yamaguchi, Koji; Tobiume, Takeshi; Iwase, Takashi; Yamada, Hirotsugu; Soeki, Takeshi; Wakatsuki, Tetsuzo; Shimabukuro, Michio; Akaike, Masashi; Sata, Masataka	2014	Nutrition journal	13	1	112	https://dx.doi.org/10.1186/1475-2891-13-112	Exclusion reason: No separate analysis for conditions
Serum C-reactive protein and cognitive function in healthy elderly Italian community dwellers	Ravaglia, G.; Forti, P.; Maioli, F.; Brunetti, N.; Martelli, M.; Servadei, L.; Bastagli, L.; Bianchin, M.; Mariani, E.	2005	J. Gerontol. Ser. A-Biol. Sci. Med. Sci.	60	8	1017-1021	10.1093/gerona/60.8.1017	Exclusion reason: No separate analysis for sexes
Serum lipoprotein levels, statin use, and cognitive function in older women	Yaffe, Kristine; Barrett-Connor, Elizabeth; Lin, Feng; Grady, Deborah	2002	Archives of neurology	59	3	378-84		Exclusion reason: No separate analysis for conditions
Serum low-density lipoprotein levels, statin use, and cognition in patients with coronary artery disease	Rej, Soham; Saleem, Mahwesh; Herrmann, Nathan; Stefatos, Anthi; Rau, Allison; Lanctot, Krista L.	2016	Neuropsychiatric disease and treatment	12		2913-2920		Exclusion reason: No separate analysis for sexes
Sex differences in the causes and consequences of white matter hyperintensities	Sachdev, P. S.; Parslow, R.; Wen, W.; Anstey, K. J.; Easteal, S.	2009	Neurobiology of aging	30	6	946-56		Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Short-term and long-term cognitive function and cerebral perfusion in off-pump and on-pump coronary artery bypass patients	Chernov, Vladimir I.; Efimova, Nataliya Yu; Efimova, Irina Yu; Akhmedov, Shamil D.; Lishmanov, Yuri B.	2006	European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery	29	1	74-81		Exclusion reason: Duplicate
Short-term and long-term neuropsychological consequences of cardiac surgery with extracorporeal circulation	Vingerhoets, G.; Van Nooten, G.; Vermassen, F.; De Soete, G.; Jannes, C.	1997	European journal of cardio-thoracic surgery : official journal of the European Association for Cardio-thoracic Surgery	11	3	424-31		Exclusion reason: Does not mention any CHD in methods or analysis
Short-term and tong-term cognitive function and cerebral perfusion in off-pump and on-pump coronary artery bypass patients	Chernov, V. I.; Efimova, N. Y.; Efimova, I. Y.; Akhmedov, S. D.; Lishmanov, Y. B.	2006	Eur. J. Cardio-Thorac. Surg.	29	1	74-81	10.1016/j.ejcts .2005.10.001	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Should global burden of disease estimates include depression as a risk factor for coronary heart disease?	Charlson, Fiona J.; Stapelberg, Nicholas J. C.; Baxter, Amanda J.; Whiteford, Harvey A.	2011	BMC medicine	9		47	https://dx.doi.org/10.1186/1741-7015-9-47	Exclusion reason: Not pertinent research (e.g., protocol registration)
Silent myocardial ischaemia due to mental stress	Deanfield, J. E.; Shea, M.; Kensett, M.; Horlock, P.; Wilson, R. A.; de Landsheere, C. M.; Selwyn, A. P.	1984	Lancet (London, England)	2	8410	1001-5		Exclusion reason: No cognitive assessment performed
Social Network Trajectories in Myocardial Infarction Versus Ischemic Stroke	Dhand, Amar; Longstreth, W. T., Jr.; Chaves, Paulo H. M.; Dhamoon, Mandip S.	2018	Journal of the American Heart Association	7	8		https://dx.doi.org/10.1161/JAHA.117.008029	Exclusion reason: No separate analysis for sexes
Stable cognition after coronary artery bypass grafting: comparisons with percutaneous intervention and normal controls	Rosengart, Todd K.; Sweet, Jerry J.; Finnin, Eileen; Wolfe, Penny; Cashy, John; Hahn, Elizabeth; Marymont, Jesse; Sanborn, Timothy	2006	The Annals of thoracic surgery	82	2	597-607		Exclusion reason: No separate analysis for sexes
Study on COgnition and Prognosis in the Elderly (SCOPE): baseline characteristics	Hansson, L.; Lithell, H.; Skoog, I.; Baro, F.; Banki, C. M.; Breteler, M.; Castaigne, A.; Correia, M.; Degaute, J. P.; Elmfeldt, D.; Engedal, K.; Farsang, C.; Ferro, J.; Hachinski, V.; Hofman, A.; James, O. F.; Krisin, E.; Leeman, M.; de Leeuw, P. W.; Leys, D.; Lobo, A.; Nordby, G.; Olofsson, B.; Opolski, G.; Prince, M.; Reischies, F. M.	2000	Blood pressure	9	03-Feb	146-51		Exclusion reason: Not pertinent research (e.g., protocol registration)
Subclinical atherosclerosis is related to lower neuronal viability in middle-aged adults: a 1H MRS study	Haley, Andreana P.; Tarumi, Takashi; Gonzales, Mitzi M.; Sugawara, Jun; Tanaka, Hirofumi	2010	Brain research	1344		54-61	https://dx.doi.org/10.1016/j.brainres.2010.05.006	Exclusion reason: Does not mention any CHD in methods or analysis

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Subcortical hyperintensities in the cholinergic system are associated with improvements in executive function in older adults with coronary artery disease undergoing cardiac rehabilitation	Santiago, Calvin; Herrmann, Nathan; Swardfager, Walter; Saleem, Mahwesh; Oh, Paul I.; Black, Sandra E.; Bradley, Janelle; Lanctot, Krista L.	2017	International Journal of Geriatric Psychiatry			No-Specified	http://dx.doi.org/10.1002/gps.4729	Exclusion reason: Duplicate
Subcortical hyperintensities in the cholinergic system are associated with improvements in executive function in older adults with coronary artery disease undergoing cardiac rehabilitation	Santiago, Calvin; Herrmann, Nathan; Swardfager, Walter; Saleem, Mahwesh; Oh, Paul I.; Black, Sandra E.; Bradley, Janelle; Lanctot, Krista L.	2018	International journal of geriatric psychiatry	33	2	279-287	https://dx.doi.org/10.1002/gps.4729	Exclusion reason: No separate analysis for sexes
Sustained Economic Hardship and Cognitive Function: The Coronary Artery Risk Development in Young Adults Study	Zeki Al Hazzouri, Adina; Elfassy, Tali; Sidney, Stephen; Jacobs, David; Perez Stable, Eliseo J.; Yaffe, Kristine	2017	American journal of preventive medicine	52	1	09-Jan	https://dx.doi.org/10.1016/j.amepre.2016.08.009	Exclusion reason: No separate analysis for conditions
Sydney Memory and Ageing Study: an epidemiological cohort study of brain ageing and dementia	Tsang, Ruby S. M.; Sachdev, Perminder S.; Reppermund, Simone; Kochan, Nicole A.; Kang, Kristan; Crawford, John; Wen, Wei; Draper, Brian; Trollor, Julian N.; Slavin, Melissa J.; Mather, Karen A.; Assareh, Arezoo; Seeher, Katrin M.; Brodaty, Henry	2013	International review of psychiatry (Abingdon, England)	25	6	711-25	https://dx.doi.org/10.3109/09540261.2013.860890	Exclusion reason: Does not mention any CHD in methods or analysis
Systematic re-evaluation of the diagnosis and treatment of coronary artery disease in hospitalized elderly: Impact on	Legrain, S.; Delpierre, S.; Lacaille, S.; Duc, P.; Lieberherr, D.; Bonnet, D.; Lahjibi-Paulet, H.; Gouronnec, A.; Boddaert, J.; Durand-Gasselin,	2012	Eur. Geriatr. Med.	3	4	219-224	10.1016/j.eurger.2012.04.001	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
medication underuse. The multicenter IRIDIA study	B.; Roy, C.; Faucounau, V.; Steg, P. G.; Tubach, F.							
Systolic blood pressure tracking over 25 to 30 years and cognitive performance in older adults	Swan, G. E.; Carmelli, D.; Larue, A.	1998	Stroke	29	11	2334-2340	10.1161/01.str.29.11.2334	Exclusion reason: Men only
The additive effects of type 2 diabetes mellitus on neurobehavioral functioning of patients diagnosed with myocardial infarction	Rafique, Rafia; Anjum, Afifa; Amer, Lubna	2016	Journal of Behavioural Sciences	26	2	55-78		Exclusion reason: No cognitive assessment performed
The association between neighborhood socioeconomic status, cardiovascular and cerebrovascular risk factors, and cognitive decline in the Health and Retirement Study (HRS).	Kuchibhatla, Maragatha; Hunter, Jaimie C; Plassman, Brenda L; Lutz, Michael W; Casanova, Ramon; Saldana, Santiago; Hayden, Kathleen M	2019	Aging & mental health		d46, 9705773	08-Jan	https://dx.doi.org/10.1080/13607863.2019.1594169	Exclusion reason: No separate analysis for conditions
The association of neurocognitive decline and other variables with return to work, hobbies, and activities of daily living after coronary artery bypass graft surgery	Gallagher Owens, S.; Agnew, J.; Curbow, B.; Selnes, O.; Fitzgerald, S.	2010	Physical and Occupational Therapy in Geriatrics	28	4	348-59		Exclusion reason: No separate analysis for sexes
The effect of coronary artery bypass surgery on brain perfusion	Degirmenci, B.; Durak, H.; Hazan, E.; Karabay, O.; Derebek, E.; Yilmaz, M.; Ozbilek, E.; Oto, O.	1998	Journal of nuclear medicine : official	39	4	587-91		Exclusion reason: Brief report

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
The effectiveness of the correction of cognitive impairment using computer-based stimulation programs for patients with coronary heart disease after coronary bypass surgery	Eryomina, Oksana Vasilyevna; Petrova, Marina Mikhaylovna; Prokopenko, Semyon Vladimirovich; Mozheyko, Elena Yuryevna; Kaskaeva, Darya Sergeevna; Gavrilyuk, Oksana Alexandrovna	2015	Journal of the neurological sciences	358	02-Jan	188-92	https://dx.doi.org/10.1016/j.jns.2015.08.1535	Exclusion reason: Sex of participants was not specified
The effects of exercise in a coronary rehabilitation programme	Newton, M.; Mutrie, N.; McArthur, J. D.	1991	Scottish medical journal	36	2	38-41		Exclusion reason: No cognitive assessment performed
The Event Related Potential Study of Emotional Stroop Task in Patients With Coronary Heart Disease Combined With Depression	Chen, X. L.; Song, Y. P.; Sun, H. W.; Li, J. T.	2016	Chinese General Practice	19	23	2757-2762	10.3969/j.issn.1007-9572.2016.23.003	Exclusion reason: Not available in English
The Greek version of the Montreal cognitive assessment in coronary artery disease in Cyprus	Charalambous, D.; Lambrinou, E.; Paikousis, L.; Barberis, V.; Middleton, N.	2016	Eur. J. Cardiovasc. Nurs.	15		S102-S103		Exclusion reason: Not pertinent research (e.g., protocol registration)
The Impact of Cognitive, Social and Physical Limitations on Income in Community Dwelling Adults With Chronic Medical and Mental Disorders	Dismuke, Clara E.; Egede, Leonard E.	2015	Global journal of health science	7	5	183-95	https://dx.doi.org/10.5539/gjhs.v7n5p183	Exclusion reason: No cognitive assessment performed
The Octopus II stabilizing system: biochemical and neuropsychological outcomes in coronary artery bypass surgery	Baker, R. A.; Andrew, M. J.; Ross, I. K.; Knight, J. L.	2001	The heart surgery forum	4 Suppl 1		S19-23		Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
The Relationship between Cognitive Impairment and Coronary Artery Disease in Middle-aged Adults.	Balbaid, Nasser T; Al-Dawalibi, Ahmad; Khattab, Abdullah M; Al-Saqr, Fahad; AbuSittah, Abdulrahman; Alqarni, Sami; Habib, Syed; Iqbal, Muhammad; Bashir, Shahid	2020	Cureus	12	1	e6724	https://dx.doi.org/10.7759/cureus.6724	Exclusion reason: Sex of participants was not specified
The relationship between regional brain volumes and the extent of coronary artery disease in mild cognitive impairment	Barekatain, Majid; Askarpour, Hedyeh; Zahedian, Faezeh; Walterfang, Mark; Velakoulis, Dennis; Maracy, Mohammad Reza; Jazi, Mohammad Hashemi	2014	Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences	19	8	739-45		Exclusion reason: No separate analysis for sexes
The relationship of hypertension in the elderly to AD, vascular dementia, and cognitive function	Posner, H. B.; Tang, M. X.; Luchsinger, J.; Lantigua, R.; Stern, Y.; Mayeux, R.	2002	Neurology	58	8	1175-81		Exclusion reason: No separate analysis for conditions
The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial	Lithell, Hans; Hansson, Lennart; Skoog, Ingmar; Elmfeldt, Dag; Hofman, Albert; Olofsson, Bertil; Trenkwalder, Peter; Zanchetti, Alberto; Group, Scope Study	2003	Journal of hypertension	21	5	875-86		Exclusion reason: Brief report
The Sydney Centenarian Study: methodology and profile of centenarians and near-centenarians	Sachdev, Perminder S.; Levitan, Charlene; Crawford, John; Sidhu, Mamta; Slavin, Melissa; Richmond, Robyn; Kochan, Nicole; Brodaty, Henry; Wen, Wei; Kang, Kristan;	2013	International psychogeriatrics	25	6	993-1005	https://dx.doi.org/10.1017/S1041610213000197	Exclusion reason: No separate analysis for conditions

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
	Mather, Karen A.; Sydney Centenarian Study, Team							
The Synergistic Effects of Anxiety and Cerebral Hypoperfusion on Cognitive Dysfunction in Older Adults With Cardiovascular Disease	Alosco, M. L.; Gunstad, J.; Beard, C.; Xu, X. M.; Clark, U. S.; Labbe, D. R.; Jerskey, B. A.; Ladino, M.; Cote, D. M.; Walsh, E. G.; Poppas, A.; Cohen, R. A.; Sweet, L. H.	2015	J. Geriatr. Psychiatry Neurol.	28	1	57-66	10.1177/0891988714541871	Exclusion reason: No separate analysis for sexes
Tissue plasminogen activator administration does not result in clinically relevant neuropsychological dysfunction in patients with myocardial ischemia	Gomez Beldarrain, Marian; Ruiz de Velasco, Ivone; Garcia-Monco, Juan C.	2002	Cerebrovascular diseases (Basel, Switzerland)	13	4	279-84		Exclusion reason: No separate analysis for sexes
Transient left ventricular dysfunction during provocative mental stress in patients with coronary artery disease	LaVeau, P. J.; Rozanski, A.; Krantz, D. S.; Cornell, C. E.; Cattanach, L.; Zaret, B. L.; Wackers, F. J.	1989	American heart journal	118	1	08-Jan		Exclusion reason: Men only
Two-year course of cognitive function and mood in adults with congestive heart failure and coronary artery disease: the Heart-Mind Study	Almeida, Osvaldo P.; Beer, Christopher; Lautenschlager, Nicola T.; Arnolda, Leonard; Alfonso, Helman; Flicker, Leon	2012	International psychogeriatrics	24	1	38-47	https://dx.doi.org/10.1017/S1041610211001657	Exclusion reason: No separate analysis for sexes
Type II diabetes and cognitive function. A population-based study of Native Americans	Lowe, L. P.; Tranel, D.; Wallace, R. B.; Welty, T. K.	1994	Diabetes care	17	8	891-6		Exclusion reason: Does not mention any CHD in methods or analysis
Use of lipid-lowering drugs in older adults with and without dementia: a community-based epidemiological study	Rodriguez, E. G.; Dodge, H. H.; Birzescu, M. A.; Stoehr, G. P.; Ganguli, M.	2002	Journal of the American	50	11	1852-1856	10.1046/j.1532-5415.2002.50515.x	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
			Geriatrics Society					
Use of p300 cognitive evoked potentials in the diagnosis of impairments of higher mental functions after cardiac surgery in conditions of cardiopulmonary bypass	Buziashvili, Yu I.; Aleksakhina, Yu A.; Ambat'ello, S. G.; Matskeplishvili, S. T.	2006	Neuroscience and behavioral physiology	36	2	115-8		Exclusion reason: Men only
Using pump for bypass surgery - on-off-on again?	Edwards, J. H.; Huang, D. T.	2010	Crit. Care	14	5	3	10.1186/cc9248	Exclusion reason: Brief report
Vascular factors predict rate of progression in Alzheimer disease	Mielke, M. M.; Rosenberg, P. B.; Tschanz, J.; Cook, L.; Corcoran, C.; Hayden, K. M.; Norton, M.; Rabins, P. V.; Green, R. C.; Welsh-Bohmer, K. A.; Breitner, J. C. S.; Munger, R.; Lyketsos, C. G.	2007	Neurology	69	19	1850-8		Exclusion reason: No separate analysis for conditions
Vascular risk and cognitive impairment in an older, British, African-Caribbean population	Stewart, R.; Richards, M.; Brayne, C.; Mann, A.	2001	Journal of the American Geriatrics Society	49	3	263-9		Exclusion reason: No separate analysis for conditions
Vascular risk factors and intensity of cognitive dysfunction in MCI	Siuda, Joanna; Gorzkowska, Agnieszka; Opala, Grzegorz; Ochudlo, Stanislaw	2007	Journal of the neurological sciences	257	02-Jan	202-5		Exclusion reason: No separate analysis for sexes
Vascular risk factors and mild cognitive impairment in the elderly population in Southwest China	Zou, Yan; Zhu, Qinlan; Deng, Yongtao; Duan, Jingxi; Pan, Ling; Tu, Qi; Dai, Rong; Zhang, Xuemei; Chu, Leung-Wing; Lu, Yang	2014	American journal of Alzheimer's disease and	29	3	242-7	https://dx.doi.org/10.1177/1533317513517042	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
			other dementias					
Vascular risk factors in mild cognitive impairment subtypes	Mariani, E.; Monastero, R.; Ercolani, S.; Mangialasche, F.; Caputo, M.; Feliziani, F. T.; Vitale, D. F.; Senin, U.; Mecocci, P.	2007	Dementia & Geriatric Cognitive Disorders	24	6	448-456		Exclusion reason: Not pertinent research (e.g., protocol registration)
Vascular risk factors in mild cognitive impairment subtypes. Findings from the ReGAl project	Mariani, E.; Monastero, R.; Ercolani, S.; Mangialasche, F.; Caputo, M.; Feliziani, F. T.; Vitale, D. F.; Senin, U.; Mecocci, P.; Re, GAl Study Group	2007	Dementia and geriatric cognitive disorders	24	6	448-56		Exclusion reason: Duplicate
Vascular, cognitive, and psychomental survey on elderly recycling volunteers in northern Taiwan	Chen, G.-C.; Chen, P.-Y.; Su, Y.-C.; Hsiao, C.-L.; Yang, F.-Y.; Hsu, P.-J.; Lin, S.-K.	2019	Frontiers in Neurology	10	JAN		10.3389/fneur.2018.01176	Exclusion reason: Does not mention any CHD in methods or analysis
Vascular, Cognitive, and Psychomental Survey on Elderly Recycling Volunteers in Northern Taiwan	Chen, Guei-Chiuan; Chen, Pei-Ya; Su, Yu-Chin; Hsiao, Cheng-Lun; Yang, Fu-Yi; Hsu, Po-Jen; Lin, Shinn-Kuang	2019	Frontiers in Neurology	9		1176	10.3389/fneur.2018.01176	Exclusion reason: Duplicate
Vascular, Cognitive, and Psychomental Survey on Elderly Recycling Volunteers in Northern Taiwan.	Chen, Guei-Chiuan; Chen, Pei-Ya; Su, Yu-Chin; Hsiao, Cheng-Lun; Yang, Fu-Yi; Hsu, Po-Jen; Lin, Shinn-Kuang	2018	Frontiers in neurology	9	10154689	1176	https://dx.doi.org/10.3389/fneur.2018.01176	Exclusion reason: No separate analysis for sexes
Verbal memory performance and completion of cardiac rehabilitation in patients with coronary artery disease	Swardfager, Walter; Herrmann, Nathan; Marzolini, Susan; Oh, Paul I.; Saleem, Mahwesh; Shammi, Prathiba; Kiss, Alexander; Cappell, Jaclyn; Lanctot, Krista L.	2011	Psychosomatic medicine	73	7	580-7	https://dx.doi.org/10.1097/PSY.0b013e318227fff9	Exclusion reason: No separate analysis for sexes

Title	Authors	Published Year	Journal	Volume	Issue	Pages	DOI	Reason for exclusion
Vitamin E, vitamin C, beta carotene, and cognitive function among women with or at risk of cardiovascular disease: the Women's Antioxidant and Cardiovascular Study	Kang Jh, Cook N. R. Manson J. E. Buring J. E. Albert C. M. Grodstein F.	2009	Circulation	119	21	2772		Exclusion reason: No separate analysis for conditions
White Matter Microstructural Integrity Is Associated with Executive Function and Processing Speed in Older Adults with Coronary Artery Disease	Santiago, Calvin; Herrmann, Nathan; Swardfager, Walter; Saleem, Mahwesh; Oh, Paul I.; Black, Sandra E.; Lanctot, Krista L.	2015	The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry	23	7	754-63	https://dx.doi.org/10.1016/j.jagp.2014.09.008	Exclusion reason: No separate analysis for conditions

Appendix C – Risk of Bias Assessment

Table 1
Definition of domains for the risk of bias assessment

Bias (domains)	Low risk	High risk
1. Ascertainment of coronary heart disease and absence of any other type of cardiovascular condition	• Absence of any cardiovascular condition (i.e., stroke, congenital heart disease, cardiac arrest, heart failure) at baseline confirmed by medical records and/or pathological evidence • Clinical diagnosis of coronary heart disease condition specified by: o Medical records; or o Self-reported history (corroborated by e.g., medical records, pathological evidence, cardiologist); or o Assessed by cardiologist/medical practitioner	• Presence of any other concomitant cardiovascular condition (i.e. a participant that had a myocardial infarction and a cardiac arrest) • Coronary heart disease based on self-report only • Corroborating evidence (e.g., medical records, medical assessment) lacking or not specified
2. Ascertainment of cognitive impairment	• Absence of cognitive impairment prior to participation in the study: o Confirmed by medical records or cognitive assessment o Assessed by a physician (i.e. family doctor) /neuropsychologist or a clinical psychologist with training in this area	• Absence of cognitive impairment prior to participation in the study: o Not confirmed by medical records or cognitive assessment. Means of confirming absence of cognitive impairment lacking or not specified o Qualifications/training of the individual performing the assessment are not specified.

Bias (domains)	Low risk	High risk

	• Researchers excluded participants that had signs of cognitive impairment or dementia after administering a cognitive screener (e.g., MMSE, MoCA)
	  ○ Confirmation from physician/neuropsychologist and/or pathological evidence
		• No mention of researchers excluding participants with signs of cognitive impairment or dementia after administration of cognitive screener
		  ○ Absence of clinical diagnosis

3. Blinding of personnel	• The evaluator was blind to participant's experimental condition • Complete blinding or no blinding but outcome unlikely to be influenced	<u>Unclear risk:</u> • No mention of evaluator knowledge of participant condition • No blinding, incomplete or broken blinding, and outcome likely to be influenced
4. Blinding of outcome assessment	• Neuropsychological/cognitive tests were scored by at least one independent evaluator that received training in scoring neuropsychological/cognitive tests	<u>Unclear risk:</u> • The assessment was performed by an evaluator, and it appears that it was scored by them as well. • Unclear if assessor was blind

Bias (domains)	Low risk	High risk
	• Complete blinding or no blinding but measurement unlikely to be influenced	• No mention of who scored the neuropsychological/cognitive tests • No blinding or broken blinding, and measurement likely to be influenced
5. Incomplete outcome data	• No missing data • Reasons for missing data not related to outcome • Missing data balanced across groups, and reasons similar • Proportion missing or plausible effect size not enough to have a clinically relevant effect	• Reasons related to outcome, and imbalance in numbers or reasons • Proportion missing or plausible effect size enough to have a clinically relevant effect • 'as-treated' analysis with substantial departure from allocation • Inappropriate use of imputation
6. Selective reporting	• Protocol is available and all pre-specified outcomes of interest to the review reported in the pre-specified way • Protocol not available but it is clear that all pre-specified and expected outcomes of interest are reported	• Outcomes not reported as pre-specified or expected • Outcomes reported incompletely so they cannot be entered in review
7. Potential confounds	• Researchers presented their results for both sexes (separately)	• Researchers did not present results for both sexes (separately)

Bias (domains)	Low risk	High risk

	• Researchers have statistically controlled for age and any other cardiovascular conditions
	• Researchers have controlled for additional potential confounds such as:
	  ○ Education
	  ○ Pharmacotherapy (e.g., anti-hypertensive medication)
	  ○ Other cardiovascular conditions (e.g., hypertension, diabetes mellitus, hypercholesterolaemia, kidney disease)
		• Researchers have not statistically controlled for age and/or cardiovascular conditions
		• Few confounds accounted for in statistical analyses (e.g., did not include education, age, hypertension, diabetes or other cardiovascular diseases as covariates)

8. Other source of bias	• Study appears to be free of other sources of risk	• Issues specific to the study design • Baseline imbalance • Blocked randomisation in unblinded trials • Differential diagnostic activity • Other bias

Table 2

Results from the risk of bias assessment at the study level

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
Arntzen et al. (2011)	High "Information on … coronary heart disease [was] obtained from self-administered questionnaires." p. 738 "Subjects with self-reported stroke were excluded" p. 738	High No mention of cognitive screening prior to participation in study.	Low No mention of personnel blinding. Outcome unlikely to be influenced because all participants had CHD.	Low No mention of who scored the cognitive tests or of blinding to participant condition. Outcome unlikely to be influenced because all participants had CHD.	Low "Complete data on baseline cardiovascular risk factors and data from at least one cognitive test were available in 5033 subjects (2227 men and 2806 women), who were included in this study." p. 738 Reasons for missing data clear and unlikely to influence outcome.	Low Pre-specified outcomes measured are reported. All the information is available in the tables and explained in the results section.	Low Statistical model adjusted for "age, education, physical activity, smoking, systolic blood pressure, total-cholesterol, HDL-cholesterol, body mass index, diabetes, coronary heart disease, and depression." p. 739	Low
Burkauskas et al. (2016)	Low "… we invited 849 consecutive patients with established CAD to take part in the study. All were attending an inpatient cardiac rehabilitation program, which they had entered within 2 weeks	Low "We had to exclude 30 of these people from the statistical analyses because they had significant	Low "The study cardiologist (J.Br.) or clinical psychologist (J.Bu.) evaluated all participants for	Low No mention of who scored the cognitive tests or of blinding to participant condition.	Low "Using these criteria, we excluded 309 (36%) of the 849 candidates: 52 (6% of the original 849) for being older	Low Protocol not available but all pre-specified outcomes are reported.	Low Several confounds accounted for: "… sociodemographic characteristics (age, sex, and	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	after receiving inpatient treatment for myocardial infarction or unstable angina pectoris." p. 92 Exclusion criteria: "A history of stroke or CABG …" p. 92	global cognitive impairment (n=1; MMSE score of 19) …" p. 93	… cognitive function." p. 93 No mention of blinding. Outcome unlikely to be influenced because all participants had CAD.	Outcome unlikely to be influenced because all participants had CAD.	than age 80, another 153 (18%) for a history of stroke or CABG, and 32 (4%) for severe concurrent somatic disease or motor function impairment. The remaining 72 (8%) candidates refused to participate in the study, had communication disabilities, or did not speak Lithuanian fluently." p. 93 Reasons for exclusion clear and unlikely to influence outcome.		education) and clinical factors (NYHA functional class, LVEF, angina pectoris, hypertension) …" p. 94	
Burkauskas et al. (2017)	Low	Unclear	Low	Low	Low	Low	Low	Low
	"Coronary artery disease (CAD) admitted to cardiac rehabilitation programs after acute coronary syndromes (ACS) such as unstable angina pectoris or	"Exclusion criteria covered subjects who were above 80 years due to increased risk of dementia and	No mention of blinding. Outcome unlikely to be influenced because all	No mention of who scored neuropsychological tests. Outcome unlikely to be influenced	"A total number of 1,292 patients were invited to participate in the study. … In sum, 465 (36%)	Protocol not available but all pre-specified and expected outcomes seem to be reported.	Several confounds accounted for: "age, gender, education, working and family status,	

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	myocardial infarction (MI)" p. 1 "Exclusion criteria covered subjects who … had a history of stroke or CABG" p. 2	Alzheimer's disease …" p. 2 Some steps taken to screen out pre-existing cognitive impairment but no cognitive screener used.	participants had CAD.	because all participants had CAD.	patients were excluded from the study." p. 2-3 Reasons for exclusion clear and unlikely to influence outcome.		current and former cardiac diagnosis and treatment, functional class as described in the guidelines provided by the NYHA, angina pectoris class, presence of hypertension …, medication, history of diabetes mellitus." p. 3	
Dijkstra et al. (2002)	Low "… first acute MI, defined as a clinical picture typical for an acute MI without cardiac arrest, a plasma concentration of aspartate aminotransferase (ASAT) twice as high as the upper limit of the normal range (80 U/1), and ECG changes specific for MI." p. 182 "Exclusion criteria were … presence of a life-threatening physical	Low "Subjects with previous or actual medical conditions with known impact on cognitive or motor functions were excluded from the selection." p. 183 "Other exclusion criteria were … chronic neural pathology (e.g.	Unclear No mention of blinding.	Unclear No mention of who scored the cognitive tests or of blinding to participant condition.	Low All data was explained in the data analysis, results and discussion sections.	Low Protocol not available but it is mostly clear that all pre-specified and expected outcomes of interest are reported via tables and in the results discussion sections.	Low Several confounds accounted for: "age, level of education, sex, and plasma concentration of aspartate transferase…" p. 182 "For an overview of the medication taken by the patients see Table 3." p. 182	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	illness (other than the present MI) …" p. 182	dementia …" p. 183						
Evans et al. (1964)	Low "All patients had been carefully evaluated medically to ensure accuracy of diagnosis … In the cardiac patients the focus was on verifying the myocardial infarction and complete examination by a neurologist was not included." p. 978	High "… complete examination by a neurologist was not included. There is thus a possibility that some MI patients may have had damage to the brain which was not apparent on gross neurological examination." p. 978	High "Except for 20 patients, all tests were administered by the first author … In most cases the patient's diagnosis was unavoidably known to the examiner at the time of testing." p. 979	Low "All tests were scored by the first author … with the patients coded to conceal identity; nevertheless, the patient's diagnosis was remembered in a few instances." p. 979 "Scoring reliability for the final 10 items was established by having 100 of the Rorschach records (50 CT and 50 MI) scored on a blind basis by a second scorer. That scoring was done by a graduate student in psychology with some	Low All data was explained in the data analysis, results and discussion sections.	Low Protocol not available but all pre-specified outcomes seem to be reported.	Unclear Authors did not take into consideration other possible variables (diabetes, hypertension, and others). However, this article was published before the confounding effects of these variables was known, and therefore cannot be considered high risk.	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
				previous Rorschach experience" p. 979				
Haring et al. (2013)	High "The composite variable of any CVD was coded as positive if the participant reported a history of myocardial infarction, angina pectoris …" p. 2 "We excluded women with a history of stroke at baseline from our analyses …" p. 2	Low "Moreover, women with MCI at baseline or missing data were not included in our analysis." p. 2 "… free of dementia at enrollment." p. 2	Low "In phase 2, certified technicians administered a modified Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery of neuropsychological assessments …" p. 2 No mention of blinding, however when reading through the description of the WHIMS study design in the Outcome Assessment section, safe to assume that the assessor was not aware of the participant's specific	Low No mention of who scored the cognitive tests or of blinding to participant condition. When reading through the description of the WHIMS study design in the Outcome Assessment section, safe to assume that the evaluator was not aware of the participant's specific cardiovascular condition.	Low "Included in this study (n=7,278) Not included in this study (n=201): H/x of Stroke (n=123) MCI at baseline (n=8) Other reasons (n=70)" p. 3 Reasons for missing data clear and unlikely to influence outcome.	Low Protocol not available but it is clear the pre-specified outcomes of interest are reported via tables and through the results and discussion sections.	Low "Model 1 adjusted for WHI Hormone Trial Randomization assignment (HTR arm), age at screening, race, education level, and baseline 3MSE … Model 2 additionally adjusted for smoking status, hypercholesterolemia, hypertension status, BMI, waist-hip ratio, depression, and aspirin use" p. 3	Unclear "Disclosures: Dr Rebecca D. Jackson reports receiving research funding from being a co-investigator of a Pfizer research grant. She also reports being on a Merck advisory committee on developing education material on fundamentals of clinical research." p. 11

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
			cardiovascular condition.					
Jaszke-Psonka et al. (2016)	Unclear "The reference group was composed of individuals after myocardial infarction without cardiac arrest …" p. 394 No mention of how the clinical diagnosis of coronary heart disease condition was specified. Possible participants may have had other concomitant cardiovascular conditions.	Unclear "The exclusion criteria were the following: … moderate or severe dementia." p. 394 Not clear if individuals who presented cognitive impairment at baseline were excluded.	Unclear No mention of blinding.	Unclear No mention of who scored the cognitive tests or of blinding to participant condition.	Low No missing data other than from those who withdrew their consent for participation in the study.	High "The following standardized clinical research tools were used for assessing cognitive function: the Mini-Mental State Examination (MMSE), a subscale of Wechsler Adult Intelligence Scale – the Digit Span test, Lauretta Bender's Visual-Motor Gestalt Test, and the Benton Visual Retention Test (BVRT)." p. 394 "In order to simplify the analysis, only scaled scores (SS) of the BVRT and	Low "The influence of the following factors on the risk of cognitive impairment was analyzed: sex, age, marital status, education, treatment with medications potentially affecting mental state, duration of SCA … invasive cardiac treatment, presence of ischemic heart disease, hypertension, and other diseases." p. 394	High "Individuals with mild hypertension without organ lesions as well as individuals with stable coronary artery disease with no previous myocardial infarction were also allocated to the control group." p. 394 Participants in the control group could have CAD. Number of participants with CAD in the control group not reported.

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
						Digit Span test were studied." p. 395 Results were not reported for all cognitive tests.		
Lipnicki et al. (2013)	High Presence of other concomitant cardiovascular conditions (see p. 3, Table 1). Not mentioned how the clinical diagnosis of coronary heart disease condition was diagnosed. However, Sydney Memory and Ageing Study does mention that it was self-report only: "the medical history included questions about vascular diseases …"	Low "Exclusion criteria included...a Mini-Mental State Examination score <24" p. 2	Low "Trained psychology graduates administered a battery of neuropsychological tests…" p. 2 No mention of blinding. Outcome unlikely to be influenced because main focus of the study was not CAD.	Low No mention of who scored the cognitive tests or of blinding to participant condition. Outcome unlikely to be influenced because main focus of the study was not CAD.	Low "Of those not assessed at follow-up, 43 were deceased and 105 declined to participate." p. 2 "Low eGFR tended to be more common among individuals lost to follow-up than among those remaining in the study" p. 5 Participants lost to follow up were statistically different from study group, however sample is large, outcome	Low All pre-specified and expected outcomes of interest are reported here or in previous publications.	High "Further limitations of our study include not considering interactions beyond those involving sex and age." p. 7	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
					unlikely to be affected.			
Morsund et al. (2019)	Low	Low	Unclear	Unclear	Low	Low	Low	Unclear
	"Aim: To study the prevalence of cognitive and emotional impairment following a minor ischemic stroke compared to an age matched group with non-ST-elevation myocardial infarction" p. 1 "NSTEMI patients were recruited from Haukeland University Hospital, ˚ Alesund Hospital, Molde Hospital, and Kristiansund Hospital in the same time." p. 2	"Exclusion criteria were as follows: … NSTEMI patients with mRS > 2 of any cause." p. 2	"Cognitive testing was performed by trained research nurses or by the neurologist responsible for the study." p. 3 No mention of blinding.	No mention of who scored the cognitive tests or of blinding to participant condition.	"In total, 324 ischemic stroke patients were included at admission and followed up at 3 months, and 288 were followed up at 12 months. Either a phone call or a letter recruited the NSTEMI group after their vascular event. 144 of 146 NSTEMI patients who accepted participation completed the questionnaire and cognitive tests." p. 3 Reasons for missing data is clearly explained.	Protocol not available but all pre-specified outcomes seem to be reported.	"… traditional risk factors including hypertension, diabetes mellitus, hypercholesterolemia, smoking, BMI ≥ 25, and brain imaging with CT and/or MRI." p. 2	"Recruitment of individuals to the control group was difficult which may have biased selection. Different study nurses and one neurologist performed testing." p. 7
Singh-Manoux et al. (2008a)	Low	High	Unclear	Unclear	Low	Low	Low	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	"MI was determined using data from questionnaires, study ECGs, hospital acute ECGs, cardiac enzymes, and physician records following MONICA criteria." p. 2101 "We excluded angina cases that were based solely on self-reported data." p. 2101	No mention of cognitive screening prior to participation in study.	No mention of blinding.	No mention of who scored the cognitive tests or of blinding to participant condition.	"Compared with those not included in the analysis, this group was younger when tested for cognition (61.0 years compared with 62.7 years), composed of fewer women (28.4% compared with 33.1%) and contained more individuals with a university degree or higher (30.4% compared with 27.5%), all P, 0.001." p. 2101 Study group differed significantly from study population. Large sample, outcome unlikely to be affected.	Protocol not available but pre-specified outcomes seem to be reported.	"Covariates used were age, sex, highest qualification on leaving full-time education …, marital status … and medication for cardiovascular disease consisting of diuretics, beta-blockers, ACE and AII inhibitors, calcium channel blockers and other antihypertensive drugs, lipid lowering drugs, nitrates, and antiplatelet drugs." p. 2101	
Singh-Manoux et al. (2008b)	Low "CHD prevalence up to Phase 7 was based on	High No mention of cognitive	Unclear No mention of blinding.	Unclear No mention of who scored the	Low "Analysis restricted to	Low Protocol not available but all	Low "Vascular risk measures were	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	clinically verified events" p. 4 "… all participants who reported an 'ever' doctor diagnosis of stroke at Phase 7 were excluded from the analyses (N=88)." p. 4	screening prior to participation in study.		cognitive tests or of blinding to participant condition.	those with complete data." Tables 1-3 "Compared to all 6550 (only 5743 of these came to the screening clinic) stroke free participants at Phase 7, this cohort included more men (72.1% against 70.6%), fewer low SES individuals (14.2% against 15.8%) and the average age of participants was lower (60.9 years against 61.07 years)." P. 543 Reasons for missing data explained. Large sample (n=3896), outcome unlikely to be influenced.	pre-specified and expected outcomes of interest are reported.	comprised of systolic blood pressure (SBP), diastolic blood pressure (DBP), serum cholesterol and body mass index (BMI)." p. 4 "Health behaviours were assessed using alcohol consumption and smoking." p. 4	
Stetkiewicz-Lewando et al. (2015)	Low "In the study group, 69 patients had experienced	High No mention of cognitive	Low The test was computerized,	Low The scoring was done by the	Low	Low Protocol not available but all	High The only variables	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
	myocardial infarction, while no infarction records were found in the medical documentation of the other 42 subjects." p. 147 "Exclusion criteria were … a history of strokes." p. 147	screening prior to participation in study.	no blinding necessary.	software, no blinding necessary.	All the data was provided in the text or tables.	pre-specified outcomes are reported.	controlled for were sex, working status and the course of the IHD (p. 150).	
Xie et al. (2019)	Low "We identified self-reported doctor-diagnosed incident CHD after wave 1" p. 3042 "… 77.5% of inci- dent CHD cases identified in this study were confirmed by ELSA researchers according to medical records." p. 3048	Low "Individuals were excluded from the current study for the following reasons: … had a confirmed diagnosis of dementia and/or Alzheimer's disease at baseline" p. 3042	Unclear No mention of blinding. Previous publications were also reviewed and no information could be found.	Unclear No mention of who scored the cognitive tests or of blinding to participant condition. Previous publications were also reviewed and no information could be found.	Low "Furthermore, we also excluded participants who were lost to follow-up from waves 2 to 8 (n = 1,644). Therefore, the analytical sample of this study comprised 7,888 participants (3,260 men and 4,628 women) with complete baseline data and at least 1 reassessment of cognitive function (at waves 2 to 8). (p.3042) Of the 9,532	Low Protocol is available and all pre-determined outcomes seem to be reported.	Unclear "These covariates included age, sex, education, marital status, body mass index, depressive symptoms, current smoking, alcohol consumption, physical activity, hypertension, diabetes, chronic lung disease, asthma, and cancer." p. 3043 "… due to lack of accurate information on the date of CHD diagnosis,	Low

Study	1. Ascertainment of CHD	2. Cognitive impairment/ dementia	3. Blinding of personnel	4. Blinding of outcome	5. Outcome data	6. Selective reporting	7. Potential confounds	8. Other
					participants who had complete data at baseline, 1,644 (17.2%) were excluded from this study because they were lost to follow-up." p. 3044 Reasons for missing data explained, outcome unlikely to be affected due to large sample size.		symptom severity, acute treatments, and medications, we were unable to control for these factors in our analyses. For instance, participants with incident CHD tend to take multiple medications during the post-CHD period." p. 3048	

Supplementary Material – PROSPERO registration

PROSPERO
International prospective register of systematic reviews

NHS National Institute for Health Research

UNIVERSITY of York
Centre for Reviews and Dissemination

Systematic review

1. * Review title.

Give the title of the review in English

Neuropsychological Sequelae of Coronary Heart Disease in Women: A Systematic Review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start.

16/08/2018

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

31/08/2020

5. * Stage of review at time of this submission.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

Reviews that have started data extraction (at the time of initial submission) are not eligible for inclusion in PROSPERO. If there is later evidence that incorrect status and/or completion date has been supplied, the published PROSPERO record will be marked as retracted.

This field uses answers to initial screening questions. It cannot be edited until after registration.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

The article is submitted for peer-review.

The article is submitted for peer-review.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Nicolas Francisco Narvaez Linares

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Mr Narvaez Linares

7. * Named contact email.

Give the electronic email address of the named contact.

[redacted]

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

[redacted]

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

[redacted]

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

University of Ottawa (Canada)

Organisation web address:

https://sciencessociales.uottawa.ca/lavcrc/

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. **NOTE: email and country now MUST be entered for each person, unless you are amending a published record.**

Mr Nicolas Francisco Linares. University of Ottawa (Canada)
Ms Marilou Poitras. University of Ottawa (Canada)
Dr Julius Burkauskas. Laboratory of Behavioral Medicine, Neuroscience Institute, Lithuanian University of Health Sciences
Ms Kalki Nagaratnam. Faculty of Health Sciences, University of Ottawa
Ms Zoey Burr. Behavioural Neuroscience Group, School of Psychology, University of Ottawa

Mr Patrick Labelle. Social Sciences Research Liaison Librarian
Dr Hélène Plamondon. University of Ottawa (Canada)

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

A doctoral research scholarship was awarded to Nicolas Francisco Narvaez Linares from the Fonds de recherche du Québec – Nature et technologies (FRQNT)

A Undergraduate Student Research Awards was awarded to Marilou Poitras from the National Science and Engineering Research Council (NSERC) of Canada

The European Social Fund under the No 09.3.3-LMT-K-712 "Development of Competences of Scientists, other Researchers and Students through Practical Research Activities" funded Julius Burkauskas research

This work was supported by a discovery grant to Hélène Plamondon from the NSERC(RG203596-13)

Grant number(s)

State the funder, grant or award number and the date of award

rg203596-13

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic).

None

We declare no conflict of interest except J.B. who in the past several years has been working as a consultant at Cogstate, Ltd. Please note that despite including studies by J.B. in this review, J.B. was not part of the team analyzing the results or consulted in this regard.

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. **NOTE: email and country must be completed for each person, unless you are amending a published record.**

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

What are the cognitive deficits associated with a coronary heart disease?

How well is the impact of the different diseases under the coronary heart disease umbrella known?

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or

attachment below.)

We will search the following electronic bibliographic databases: MEDLINE, PsycINFO, Embase, AMED, Cochrane Library, CINAHL, Web of Science, Scopus

The search will be done by Patrick Labelle, Librarian specialized in systematic reviews and meta-Analysis research, at the University of Ottawa using the following key words

CORONARY HEART DISEASE

exp myocardial ischemia/

heart diseases/

(myocard* adj3 (ischaemi* or ischemi*)).ti, ab

(myocard* adj3 infarct*).ti, ab

(heart adj3 (ischaemia or ischemi*)).ti, ab

(coronary adj3 (disease* or thrombo*)).ti, ab

(heart adj3 (infarct* or disease* or disorder* or attack* or failure*)).ti, ab

angina*.ti, ab

(cardiac adj3 arrest*).ti, ab

or/1-9

COGNITION

cognition/

cognition disorders/

cognitive dysfunction/

exp neuropsychological tests/

exp memory/

exp neurobehavioral manifestations/

mental processes/

cognition.ti, ab

((cognit* or memory or cerebr* or mental* or neurocognit* or neuropsycholog* or neurobehavi*) adj3 (declin* or defici* or function* or impair* or los* or deteriorat* or degenerat* or complain* or disturb* or disorder* or dysfunction* or decrement* or problem* or outcome*)).ti, ab.

((neuropsycholog* or cognitive) adj3 (test* or measure* or instrument* or assessment*)).ti, ab

psychometric*.ti, ab

or/11-21

COMBINE

10 and 22

Alternatives

Same search with adj2

Same search with adj

Same search with learning/ and adj3

There will be no language restrictions. No restriction will be add. The searches will be re-run just before the final analyses and further studies retrieved for inclusion.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search results.

https://www.crd.york.ac.uk/PROSPEROFILES/129133_STRATEGY_20200513.pdf

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Do not make this file publicly available until the review is complete

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

Coronary heart disease (CHD) is a catch-all phrase for a variety of conditions that affect the heart's structure and function. CHD is a type of heart disease that develops when the arteries of the heart cannot deliver enough oxygen-rich blood to the heart. (From: https://www.nhlbi.nih.gov/health-topics/ischemic-heart-disease) also known as coronary artery disease (CAD) or ischemic heart disease (IHD).

The types of CHD that will be studied in this systematic review are: a) stable angina; b) angina pectoris; c) unstable angina; d) Myocardial Infarction (heart attack); e) acute myocardial infarction; f) Sudden cardiac death

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Exclusion criteria: Children/adolescent studies (0 to 17 years old)

i. Longitudinal studies including children/adolescent

2. Studies that included only men

3. Coronary heart disease studies, but not relevant

i. This could be a clinical study looking at different outcomes, but that are not relevant for our research

4. Other cardiovascular diseases

i. Stroke, cardiac arrest, congestive heart disease, heart failure, etc.

5. Other medical conditions

6. No psychological assessment

i. There was no cognitive or neuropsychological assessment

7. Not Relevant research

i. Thesis/dissertation (master and PhD), conference presentation/paper, books, Abstracts, Chapter sections, Oral presentation, Transitional approaches

8. Studies presented in languages other than English

9. Uncertain studies/Not sure (head author will take the decision)

i. Articles that were not found were checked="checked" value="1" in three different databases.

10. Not relevant studies

i. Animals (rats, mice), Meta-analysis or Systemic Review, Program evaluation, Case studies, Erratum studies

Inclusion criteria

1. Any type of coronary heart diseases:

Coronary artery disease, Ischemic heart disease Stable angina, Angina pectoris, Unstable angina, Myocardial infarction, Acute myocardial infarction, Heart attack, Sudden cardiac death

2. Neuropsychological assessment and variations:

Neuropsychiatric assessment, Psychological assessment, Psychiatric assessment, Cognitive assessment, Psychoeducational assessment

3. Studies that included Women

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Not applicable

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

Any study, no matter the goal, that included women who had a coronary heart disease and did a neuropsychological or cognitive assessment

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

a) Did not be full text reviews studies will be excluded if:

b) Did not separate analysis for conditions (e.g., authors include in their definition of CHD other cardiovascular conditions (i.e., heart failure) but did not do a separate analysis of the different conditions)

c) Did not mention the sex of participants

d) Only men

e) Articles not available in English

f) Articles that are not available (corresponding authors will be contacted at least twice before classifying a research in this category)

g) Articles not found (we could not find the article in the different databases)

h) Not relevant research (e.g., congestive heart disease)

i) Does not mention any CHD in their methods or analysis (After reading the methods and result sections, there was no mention of a CHD or it is synonyms (including each CHD)

j) Did not perform a neuropsychological assessment.

k) Brief article with little information (the article is so short that it is impossible to extract any information)

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

This review will aim to provide what kind of neuropsychological tests are used to assess the effects of coronary heart disease in women.

This review will also allow to report the cognitive impact of a coronary heart disease in women.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state 'None' or 'Not applicable' as appropriate to the review

Not applicable

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

Not applicable

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with the one the first co-authors (NFNL).

Studies that remained in the full-text review section will be screened independently by two review authors to identify studies that potentially meet the inclusion criteria outlined above and will be retrieved and independently assessed for eligibility by two team members. Any disagreement between them over the eligibility of particular studies will be resolved through discussion with both first co-authors (NFNL & MP).

A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: participant's demographic information, exclusion criteria, type of CHD, type of neuropsychological tests used, and the results from the different cognitive domains that were assessed. Two review authors will extract data independently, discrepancies will be identified and resolved through discussion with the two first co-authors NFNL & MP.

Missing data will not be requested from study authors.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

Every step will be reviewed by a peer. In case of disagreement between two individuals, one of the first Authors will be involved in the selection step, the risk of bias assessment tool that will be used is the Cochrane Collaboration's tool for assessing risk of bias in randomised trials by Higgins et al. (2011; doi: 10.1136/bmj.d5928). In addition, we will use the adapted version of Cochrane Collaboration's tool from Stefanidis et al. (2018; doi: 10.1007/s11065-017-9359-z)

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This **must not be generic text** but should be **specific to your review** and describe how the proposed approach will be applied to your data. If meta-analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

The general approach to synthesis for this review will be narrative (descriptive). Quantitative synthesis will be used if the included studies are sufficiently homogenous.

As for the narrative approach of this review, we will report how the different cognitive areas (e.g., general intellection functioning, attention/Working memory, etc) were assessed (which psychological tests). In addition, we will report if there was any clinical significance between control groups and experimental. We will use Excel Microsoft to compile the results.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

None planned.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Living systematic review
No

Meta-analysis
No

Methodology
Yes

Narrative synthesis
No

Network meta-analysis
No

Pre-clinical
No

Prevention
Yes

Prognostic
No

Prospective meta-analysis (PMA)
No

Review of reviews
No

Service delivery
No

Synthesis of qualitative studies
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
Yes

Care of the elderly
No

Child health
No

Complementary therapies
No

COVID-19
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
Yes

Infections and infestations
No

International development
No

Mental health and behavioural conditions
No

Musculoskeletal
No

Neurological
Yes

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Surgery
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Canada

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol.

Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

No I do not make this file publicly available until the review is complete

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

In addition to producing a report for the funders of this review, which will be made available free of charge on their website, a paper will be submitted to a leading journal in this field as well as different poster presentations at conferences.

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Systematic Review

Coronary Heart Diseases

Women

Neuropsychological Assessment

Cognitive impairment

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published.New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

3.8.0 References

See Chapter 8 – Références de la thèse for the references. The specific references for this article are available in the published format (see online publication)

Chapitre IV – Enquête par questionnaire auprès d'un échantillon de femmes ayant vécu un infarctus du myocarde

4.0 Myocardial Infarction in a sample of Canadian Women: An exploratory study of symptomology and prominent risk factors

Narvaez Linares, N. F.[a], Person, E.[a], & Plamondon, H.[a †]

[a] Behavioural Neuroscience Group, School of Psychology, University of Ottawa, 136 Jean-Jacques Lussier, Ottawa, On, K1N 6N5, Canada

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CRediT author statement

Conceptualization	N.F.N.L..; H.P.
Methodology	N.F.N.L.
Formal Analysis	N.F.N.L.; E.P.
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This manuscript is in development, and significant modifications will be made before it is submitted for publication (e.g., adding different variables studied not presented here).

Abstract

Myocardial infarction (MI) is one of the leading causes of death in women. However, research and clinical trials on these conditions have remained centred on men, significantly affecting the knowledge base of clinicians, women, and the general public. In this online survey, we aimed to characterize symptoms of MI, the prevalence of different factors commonly present (i.e., hypercholesterolemia, hypertension, diabetes mellitus) and specific characteristics (e.g., menopause, pregnancy) with a history of MI. A sample of Canadian women who experienced a MI (n = 96) responded to a 15-min online survey about their sociodemographic characteristics and medical history. The survey was available in French and English and was created based on the World Health Survey of the World Health Organization. We found that in addition to MI symptoms commonly reported in both sexes, women reported symptoms such as anxiety, shortness of breath, and unusual tiredness. Furthermore, some symptom clusters were identified. Hypertension and hypercholesterolemia were associated with each other and were diagnosed prior to a first MI in most participants. These results support commonalities between the trajectory of MI in Canadian women and those observed in other women's samples.

Keywords: myocardial infarction, heart attack, women, specific symptoms, risk factors, hypercholesterolemia, hypertension, diabetes mellitus Type 2

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
CHD	Coronary heart disease
HD	Heart disease
MI	Myocardial infarction
T2D	Diabetes mellitus Type 2

4.1.0 Introduction

Cardiovascular disease (CVD), the leading cause of death worldwide (WHO, 2017c), is an umbrella term for a variety of medical conditions affecting the circulatory system (null null et al., 2009), including dysfunctions of the heart (e.g., coronary heart disease; CHD) or blood vessels (e.g., ischemic stroke). Heart disease (HD), the second leading cause of death among Canadians, is a type of CVD that accounts for the death of one Canadian every 7 minutes (Public Health Agency of Canada [PHAC], 2017). The largest subcategory of HD is CHD, defined as any condition specifically affecting the heart's structure or function (null null et al., 2009). Coronary artery disease and ischemic heart disease are also terms used to refer to CHD. Atherosclerosis and the associated narrowing/hardening of coronary arteries contribute to inflammatory processes (Davis, 2005; Lüscher, 2016) and reduced oxygen and nutrient supplies (Pepine et al., 2006), which cause chronic hypoperfusion to the heart and lead to CHD. If left untreated, this condition eventually results in myocardial infarction (MI; Naik et al., 2006; Thygesen et al., 2012) – commonly known as a heart attack – from which one person dies every 40 seconds in the United States (Virani, et al., 2020). In Canada, approximately 8.5% of adults over the age of 20 years have been diagnosed with CHD, 24% of whom have experienced a MI (PHAC, 2017).

Unfortunately, although a woman dies from HD every 20 minutes in Canada (Heart & Stroke, 2018) and every minute in the United States (Mikhail, 2005), sex[4] bias remains prevalent in medical research assessing heart health (Clayton & Arnegard, 2018): an estimated two-thirds of the current studies on HD remain centred on findings among men (Heart & Stroke, 2018). For

[4] Gender refers to the social and psychological constructs based on a person's identity, whereas sex refers to the biological aspects of a person. We will use the term sex in this manuscript to refer to research that studied either biological men or women or both.

example, when treating women, healthcare policymakers and providers often refer to medical guidelines that are derived from research conducted on men (Ballantyne & Rogers, 2011; Yoon et al., 2014). Consequently, researchers investigating interventions for MI often fail to establish proper conclusions on the safety and efficacy of these interventions for women (Johnson et al., 2014).

This discrepancy is reflected in the quality of care provided by medical professionals. In the early 2000s, Mosca et al. (2005) found that fewer than 20% of physicians reported awareness of increased vulnerability to CVD in women compared to men. A decade later, Bairey Merz et al. (2017) identified that only 22% of primary care physicians and 42% of cardiologists reported being adequately qualified to assess HD risk in women. As such, women are less likely than men to be informed of individual HD risks and to discuss these risks with their physicians (Leifheit-Limson et al., 2015). Unsurprisingly, women experiencing MI are undertreated and receive reduced medical care for this condition compared to men, leading to increased mortality rates (T. A. Beery, 1995; Bucholz et al., 2014; Li et al., 2016). Moreover, Greenwood et al. (2018) demonstrated that women are less likely to survive a MI when treated by male versus female physicians. This inequity extends to ethnicity/race. Despite a greater risk of MI in Black women, they receive less adequate preventive therapies (i.e., acetylsalicylic acid, statins) and/or information on therapeutic lifestyle changes compared to men and to White women (Abuful et al., 2006; Jha Ashish K. et al., 2003). Together, these factors contribute to sex disparities in diagnosis, survival rates, and treatment following a MI.

4.1.1 MI Symptomatology in Women

The clinical presentation of MI in women remains underrecognized during a medical assessment. Women's symptoms are often labelled as "atypical", strongly contributing to a lack

of proper MI diagnosis (Kosuge et al., 2006; Mosca et al., 2011). Lichtman et al. (2018) found that after consulting a physician for their cardiovascular symptoms, 53% of women – compared to 37% of men ($p < 0.001$) – reported being told that their symptoms were not heart-related, even though they were experiencing a cardiovascular event at that moment. This lack of medical knowledge contributes to women's reduced awareness about MI symptomatology and presentation. For example, McDonnell et al. (2014) showed that fewer than 50% of women are aware that MI symptoms differ between sexes, a disparity related in part to the enduring belief that MI predominantly affects men (Clayton & Arnegard, 2018). Promisingly, whereas only 30% of women knew HD to be the leading of cause of women's death in 1997, Virani et al., (2020) reported this proportion to reach 56% in 2012, supporting increased, but still insufficient, awareness.

A hallmark symptom observed in men and women experiencing MI is angina pectoris (Ferry et al., 2019; Lichtman et al., 2018), commonly referred to as chest pain. Otherwise, MI symptoms in women tend to be more diffuse, including an ache or pressure across the upper back and upper abdomen, shortness of breath, extreme fatigue, dizziness, lightheadedness, and fainting. In contrast, men report localized symptoms such as an aching sensation in the arms and neck, jaw pain, and heartburn (Dey et al., 2009; Kim et al., 2010; Lichtman et al., 2018). Typically, women's symptoms are more subtle (Kim et al., 2010; Lichtman et al., 2018), and more likely to be associated to non-threatening life conditions such as acid reflux, flu, anxiety, and even normal aging (Albarran et al., 2007; Dempsey et al., 1995). As such, 78% of women miss early detection of MI symptoms (Heart & Stroke, 2018). Furthermore, some symptoms of menopause (e.g., hot flashes, cold sweats, tiredness) may impair the assessment of MI symptoms (Nasreen, 2019), making menopausal women more likely than non-menopausal women to

dismiss MI symptoms and delay seeking medical assistance (Canto et al., 2007; Lefler & Bondy, 2004). This is particularly important given the sharp increase in the incidence of MI approximately 9 to 10 years following the onset of menopause (Anand et al., 2008; Misra et al., 2001). Virani et al. (2020) reported that women have their first MI, on average, at 72.0 years old compared to men at 65.6 years old.

4.1.2 Notable MI Risk Factors in Women

Several risk factors increase the likelihood of having a MI (Pedersen et al., 2016). Seeing as most research on risk factors has been conducted in men, the extant literature likely underestimates environmental and physiological factors that may be more critical for women. While men and women share most HD risk factors (e.g., smoking, body mass index [BMI]; Andrés et al., 2011; Millett et al., 2018), there is support for distinct factors that represent a higher relative risk for women compared to men (Anand et al., 2008; Andrés et al., 2011; Mosca et al., 2011). Notably, hypercholesterolemia, hypertension, and diabetes mellitus type (T2D) share common pathophysiological aspects (Bloomgarden, 2007; Petrie et al., 2018; Sehestedt et al., 2011), which have common risk factors like smoking, being overweight or obese, and aging. These diseases are strikingly prominent in women. In one of the few studies looking at the association between these diseases and stroke and MI in both sexes, Lu et al. (2019) found that a history of hypertension and hypercholesterolemia increases the risk of MI.

4.1.2.1 Hypercholesterolemia

Hypercholesterolemia is a well-established risk factor for the development of atherosclerosis, which increases MI incidence (Mehta, Beckie Theresa M., et al., 2016; Pearson & Myerson, 1997). Plasma cholesterol levels are primarily regulated by high-density lipoproteins (HDL) and low-density lipoproteins (LDL; Félix-Redondo et al., 2013), often referred to as

'good' and 'bad' cholesterol, respectively. While overall cholesterol levels are lower in young women, levels rise acutely after menopause, leading to an atherogenic lipid profile (Polotsky & Polotsky, 2010), characterized by decreased HDL levels, increased LDL and triglycerides levels (Meagher, 2004), and an increased risk of MI for postmenopausal women (Pardhe et al., 2017).

4.1.2.2 Hypertension

Hypertension has a long history as the leading cause of HD (Jónsdóttir et al., 2002; S. C. Smith et al., 2006). Os et al. (1993) attributed 39% of MI to untreated hypertension, and Levy et al. (1996) later confirmed MI risk to be 6-fold in patients with hypertension, related to promptness in developing CHD. Consistent with earlier studies, the American Heart Association reported that hypertension was comorbid in 69% of Americans who experienced their first MI (Benjamin et al., 2019). However, sparse, sex-specific data support a higher prevalence of hypertension as a risk factor for MI in women than in men (Andrés et al., 2011). More importantly, women demonstrate a marked increase in hypertension incidence as the physiological process of menopause begins due to associated hormonal changes (Roger et al., 2011; Gudmundsdottir et al., 2012). After achieving a menopausal state, women are at greater risk of dying from hypertension-related CVD than men (Gudmundsdottir et al., 2012).

4.1.2.3 Diabetes Mellitus Type 2

Andrés et al. (2011) found a higher prevalence of T2D in women who experienced MI compared to men, highlighting a sex-related cardiovascular vulnerability. In a comprehensive study, Barrett-Connor and Bush (1991) showed T2D to triple women's risk of developing a MI. In a meta-analysis, Huxley et al. (2006) corroborated these findings, demonstrating a 44% increased relative risk of developing CVD in women with T2D compared to men with the same glycemic condition. Although the physiological mechanisms remain to be fully understood, the

interaction between hormones (e.g., estrogen), blood sugar, and insulin may contribute to the heightened risk of atherosclerosis, plaque rupture, and hypertension (Chiha et al., 2012). Huxley et al. (2006) found that the risk of a fatal CHD was 50% higher in women with T2D compared to men, and the presence of hypertension and hyperlipidemia may explain why women have a less propitious cardiovascular profile.

4.1.3 Study Objectives

This study is part of a larger project evaluating the influence of controllable and uncontrollable factors in the context of a history of MI in women. Consequently, this is a correlational cross-sectional study using a convenience sample. We are only describing the MI participants in this article. We aimed to investigate how sociodemographic factors and self-reported factors (factors presented in section 4.1.2) are associated with a history of MI in a sample of Canadian women. In addition, we investigated possible links between MI and sex-specific characteristics (i.e., menopause).

4.2.0 Method

We followed Protogerou and Hagger's (2020) checklist for survey design quality when writing this manuscript. A panel of experts in psychology research and quality assessment created these guidelines to increase the quality and validity of survey studies in psychology by reporting crucial information.

4.2.1 Participant Characteristics

Participants were eligible to complete the online survey if they were women aged 45 to 80 years old residing in Canada. Participants were included if they: (a) reported that a physician had diagnosed them with MI (this information was self-reported); and (b) had a good

understanding of English or French. Participants were asked not to participate if they: (a) have/had a substance use disorder; (b) were currently living with or had lived with a neurological disorder or a significant psychiatric disorder; or (c) had been diagnosed with dementia. These criteria were selected because participants were invited to be part of a larger study evaluating the neuropsychological, psychological, and physiological profile of women with a history of MI.

4.2.2 Sampling Procedures

Participants were recruited through: (a) the University of Ottawa Heart Institute and its patient alumni association with flyers and posters, (b) advertisements in community centers, (c) paid and unpaid ads using social media platforms (e.g., Facebook, Twitter, Kijiji), and (d) through server lists (e.g., automated mailing lists). The survey was available online from November 1, 2018, to July 5, 2020. Participants were compensated with the opportunity to enter their name in a draw to win a prepaid Visa gift card valued at $50 (CAD). For every 50 participants, a winner was randomly selected among those who had entered their names. The ethics board of the University of Ottawa (H-06-18-639) approved this study. Prior to answering the survey, participants had to answer 'yes' to an informed consent form.

4.2.3 Data Collection

Participants completed the survey using Qualtrics®. Each survey was downloaded individually. The data were extracted and reviewed by two independent researchers to ensure accuracy prior to analyses.

4.2.4 Instrumentation

The survey was developed internally, based on existing surveys. Questions were constructed using a dichotomous (yes or no) or 5-point Likert scale; follow-up questions were prompted by particular responses, allowing us to gather additional information. As such, we

collected individualized data based on participants' medical conditions, while keeping survey completion time under 20 min. For questions pertaining to specific medical conditions, participants had the option to indicate they did not know if they had said condition. This option minimized potential confounds that could arise by imposing a choice between yes or no. Participants were asked the year of MI event(s), the year and month of CHD diagnosis (when applicable), and the year of diagnosis of the three risk factors (when applicable).

The questions related to sociodemographic variables and risk factors were inspired by comparable sections from The World Health Survey of the World Health Organization (WHO, 2002). To best address the Canadian context, the formulation and elaboration of our set of questions and responses were guided by questionnaires used by Statistics Canada (Government of Canada, 2000). The website of the Heart and Stroke Foundation of Canada was used to formulate the questions related to MI. The definition of CHD was any disease involving the heart's blood vessels and the heart itself.

The survey was initially developed in French. To ensure an equivalent English version, we followed recommended guidelines for translation and adaptation of questionnaires provided by the World Health Organization (2017a). Once the survey was translated into English, bilingual graduate students in Psychology ensured that translations led to concordant versions in both languages. Then, a panel of bilingual researchers (N.F.N.L., and H.P.) identified and resolved expressions and concepts that were judged inadequate to produce a final document – see Appendix A for the final version of the questionnaire.

We created an interactive survey to avoid having our participants spend too much time finding the questions and their respective answers. Depending on a participant's answer to a question, the survey was designed to present subsequent questions or survey sections or skip

questions or survey sections. For example, if a participant reported they had a MI/CHD, the section for MI/CHD information would be activated, while for those who did not have a MI/CHD, they would skip the entire section (would never see the questions and answers of this section). Except for age, height and weight, the answers to the questions were presented in a list format.

4.2.5 Analytic Strategy

Statistical analysis was performed using IBM SPSS Statistics 26 (IBM, 2019). Data distribution and assumptions were assessed for all variables depending on each analysis. Dichotomous and categorical variables are presented as frequencies and percentages. We replaced outliers (*z*-score or *SD* greater than ± 3) by the closest extreme value (boxplot). Associations between sociodemographic factors, women's characteristics, and risk factors were analyzed using bivariate Pearson correlations. Associations between nominal variables were analyzed using a Pearson's phi correlation coefficient if they had 2 levels, and Cramer's V if one of the variables had three or more levels. We used ANCOVA with age as a covariate to explore the effect of women's characteristics (pregnancy, menopause), CHD, and risk factors on the number of years since the first MI event. The *p*-level was set at 0.05 for all analyses.

4.3.0 Results

The average age of the sample was 62.28 years old. The majority of the women reported being White, speaking English, and residing in Ontario. Most participants had at least a post-secondary education, were married, had a BMI (self-reported) situated between the healthy and pre-obesity range, had an overall household income over $40,000 CAD, and were most likely to be unemployed/retired. Participant characteristics are presented in Table 1, and the narrative of

206 **Table 8** (Table 1 for Chapter IV) Participant characteristics

Characteristics	N	n	%
Language of survey	96		
English		93	96.88
French		3	3.13
Province of residence	96		
Ontario		58	60.42
Alberta		8	8.33
Nova scotia		8	8.33
Manitoba		7	7.29
British Columbia		6	6.25
New Brunswick		4	4.17
Québec		4	4.17
Saskatchewan		1	1.04
Age group	96		
35 – 44		1	1.04
45 – 54		16	16.67
55 – 64		37	38.54
65 – 74		31	32.29
75 – 84		10	10.42
85 +		1	1.04
Ethnicity	95		
White		89	93.68
Arab or West Asian		2	2.11
Chinese		2	2.11
Indigenous (First Nations, Métis, Inuit, Other)		1	1.05
Filipino		1	1.05
BMI (Kg/m^2)	89		
Healthy weight (18.5 - 24.9)		23	25.84
Pre-obesity (25.0 - 29.9)		32	35.96
Obesity class I (30.0 - 34.9)		19	21.35
Obesity class II (35.0 - 39.9)		8	8.99
Obesity class III (> 40)		7	7.87
Marital status	96		
Currently married		51	53.13
Divorced		17	17.71
Common-law or in a relationship		13	13.54
Single		6	6.25
Widowed		7	7.29
Separated		2	2.08
Education level	96		
No certificate, diploma, or degree		5	5.21
Secondary (high) school diploma or equivalency certificate		27	28.13

Certificate of apprenticeship, certificate of Qualification, or Trades certificate		5	5.21
College, Cégep, or other non-university certificate diploma		27	28.13
University certificate or diploma below bachelor level		2	2.08
Bachelor's degree		21	21.88
Professional degree (e.g., MD)		2	2.08
Master's degree		7	7.29
Earned Doctorate		0	-
Household income (CAD $)	93		
<19,999		6	6.45
20,000 - 29,999		13	13.98
30,000 - 39,999		9	9.68
40,000 - 49,999		10	10.75
50,000 - 59,999		8	8.60
60,000 - 69,999		13	13.98
70,000 - 79,999		5	5.38
80,000 - 89,999		6	6.45
90,000 - 99,999		7	7.53
+100,000		16	17.20
Employment	92		
Full-time employee		18	19.57
Part-time employee		14	15.22
Self-employed		9	9.78
Unemployed or retired		48	52.17
On social welfare		3	3.26
Type of contraception	95		
No contraceptive		93	97.89
Oral contraceptive pill		0	-
Contraceptive patch		0	-
Vaginal ring		0	-
Intrauterine contraception		2	2.11
Injectable contraception		0	-
Hormonal replacement therapy	96		
No		94	97.92
Yes		2	2.08
Menopause	95		
No		11	11.58
Yes		84	88.42
State of menopause	84		
"I am in the process of the menopause period"		12	14.29
"My menopause is over"		72	85.71
Type of surgery (reproductive organs)	94		
"I had a bilateral oophorectomy''		2	2.13

"I had a hysterectomy, with or without oophorectomy"		25	26.60
No surgery		67	71.28
If surgery	27		
Before their menopause		22	81.48
During their menopause		3	11.11
After their menopause		2	7.41
Pregnancy	96		
No		21	21.88
Yes		75	78.13
Number of childbirths	75		
0		4	5.33
1		15	20.0
2		31	41.33
3		17	22.67
4		5	6.67
5		3	4.00
Heart complications following delivery	75		
No		72	96.0
Yes		3	4.0
Number of MI	96		
1		72	75.0
2		15	15.63
3		6	6.25
4		0	-
5+		3	3.13
Diagnosis of CHD	96		
No		35	36.46
Yes		61	63.54

the data preparation and descriptive statistics (e.g., frequency, mean) is reported as supplementary material. Table 2 presents the distribution of MI symptoms and Table 3 presents the information about the three risk factors. Raw data will be shared upon request.

4.3.1 Sociodemographic Factors

On average, participants completed the survey in 16.79 minutes (SD = 6.19). Seventy-four participants reported their exact age ($\bar{x}$ = 62.28 years; *SD* = 8.43), whereas the remainder selected an age category. For the analyses, participants who did not disclose their exact age (*n* = 22) were assigned the median of each corresponding category ($\bar{x}$ = 62.85, *SD* = 8.73). The average BMI in this study was 29.10 Kg/m^2 (*n* = 89; *SD* = 5.90). We assessed the BMI by comparing participants in two categories: a BMI over 30 (*n* = 33; 37.08%) compared to a BMI under 30 (*n* = 56; 62.92%). We added this supplementary analysis to investigate if one of the broader categories would have an association or not. The BMI category was negatively correlated with household income (r = - 0.22, p = 0.038) and age (r = - 0.22, p = 0.038). We found no significant association between the number of MI events and BMI categories (χ^2 = 2.74, p = 0.25).

4.3.2 Women's Reproductive Characteristics

Three quarters of participants (78.13%; *n* = 75) experienced a pregnancy, 94.67% (*n* = 71) of which reported at least one childbirth, with an average of 2.17 children (*SD* = 1.47). We investigated possible links between childbirth and MI. The first MI event was experienced on average 29.27 years (*SD* = 10.73; *n* = 55) following last childbirth. Only three women mentioned heart complications following delivery. Neither pregnancy itself nor the number of childbirths were significantly correlated with the number of MI (r = 0.15, p = 0.36 and r = 0.08, p = 0.48, respectively).

Table 9 (Table 2 for Chapter IV) *Symptoms of MI*

Symptoms	N	n	%
Type of symptoms	96		
Unusual tiredness		35	36.46
Sleeping problems		13	13.54
Shortness of breath		36	37.50
An uncomfortable pressure, compression, or pain in the chest that lasted a few minutes, then came and went		58	60.42
Pain or discomfort on one arm		23	23.96
Pain or discomfort on both arms		13	13.54
Pain or discomfort on the back		29	30.21
Pain or discomfort on the neck		21	21.88
Pain or discomfort on the jaw		22	22.92
Pain or discomfort on the upper part of the abdomen		32	33.33
Signs of cold sweats		31	32.29
Signs of loss of consciousness		8	8.33
Signs of nausea/vomiting		33	34.38
Signs of dizziness		26	27.08
Signs of anxiety		43	44.79

There was no significant correlation between the number of childbirths and the time elapsed between the last childbirth and the first MI event (r = 0.02, p = 0.88

We found no correlation between menopausal status and the number of MI events (r = 0.11, p = 0.69), possibly due to the majority of our sample reporting having experienced menopause. Based on the reported year of the first MI event, results indicated no association between reproductive organ surgery and time of MI occurrence (F [1, 74] = 0.48, p = 0.49, η^2 = 0.006). We found that women who reported having undergone reproductive organ surgery also reported lower household income (r = - 0.23, p = 0.030).

4.3.3 Heart Disease Information

On average, the first MI event was reportedly diagnosed 6 years and 6 months (n = 69; SD = 3 years and 3 months) prior to completing the questionnaire whereas CHD was reportedly diagnosed on average 7 years and 1 month prior (n = 60; SD = 6 years and 1 month). Participants' first MI and CHD diagnoses typically occurred within the same year. Only two participants reported receiving a CHD diagnosis several years prior to their first MI. One participant did not remember when she received the CHD diagnosis and was therefore excluded from this analysis. Fifteen participants failed to report the year of their first MI, and four did not remember.

4.3.4 Symptoms of Myocardial Infarction

Participants reported the symptoms associated with their last MI. On average, women reported 4.41 (SD = 2.16) symptoms. Figure 1 shows a schematic representation of the most commonly reported symptoms and Table 2 presents the complete list of symptoms. Reproductive status (non-menopausal, menopausal or post-menopausal) when experiencing MI had no significant impact on the number of reported symptoms, F (2,92) = 0.36, p = 0.70.

277 **Table 10** (Table 3 for Chapter IV) *Risk Factors of the Sample*

Characteristics	N	n	%
Hypercholesterolemia	96		
No		40	41.67
Yes		51	53.13
I do not know		5	5.21
When was the diagnosis given	51		
Before first MI event		18	50.0
Same year as MI event		17	47.22
After MI event		1	2.78
Not Reported		15	-
Hypertension	96		
No		43	44.79
Yes		50	52.08
I do not know		3	3.13
When was the diagnosis given	50		
Before first MI event		26	70.27
Same year as MI event		10	27.03
After MI event		1	2.70
Not reported		13	-
Diabetes Mellitus Type 2	96		
No		68	70.83
Yes		20	20.83
I do not know		8	8.33
When was the diagnosis given	12		
Before first MI event		4	33.33
Same year as MI event		4	33.33
After MI event		4	33.33

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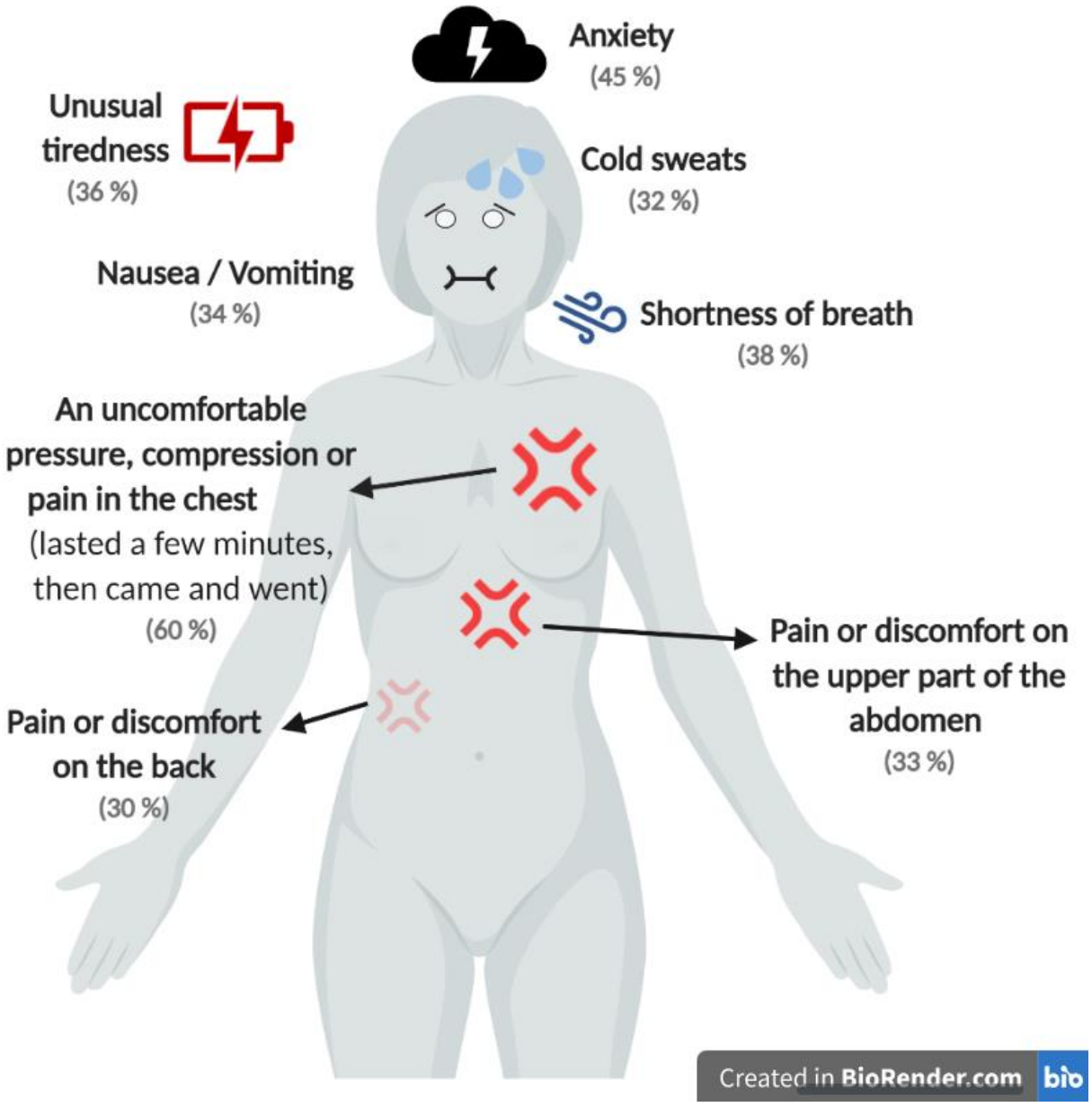
Figure 4 (Figure 1 for Chapter IV) Distribution of Commonly reported MI symptom



We examined which symptoms were often reported together and identified different symptom clusters. Unusual tiredness was correlated with sleeping problems ($r = 0.21$, $p = 0.04$), shortness of breath ($r = 0.26$, $p = 0.01$), pain in both arms ($r = -0.24$, $p = 0.02$), and dizziness ($r = 0.22$, $p = 0.03$). Feeling short of breath correlated with cold sweats ($r = 0.20$, $p = 0.05$), nausea/vomiting ($r = 0.30$, $p = 0.003$), and anxiety ($r = 0.21$, $p = 0.04$). Pain in the back correlated with pain in the jaw ($r = 0.24$, $p = 0.021$). Pain in the neck correlated with pain in the jaw ($r = 0.43$, $p < 0.001$) and loss of consciousness ($r = 0.21$, $p = 0.045$). Cold sweats correlated with nausea/vomiting ($r = 0.20$, $p = 0.046$) and anxiety correlated with dizziness ($r = -0.22$, $p = 0.03$). The correlations between all symptoms can be found in Table S2.

4.3.5 Risk factors

Tables S1summarizes all statistical findings for the three risk factors, as such we reported only relevant statistical findings in the next sections.

Time of the first MI did not differ depending on whether women were diagnosed with high cholesterol or not, $F(1,71) = 0.12$, $p = 0.73$. High cholesterol diagnoses were reportedly provided on average 15.0 years (*SD* = 10 years and 1 month) before the first MI event. Women who reported hypercholesterolemia tended to be older ($r = 0.20$, $p = 0.057$). Women with hypercholesterolemia tended to also report a hypertension diagnosis ($r = 0.34$, $p = 0.001$), but not T2D ($r = -0.066$, $p = 0.552$).

Women with and without hypertension diagnosis did not differ in the time of occurrence for the first MI, $F(1,71) = 0.20$, $p = 0.66$, $\eta^2 = 0.003$. On average, hypertension diagnosis was reportedly given 13 years prior to first MI (*SD* = 10 years and 2 months). Diagnosed hypertensive status was not correlated with T2D ($r = 0.18$, $p = 0.090$).

Women diagnosed with T2D did not report having had their first MI event earlier or later

than women without T2D, F (1,68) = 2.59, p = 0.11, η^2 = 0.037.

4.3.5.1 Comorbidity of Risk Factors

Slightly over a quarter of our sample reported no risk factors (n = 25; 26.06%) while 28.13% (n = 27) reported at least one, 40.63% (n = 39;) reported two, and 5.21% (n = 5) reported the three risk factors ($\bar{x}$ = 1.25; SD = 1.19). Fourteen participants were excluded from further analysis as they reported not knowing if they had any of the selected risk factors. Among women who reported only one MI (n = 63), a quarter (25.40%; n = 16) did not have any of the risk factors, slightly less than a third (30.16%; n = 19) had at least one risk factor, slightly more than a third (36.51%; n = 23) had at least two, and 7.94 % (n = 5) had all three. Only 14 women could be included in the 2 MI group, 3 in the 3 MI group, and 2 in the 5+ MI. Therefore, the subgroups were too small and disproportionate to statistically compare the number of risk factors.

4.4.0 Discussion

Our primary objective was to contribute to women-centric cardiovascular literature by further characterizing the distribution of MI symptoms in women within a Canadian context. In addition, we also aimed to explore the prevalence of predominant risk factors (i.e., hypercholesterolemia, hypertension, and T2D) in women with a history of MI, and investigate which women's characteristics seem to be related to a history of MI. We found that women in our sample experienced many of the symptoms that are commonly labelled as 'atypical' based on the existing literature, and that some of these symptoms appear in clusters. Furthermore, we found an association between hypercholesterolemia and hypertension, while neither were linked with presence of T2D.

4.4.1 Myocardial Infarction Symptoms and Coronary Heart Disease

As expected, the symptoms reported by women with a history of MI in our study are similar to those reported by the American Heart Association report (Virani, et al., 2020). In addition, the average number of symptoms reported by our sample (4.41 ± 2.16) is similar to the results obtained by a prospective observational study (*N* = 3501) by Brush et al. (2020), which found that women report significantly more symptoms of MI than men. In comparing the symptoms reported by our sample to the American Heart Association report for women (Virani, et al., 2020), we observed similarities: signs of anxiety, unusual tiredness, nausea/vomiting, and pain or discomfort on the upper part of the abdomen; symptoms which are often considered 'atypical'.

Moreover, when we correlated the different symptoms experienced by our participants, we found that some of the symptoms occur simultaneously whereas some are present independently. For example, women who felt short of breath tended to also report cold sweats and nausea/vomiting when they experienced a MI. These symptom clusters present some resemblances to the symptom phenotypes in the VIRGO study (Brush et al., 2020), although our sampled women surprisingly did not report any symptoms clustered with a pressure on the chest. Brush et al. (2020) found that women had different symptoms and phenotypes than men. Indeed, women experienced significantly more symptoms than men (4.3 ± 2.3 *vs* 3.9 ± 2.1; respectively) in addition to more abstract symptoms (2.7 ± 1.4 *vs* 2.6 ± 1.4 ; respectively) like diaphoresis (28.9% *vs* 37.5%), nausea (44.6% *vs* 34.9%), and back pain (16.5% *vs* 10.2%). As for phenotypes, while women reported 426 different clusters of symptoms, which was significantly higher, men reported 280. For the top 25 frequent clusters of phenotypes, 2 were similar between men and women, 6 were different between men and women, and 17 were similar for both sexes, but in a different order (based on frequency). Due to the more diffuse nature of women's

symptoms (Lichtman et al., 2018), an increased understanding of common symptom clusters could promote early detection of MI in women. This implication is particularly crucial for women who are undergoing menopause, given the overlap of some menopause symptoms with those of MI (e.g., fatigue, tiredness). Therefore, characterizing symptom clusters in various populations (e.g., age, ethnicity/race) would allow the scientific and medical communities to better inform women about prominent clusters indicative of MI, and help distinguish these symptoms from signs of normal aging.

4.4.2 Hypercholesterolemia, Hypertension, and Diabetes Mellitus

Half of the sampled women with a history of MI reported hypercholesterolemia. Of these, close to half received their diagnosis prior to a first MI while the other half received it concurrently with the first MI event. Unhealthy cholesterol levels are strongly linked with HD, and more specifically with CHD (Meagher, 2004). Increased LDL levels have been associated with plaque build-up on artery walls (Bentzon et al., 2014) and atherosclerosis (LaRosa et al., 1990), and while HDL possess anti-inflammatory and anti-thrombotic properties, insufficient HDL levels may negate the cardioprotective effects usually induced by this type of fat (Stampfer et al., 1991; Misra et al., 2001; Feingold & Grunfeld, 2018). Through an indolent progression (Bentzon et al., 2014), these physiological alterations could elevate MI risk (Ouyang et al., 2006). For example, in a large community-based study (N = 69,016), researchers found that one in 137 had a diagnosis of familial hypercholesterolemia and were more often women (Benn et al., 2012). Among those with this diagnosis, the prevalence of CHD was one-third; highlighting the close relationship between hypercholesterolemia and CHD and MI. It is well known that women receive less care and treatment for their condition (Balla et al., 2020), which puts them at a higher risk of experiencing a cardiac event. Therefore, this may explain why half of our sample

received their diagnosis at the same time as their first MI, and not before.

Similar to hypercholesterolemia, half of the women in our study reported being diagnosed with hypertension, a prevalence concordant with many other studies of women with MI (Kudenchuk et al., 1996; Lam et al., 2015; Venetsanos et al., 2017; Venskutonyte et al., 2010). Among our participants with hypertension, 70% had been diagnosed prior to having their first MI, supporting the importance of this risk factor when studying the development of CHD (Wei et al., 2017). Considering that hypertension is associated with increased myocardial stress to maintain efficient blood flow through the body (Beevers et al., 2001), it contributes over time to the development of atherosclerosis and MI (Rakugi et al., 1996). In this context, Nakanishi et al. (2017) reported that patients with hypertension have increased presence, extent, and severity of atherosclerosis, as well as significantly more cardiac events – such as MI – compared to non-hypertensive individuals. Our findings are in line with the proposed chronology of events, with women generally reporting having received a hypertension diagnosis years before their first MI event.

With respect to T2D, a link with MI could not be established as most participants did not have this condition. This may be related to the fact that the majority of our sample did not fall into the obesity category, a prominent risk factor for the development of T2D (Fletcher et al., 2002). Incidentally, women in our sample were equally diagnosed with T2D before, during, and after their MI event. Many factors could explain the distribution, T2D being a complex pathology often highly associated with genetic risk (Leong et al., 2016) and characterized by people remaining asymptomatic for long periods of time. For example, it is estimated that up to 50% of people living with T2D have not received a diagnosis (M. Harris, 2008), making it likely that some of the women in our sample were unknowingly living with this condition.

Our data showed a link between hypertension and hypercholesterolemia, partially supporting the association between hypertension and high cholesterol, and hypertension and T2D that is often noted in the literature. The absence of an association with T2D may partly be explained by the fact that our participants were mostly situated between the healthy and pre-obesity categories, which could contribute to some disparities between our results and that of other groups (Al-Goblan et al., 2014). Controllable risk factors such as hypercholesterolemia, hypertension, and T2D strongly contribute to sex differences in MI risk (Anand et al., 2008; Campbell, 2008), Moski et al. (2015) showed that the occurrence of hypertension and T2D appears elevated in samples of women compared to men. In a study where the three risk factors were assessed, Lu et al. (2019) found that hypertension and hypercholesterolemia increased the risk of MI. This finding aligns with ours, with more than two-fifths (45.83%; $n = 44$) of the sampled women reporting two or more risk factors. Comorbidity in risk factors is known to increase MI risk, especially in women: Mahmoodi et al. (2007) showed the risk of MI to be ~ 6 times higher for women with concurrent hyperlipidemia, hypertension, and T2D problems.

4.4.3 Women's Reproductive and Sociodemographic Characteristics

Pregnancy increases the risk of having a MI by three to four-fold (Ladner et al., 2005; James et al., 2006). Our data failed to find an association between pregnancy and a history of MI or CHD diagnoses, although this difference could be explained by a smaller sample size. Notwithstanding, as Kealey (2010) stated in a review article, considering that the risk of MI significantly increases with age, there is a legitimate concern from the medical community regarding women who have children at an older age (Martin et al., 2017), especially if women are Black or Latinx. While some studies have found a link between oophorectomy/hysterectomy surgeries and increased risk of CHD or MI (Colditz et al., 1987; Ding et al., 2018; Gordon et al.,

1978), others found no such associations (Howard et al., 2005; Jacoby et al., 2009). Our observations support the latter, with no detectable associations between reproductive surgery and MI occurrence.

4.5.0 Study Limitations

One of the major limitations of this study is that we do not have a comparison group (women without a MI). Another particular limitation of this study is that the information provided by participants was self-reported. Therefore, we relied on our sample to accurately remember and understand their health history. Additionally, we did not collect medication information, which restrained the interpretation of data considering the adverse effects of medication (e.g., tiredness that could explain why some participants are not engaging in physical exercise). Considering that our study is cross-sectional, the internal validity is low because inferences cannot be made (Carlson & Morrison, 2009)

While there is undeniably a possibility that the prevalence of the risk factors of interest was overestimated (Navin Cristina et al., 2016), it should be noted that the incidence of hypertension in our sample was similar to that of previous studies. We did not collect the same information from men to allow a concurrent comparison, although the abundance of existing research in men slightly attenuates this limitation. The generalizability of our findings is reduced due to the inclusion of women in a limited age range (45-80), especially given the rise of HD in younger women (S. Arora et al., 2019). Despite having a smaller sample size, our findings are consistent with those of previous studies. Nevertheless, with smaller sample sizes it is important to remain cautious in interpretating the data because of low statistical power, possible inflated false discovery rate and effect size estimation, and low reproductibility (Button et al., 2013;

Colquhoun, n.d.; Forstmeier et al., 2017).

4.6.0 Conclusion

This research aimed to contribute to characterizing women's MI symptoms and to study in more detail the prominent risk factors associated to MI within a Canadian context. We found that women experienced a variety of symptoms when they had a MI. We urge the medical community to stop using the term 'atypical' when describing symptoms that differ from those commonly seen in men.

4.7.0 Acknowledgements

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4.8.0 References

See Chapter 8 – Références de la thèse for the references.

Supplemental Material: Narrative Summary of All Variables Assessed

Please note: these data are summarized in Tables 1-3 in the manuscript.

4.3.1 Sociodemographic

Participants in this study were women (*n* = 96), of whom 96.88% (*n* = 93) completed the survey in English, taking on average 16.79 min (*SD* = 6.19; *n* = 92). Four outliers were removed because the survey completion time was above the maximum of the boxplot (29.78 minutes). The racial/ethnic composition of the sample was: White (*n* = 89; 93.68%), Arab or West Asian (*n* = 2; 2.11%), Chinese (*n* = 2; 2.11%), Filipino (*n* = 1; 1.05%), and Indigenous (*n* = 1; 1.05%). One participant did not disclose her ethnicity. Ontario was the primary province of residence (*n* = 58; 60.42%).

Seventy-four participants reported their exact age ($\bar{x}$ = 62.28 years; *SD* = 8.43), whereas the remainder selected an age category. We report here the categories of age for the sample (*N* = 96): 35 - 44 (*n* = 1; 1.04%), 45 - 54 (*n* = 16; 16.67%), 55 - 64 (*n* = 37; 38.54%), 65 - 74 (*n* = 31; 32.29%), 75 - 84 (*n* = 10; 10.42%), and one participant (1.04%) was 85+. One participant was 39 years old and one was 85 years old, which fell outside our selected age range. However, considering the known difficulty of recruiting participants for cardiovascular research, we opted to include them.

Participants were asked to provide their height (feet and inches [in] or meters; m) and weight (pounds or kilograms [Kg]). We calculated participants' BMI using the standard formula: $BMI\ (Kg/m^2) = \frac{Weight\ (Kg)}{(m^2)}$. Seven participants did not provide this information and were excluded from the calculation. Three participants were considered outliers; therefore, we corrected these values with the highest value of the boxplot (42.0 Kg/m^2). The average BMI was 29.10 Kg/m^2 (*n* = 89; *SD* = 5.90). We clustered participants according to their calculated BMI:

twenty-three (25.84%) fell in the healthy weight range (18.5-24.9 Kg/m^2), thirty-two (35.96%) in the pre-obesity range (25-29.9 Kg/m^2), nineteen (21.35%) in the obesity class I range (30-34.9 Kg/m^2), eight (8.99%) in the obesity class II range (35-39.9 Kg/m^2), and seven (7.85%) in the obesity class III range (< 40 Kg/m^2).

With respect to marital status, half of the participants were married (*n* = 51; 53.13%), seventeen divorced (17.71%), thirteen were common-law or in a relationship (13.54%), and the remaining were widowed (*n* = 7; 7.29%), single (*n* = 6; 6.25%), or separated (*n* = 2; 2.08%).

Participants reported the highest education level achieved, which we grouped into three categories for further analysis: a) No college education (*n* = 37; 38.54% [i.e., no certificate, diploma or degree; secondary (high) school diploma or equivalency certificate; certificate of apprenticeship, certificate of qualification or trades certificate]) ; b) college education level (*n* = 29; 30.21% [i.e., College, Cégep, or other non-university certificate diploma, and university Certificate or diploma below bachelor level]); and c) higher education level (*n*=30; 31.25% [i.e., Bachelor's degree, professional degree, master's degree]).

Similar to the education variable, we clustered the household annual income (in Canadian dollars) in six categories for analysis: annual income (in thousands [K]): a) less than 19K (*n* = 6; 6.45%); b) between 20K and 39K (*n* = 22; 23.66%); c) between 40K and 59K (*n* = 18; 19.35%); d) between 60K and 79K (*n* = 18; 19.35%); e) between 80K and 99K (*n* = 13; 13.98%); and f) over 100K (*n* = 16; 17.20%). Three participants did not disclose annual income.

Lastly, regarding employment status, eighteen participants reported full-time employment (19.57%), fourteen reported part-time employment (15.22%), nine reported self-employment (9.78%), forty-eight reported being unemployed or retired (52.17%), and three reported receiving social welfare aid (3.26%). Four participants did not disclose their employment status.

4.3.2 Women's Characteristics

Consistent with the mean age of the participants, 88.42% of them were menopaused (*n* = 84). Among these, seventy-two (85.71%) had completely transitioned (i.e., no menstrual periods for 12 consecutive months). Most of them were not taking any hormonal contraception 97.89%; *n* = 93) and indicated not being on hormonal replacement therapy (97.92%; *n* = 94) at the present moment, respectively. One woman did not answer these questions.

Close to three-quarters (*n* = 67; 71.28%) of women did not have a surgery of the reproductive organs, two women disclosed a past bilateral oophorectomy (2.13%), twenty-five (26.60%) a hysterectomy with or without a bilateral oophorectomy, and two participants did not answer the question. Among the twenty-seven women that had a surgery, twenty-two (81.48%) had the surgery prior to menopause, three (11.11%) had it while transitioning to the menopause period, and two (7.41%) were operated post-menopause.

4.3.3 Heart Disease Information

Participants were asked for the year of MI event(s) and year and month if they received a diagnosis of CHD, which was defined as any disease that involves the blood vessels of the heart and the heart itself. Three-quarters (75.0%; *n* = 72) experienced one MI event, while 15.63% (*n* = 15), 6.25% (*n* = 6;), and 3.13% (*n* = 3), respectively, reported having experienced 2, 3 and 5 or more MI incidents (1.41 MI events [*SD* = 1.19] once averaged). Most participants (*n* = 77; 80.21%) remembered the year when they had they first MI. In average, participants received their first MI diagnosis 6.56 (± 2.56) years from July 2020 (when the survey closed).

4.3.4 Symptoms of Myocardial Infarction

Most participants recalled between 2 and 6 symptoms (*n* = 76; 79,17%). Eight symptoms were commonly reported: a) an uncomfortable pressure, compression or pain in the chest that

lasted a few minutes, and then came and went (*n* = 58; 60.42%); b) signs of anxiety (*n* = 43; 44.79%); c) shortness of breath (*n* = 36; 37.50%); d) unusual tiredness (*n* = 35; 36.46%); e) signs of nausea/vomiting (*n* = 33, 34.38%); f) pain or discomfort on the upper part of the abdomen (*n* = 32; 33.33%); g) signs of cold sweats (*n* = 31; 32.29%); h) pain of discomfort on their back (*n* = 29; 30.21%).

4.3.5 Risk Factors

4.3.5.1 Hypercholesterolemia

Slightly over half of our participants were diagnosed with hypercholesterolemia (*n* = 51; 53.13%) and five (5.21%) reported not knowing if they had this condition. Fifteen participants were excluded from specific analysis related to MI because they did not report the date of their hypercholesterolemia diagnosis. A similar proportion of women reported receiving the diagnosis prior (*n* = 18; 50.0%) or the same year (*n* = 17; 47.22%) of their MI event, and only one person received it after (2.78%).

4.3.5.2 Hypertension

Half our participants (*n* = 50; 52.08%) reported a diagnosis of high blood pressure while three (3.13%) mentioned not knowing if they had this condition. Of those, twenty-six (70.25%) reportedly received the diagnosis before experiencing a first MI, ten (27.03%) were informed the same year as their first MI and one woman was informed after (2.70%). The average difference between the first MI and the time of diagnosis was 13 years (*SD* = 10.18). Thirteen participants were excluded from specific analysis related to MI exclusively because they did not report the date of their hypertension diagnosis.

4.3.5.3 Diabetes Mellitus Type 2

The majority of sampled women had not been diagnosed with T2D (*n* = 69; 71.88%) and

8 were not aware of their status as to this condition (8.33%). Among women diagnosed with T2D (*n* = 19; 19.79%), the same number of participants received the diagnosis before, the same year, and after (*n* = 4; 33.33%) the first MI event. Seven participants were excluded from specific analysis related to MI because they did not report the date of their T2D diagnosis.

Table 11 (Table S1 for Chapter IV) *Summary of statistical findings*

Variable 1	Variable 2	Type of statistics	Results
Sociodemographic			
BMI	Education level	Bivariate Pearson Correlation	r = -0.22, ***p* = 0.034**
BMI	Age	Bivariate Pearson Correlation	r = -0.22, ***p* = 0.041**
BMI	Marital status	Point-Biserial Correlation	r = -0.05, p = 0.62
BMI	Employment status	Bivariate Pearson Correlation	r = -0.19, p = 0.090
BMI (category)	Household income	Spearman's rank coefficient correlation	r = -0.22, ***p* = 0.038**
BMI (category)	Age	Point-Biserial Correlation	r = -0.22, ***p* = 0.038**
BMI (category)	Education level	Spearman's rank coefficient correlation	r = -0.19, p = 0.074
BMI (category)	Number of MI	Cramer's Phi	χ^2 = 2.74, p = 0.25
			r = 0.18, p = 0.25
Household income	Marital status	Cramer's Phi	r = 0.36, ***p* = 0.032**
Household income	Education level	Spearman's rank coefficient correlation	r = 0.26, ***p* = 0.012**
Household income	Employment status	Cramer's Phi	r = 0.36, ***p* = 0.001**
Women's characteristics			
Menopause status	Number of MI	Point-Biserial Correlation	r = 0.11, p = 0.69
Menopause status	CHD diagnosis	Bivariate Pearson Correlation (Phi)	r = 0.21, p = 0.13
Reproductive organs surgery	First MI event	ANCOVA	$F(1, 74) = 0.478$, p = 0.49, η^2 = 0.006
Reproductive organs surgery	Household income	Cramer's Phi	r = -0.23, ***p* = 0.030**
Reproductive organs surgery	CHD diagnosis	ANCOVA	$F(1, 55) = 0.782$, p = 0.38, η^2 = 0.014
Pregnancy	Number of MI	Point-Biserial Correlation	r = 0.15, p = 0.35

Pregnancy	CHD diagnosis	Bivariate Pearson Correlation (Phi)	r = -0.090, p = 0.40
Number of childbirths	Number of MI	Bivariate Pearson Correlation	r = 0.08, p = 0.48
Number of childbirths	CHD diagnosis	Point-Biserial Correlation	r = 0.17, p = 0.14
Number of childbirths	Difference between last childbirth and first MI event (years)	Bivariate Pearson Correlation	r = 0.020, p = 0.88
Number of childbirths	Difference between last childbirth and CHD diagnosis (years)	Bivariate Pearson Correlation	r = 0.12, p = 0.43
CHD and MI information			
CHD diagnosis	Number of MI	Point-Biserial Correlation	r = 0.15, p = 0.14
CHD diagnosis	First MI event	Bivariate Pearson Correlation	r = 0.91, $\mathbf{p < 0.001}$
Menopause status	Number of symptoms	ANCOVA	F (2,92) = 0.355, p = 0.70
Menopause status	Specific MI symptom (chest)	Bivariate Pearson Correlation (Phi)	r = 0.26, $\mathbf{p = 0.039}$
Risk factors			
Hypercholesterolemia	Age	Point-Biserial Correlation	r = 0.20, p = 0.057
Hypercholesterolemia	Education level	Cramer's Phi	r = -0.08, p = 0.43
Hypercholesterolemia	Household income	Cramer's Phi	r = -0.03, p = 0.79
Hypercholesterolemia	Employment status	Cramer's Phi	r = 0.08, p = 0.46
Hypercholesterolemia	Marital status	Bivariate Pearson Correlation (Phi)	r = -0.20, p = 0.85
Hypercholesterolemia	Reproductive organs surgery	Bivariate Pearson Correlation (Phi)	r = -0.12, p = 0.28
Hypercholesterolemia	Pregnancy	Bivariate Pearson Correlation (Phi)	r = 0.04, p = 0.70

Hypercholesterolemia	Number of childbirths	Point-Biserial Correlation	r = -0.21, p = 0.077
Hypercholesterolemia	Menopause status	Cramer's Phi	r = 0.25, p = 0.067
Hypercholesterolemia	First MI event	ANCOVA	$F(1,71)$ = 0.123, p = 0.73
Hypercholesterolemia	BMI	Student's t-test	t(82) = -0.23, p = 0.82
Hypercholesterolemia	Hypertension	Bivariate Pearson Correlation (Phi)	r = 0.34, **p = 0.001**
Hypercholesterolemia	Diabetes mellitus	Bivariate Pearson Correlation (Phi)	r = -0.07, p = 0.55
Hypertension	Age	Point-Biserial Correlation	r = 0.08, p = 0.46
Hypertension	Education level	Cramer's Phi	r = 0.09, p = 0.67
Hypertension	Household income	Cramer's Phi	r = 0.13, p = 0.90
Hypertension	Employment status	Cramer's Phi	r = 0.15, p = 0.75
Hypertension	Marital status	Bivariate Pearson Correlation (Phi)	r = -0.10, p = 0.33
Hypertension	Reproductive organs surgery	Bivariate Pearson Correlation (Phi)	r = -0.03, p = 0.80
Hypertension	Pregnancy	Bivariate Pearson Correlation (Phi)	r = 0.12, p = 0.26
Hypertension	Number of childbirths	Point-Biserial Correlation	r = -0.04, p = 0.76
Hypertension	Menopause status	Cramer's Phi	r = 0.18, p = 0.23
Hypertension	First MI event	ANCOVA	$F(1,71)$ = 0.20, p = 0.66, η^2 = 0.003
Hypertension	BMI	Student's t-test	t(84) = -1.525, p = 0.13
Hypertension	Diabetes mellitus	Bivariate Pearson Correlation (Phi)	r = 0.18, p = 0.09
Diabetes mellitus	Age	Point-Biserial Correlation	r = -0.06, p = 0.61
Diabetes mellitus	Education level	Cramer's Phi	r = 0.07, p = 0.53
Diabetes mellitus	Household income	Cramer's Phi	r = -0.04, p = 0.74
Diabetes mellitus	Employment status	Cramer's Phi	r = 0.06, p = 0.59

Diabetes mellitus	Marital status	Bivariate Pearson Correlation (Phi)	r = -0.23, ***p* = 0.031**
Diabetes mellitus	Reproductive organs surgery	Bivariate Pearson Correlation (Phi)	r = 0.09, p = 0.40
Diabetes mellitus	Pregnancy	Bivariate Pearson Correlation (Phi)	r = 0.07, p = 0.49
Diabetes mellitus	Number of childbirths	Point-Biserial Correlation	r = -0.05, p = 0.70
Diabetes mellitus	Menopause status	Cramer's Phi	r = 0.14, p = 0.46
Diabetes mellitus	First MI event	ANCOVA	F (1,68) = 2.59, p = 0.11, η^2 = 0.037
Diabetes mellitus	BMI	Student's t-test	t(80) = -1.287, p = 0.20

Table 12 (Table S2 for Chapter IV) *Correlations between self-reported syptoms*

		Sleeping Problems	Shortness of Breath	Chest Pain	Arm Pain (1)	Arm Pain (2)	Back Pain	Neck Pain	Jaw Pain	Pain in the upper abdomen	Cold Sweats	Loss of consciousness	Nausea / Vomiting	Dizziness	Anxiety
Unusual Tiredness	*r*	**.21***	**.26***	-.18	.03	**-.24***	.020	.070	.10	.20	.08	.09	.14	**.22***	.10
	p	.04	.01	.07	.76	.02	.85	.50	.32	.052	.45	.41	.19	.03	.33
Sleeping Problems	*r*		.13	.07	-.08	.021	.07	.012	.07	-.09	.18	-.01	.03	-.10	.19
	p		.19	.49	.44	.84	.49	.91	.47	.40	.08	.93	.74	.31	.06
Shortness of Breath	*r*			-.12	.02	.01	-.04	-.05	.09	-.05	**.20***	.00	**.30***	.061	**.21***
	p			.24	.86	.94	.69	.66	.39	.66	.050	1.0	.003	.56	.04
Chest Pain	*r*				.11	.01	.12	.12	-.02	.03	.10	.013	.003	-.034	.13
	p				.31	.93	.27	.25	.89	.77	.32	.90	.98	.74	.21
Arm Pain (1)	*r*					.11	.01	.12	.12	-.02	.03	.10	.01	.003	-.03
	p					.31	.93	.27	.25	.89	.77	.32	.90	.98	.74
Arm Pain (2)	*r*						-.13	.09	.15	-.15	.052	-.01	.03	-.10	.01
	p						.22	.41	.16	.14	.61	.93	.74	.31	.92
Back Pain	*r*							.15	**.24***	.02	-.07	-.20	.19	-.10	.09
	p							.16	.021	.88	.52	.053	.06	.36	.37
Neck Pain	*r*								**.43***	-.05	.07	**.21***	-.07	.13	.08
	p								.00	.61	.53	.045	.53	.20	.43

		Sleeping Problems	Shortness of Breath	Chest Pain	Arm Pain (1)	Arm Pain (2)	Back Pain	Neck Pain	Jaw Pain	Pain in the upper abdomen	Cold Sweats	Loss of consciousness	Nausea / Vomiting	Dizziness	Anxiety
Jaw Pain	*r*									-.12	.15	-.08	.18	.002	.16
	p									.23	.14	.47	.08	.98	.13
Pain in the upper abdomen	*r*										.17	-.053	.14	.07	-.15
	p										.091	.61	.18	.52	.15
Cold Sweats	*r*											-.05	**.20***	.08	.18
	p											.65	.046	.44	.07
Loss of consciousness	*r*												-.14	.16	-.044
	p												.18	.13	.67
Nausea / Vomiting	*r*													-.10	.054
	p													.35	.60
Dizziness	*r*														**-.22***
	p														.032

Note. All correlations in this table are Bivariate Pearson Correlation (Phi). * indicates a significant correlation at $p < 0.05$.**Appendix A - Questionnaire**

Cognitive and Emotional Consequences in Women following a Myocardial Infarction

Socio-demographic background

Please indicate the province where you live:

☐ Ontario

☐ Quebec

☐ British Columbia

☐ Alberta

☐ Manitoba

☐ Saskatchewan

☐ Nova Scotia

☐ New Brunswick

☐ Newfoundland and Labrador

☐ Prince Edward Island

☐ Northwest Territories

☐ Yukon

☐ Nunavut

Please indicate your gender:

☐ Woman

☐ Transsexual woman

☐ Man

☐ Transsexual man

☐ I prefer not to answer this question

Please indicate your age in the box below:

If you prefer not to disclose your age, please tick the box that corresponds to your age group:

☐ 35 to 44 years

☐ 45 to 54 years

☐ 55 to 64 years

☐ 65 to 74 years

☐ 75 to 84 years

☐ 85 years and over

What is your height and weight?

☐ kg or ☐ pounds

☐ cm ☐ feet, inches

☐ I prefer not to answer this question.

Note: We will use this data to determine your body mass index.

What is your current marital status?

☐ Currently married

☐ Single - Never married

☐ Common-law partner or in a relationship

☐ Separated

☐ Divorced

☐ Widow

Indicate the highest level of education you completed

☐ No certificate, diploma or degree

☐ Secondary (High) School diploma or equivalency certificate

☐ Certificate of Apprenticeship, Certificate of Qualification or Trades certificate

☐ College, CEGEP or other non-university certificate or diploma

☐ University certificate or diploma below bachelor level

☐ Bachelor's degree

☐ Professional degree (e.g., medicine)

☐ Master's degree

☐ Earned Doctorate

What is your household income?

☐ Less than $ 19,999

☐ Between $ 20,000 and $ 29,999

☐ Between $ 30,000 and $ 39,999

☐ Between $ 40,000 and $ 49,999

☐ Between $ 50,000 and $ 59,999

☐ Between $ 60,000 and $ 69,999

☐ Between $ 70,000 and $ 79,999

☐ Between $ 80,000 and $ 89,999

☐ Between $ 90,000 and $ 99,999

☐ More than $ 100,000

What is your current employment status?

☐ Full time employee

☐ Part-time employee

☐ Self-employed

☐ Unemployed

☐ On social welfare

What is your ethnic group?

☐ Caucasian

☐ Chinese

☐ South Asian

☐ Aboriginal (First Nations, Métis, Inuit, other)

☐ Black

☐ Filipino

☐ Latino-American

☐ Arab or West Asian

☐ Korean

☐ Japanese

☐ Other visible minority

☐ Multiple visible minority

☐ I prefer not to answer this question

Questions about your family members

In the following section, we will ask questions about family members and:

- The incidence of cardiovascular disease
- Type 2 diabetes
- Exercise
- Consumption of cigarettes, alcohol, fatty foods

For each family members, please indicate your level of comfort in answering further questions (*see below):*

	Father	Paternal grandfather	Paternal grandmother	Mother	Maternal grandfather	Maternal grandmother
…Is alive and I am comfortable answering these questions						
…Is alive but I am not comfortable answering these questions						
…Has passed away and I am comfortable answering these questions						
…Has passed away but I am not comfortable answering these questions						
…I prefer not to answer questions about this family member						

If alive and comfortable	Father	Paternal grandfather	Paternal grandmother	Mother	Maternal grandfather	Maternal grandmother
... had a heart attack or stroke						
… regularly exercise for his age (at least 2h30 per week)?						
… smokes regularly (more than 20 cigarettes per day)						
... is overweight						
... regularly consumes (more than 4 times a week) high-fat foods such as fried foods						
... regularly drinks alcohol (2 drinks a day and a maximum of 10 a week for women; for men, 3 a day and a maximum of 15 a week)?						
... has type 2 diabetes						
... has cholesterol problems						
... Has high blood pressure						
No statement applies to his/her situation						

Has passed away and comfortable	Father	Paternal grandfather	Paternal grandmother	Mother	Maternal grandfather	Maternal grandmother
... had a heart attack or stroke						
... regularly exercised (at least 2 :30 a week)						
... smoked regularly (more than 20 cigarettes per day)						

... was overweight						
... regularly consumed (more than 4 times a week) high-fat foods such as fried foods						
... regularly drank alcohol (2 drinks a day and a maximum of 10 a week for women; for men, 3 a day and a maximum of 15 a week)						
... had type 2 diabetes						
... had cholesterol problems						
... had high blood pressure						
No statement applies to this situation						

Questions for women

Definition: The menopause is the moment when a woman has had no menstrual period for 12 consecutive months

Are you menopaused?

☐ Yes

☐ No

If no - it has not started yet

Does any of the statements apply to your situation:

☐ I had bilateral oophorectomy

☐ I had a hysterectomy, with or without bilateral oophorectomy

☐ None of the above

Note: Bilateral oophorectomy is the removal of both your ovaries. A hysterectomy is the removal of your uterus

If yes - I am in the process of the menopause period

Which of these statements applies to your situation?

☐ I had bilateral oophorectomy

☐ I had a hysterectomy, with or without bilateral oophorectomy

☐ None of the above

Note: Bilateral oophorectomy is the removal of both your ovaries. A hysterectomy is the removal of your uterus

Or

If yes - my menopause is over

Which of these statements applies to your situation?

☐ I had bilateral oophorectomy

☐ I had a hysterectomy, with or without bilateral oophorectomy

☐ None of the above

Note: Bilateral oophorectomy is the removal of both your ovaries. A hysterectomy is the removal of your uterus

<u>If you had one of the surgeries, did it happen:</u>

☐ Before your menopause

☐ During your menopause

☐ After your menopause

<u>Are you on any Hormonal Contraception?</u>

☐ No

☐ Oral Contraceptive pill

☐Contraceptive patch

☐Vaginal ring

☐Intrauterine Contraception (IUC)

☐Injectable contraception

If yes, since when?

Year: ☐

<u>Are you pregnant or have you ever been pregnant?</u>

☐ No

☐ Yes

If yes –

- How many children did you give birth to? ☐
- When was your last childbirth?
  - Year : ☐
  - Have you had any heart complications as a result of your deliveries?
    - ☐ No
    - ☐ Yes

Are you on the Hormone Replacement Therapy?

☐ No

☐ Yes

If yes, since when?

Year ☐☐☐☐

Questions about heart disease

Have you ever had a Myocardial Infarction (Heart Attack)?

☐ No

☐ Yes

If yes –How many myocardial infarction (heart attack) did you have?

☐ Your most recent

Year ☐☐☐☐

Month ☐☐

☐ I do not remember

☐ 2

Year ☐☐☐☐

Month ☐☐

☐ I do not remember

☐ 3

Year ☐☐☐☐

Month ☐☐

☐ I do not remember

☐ 4

Year

Month

☐ I do not remember

☐ 5 and more

Remember your last Myocardial Infarction (Heart Attack). Can you indicate the symptoms that you felt during this event?

☐ Unusual tiredness

☐ Sleeping problems

☐ A short breath

☐ An uncomfortable pressure, compression or pain in your chest that lasted a few minutes, and then came and went

Pain or discomfort:

☐ On one arm

☐ On both arms

☐ The back

☐ The neck

☐ The jaw

☐ On the upper part of the abdomen

Signs of:

☐ Cold sweats

☐ Loss of consciousness

☐ Nausea / Vomiting

☐ Dizziness

☐ Anxiety

Have you had a diagnosis of coronary heart disease?

☐ No

☐ Yes

If yes, When?

Year

Month

Note: A coronary heart disease is a disease that involves the blood vessels of the heart and the heart itself

Questions about your habits

Please answer the following questions:

Do you have High Blood Pressure (hypertension)?

☐ I do not know

☐ No

☐ Yes

If yes –

- Since when?
- Is it monitored?

☐ Yes

☐ No

Do you have high cholesterol?

☐ I do not know

☐ No

☐ Yes

If yes –

- Since when?
- Is it monitored?

☐ Yes

☐ No

Do you have type 2 diabetes?

☐ I do not know

☐ No

☐ Yes

If yes –

- Since when? ☐
- Is it monitored?

☐ Yes

☐ No

Do you currently smoke, or have you ever smoked tobacco products such as cigarettes, cigars or pipe?

☐ No, I have never smoked cigarettes

☐ Yes, I do smoke cigarettes

- I smoke ☐ cigarette(s) per day
- I smoke ☐ pack(s) per week
- I have been smoking for ☐ year(s)
- I tried to stop ☐ time(s)

☐ Yes, I smoked cigarettes

- I smoked ☐ cigarette(s) per day
- I smoked ☐ pack(s) per week
- I smoked for ☐ year(s)

- I stopped ☐ year(s) ago

How often do you drink alcohol a week?

☐ Less than once a week

☐ 1-2 times a week

☐ 2-4 times a week

☐ 5-6 times a week

☐ Daily

What is your daily alcohol consumption?

☐ I do not drink alcohol regularly

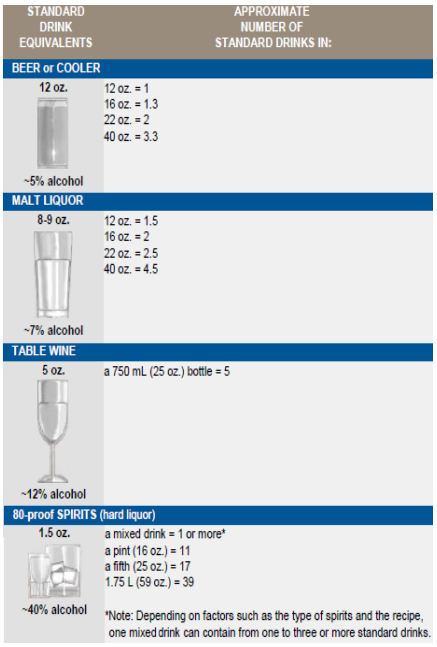
☐ 1-2 drinks

☐ 3-4 drinks

☐ 5-6 drinks

☐ More than 7 drinks

Please refer to the following image to answer this question



https://pubs.niaaa.nih.gov/publications/practitioner/pocketguide/pocketguide2.htm

How many portions of fruits and vegetables do you eat on a typical day?

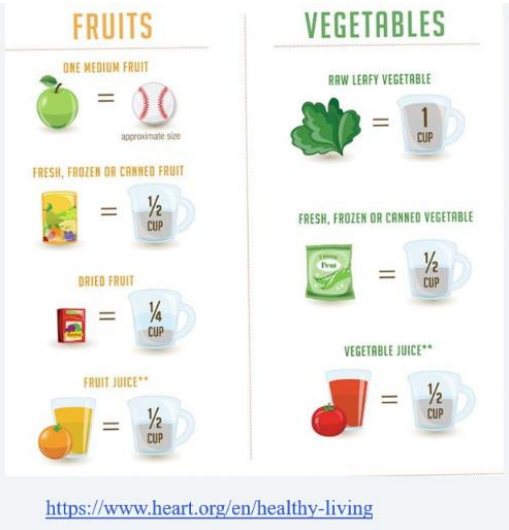
☐ Less than 2 portions

☐ 3 to 4 portions

☐ 5 to 6 portions

☐ 7 to 8 portions

☐ More than 9 portions



How often do you eat red meat?

☐ I do not eat red meat

☐ Less than once a week

☐ 1-2 times a week

☐ 3-4 times a week

☐ Almost every day

How often do you eat high-fat foods such as instant food, fried foods, cookies, chips or cakes?

☐ Less than once a week

☐ 1-2 times a week

☐ 3-4 times a week

☐ 5-6 times a week

☐ Almost every day

Do you exercise?

☐ No

☐ Yes – moderate physical activity

☐ Yes – vigorous physical activity

☐ How often?

☐ At least 30 minutes a week

☐ At least 1 hour a week

☐ At least 1h30 a week

☐ At least 2 hours a week

☐ At least 2h 30 a week

Moderate physical activity: physical activity that makes you breathe a little harder than you normally would

Vigorous physical activity: physical activity that makes you breathe harder than you normally would

Do you feel stressed or anxious in your life in general?

☐ Never

☐ Rarely

☐ Occasionally

☐ Often

☐ Most of the time

Are you overweight?

☐ I am at a healthy weight

☐ I would like to lose between 1-15 pounds to be at a healthy weight

☐ I would like to lose between 16-30 pounds to be at a healthy weight

☐ I would like to lose between 31-45 pounds to be at a healthy weight

☐ I would like to lose more than 46 pounds to be at a healthy weight

In general, do you have a good sleep hygiene?

☐ No

☐ Yes

If yes – since when?

☐ Only since my cardiac event

☐ This has always been a problem for me

Chapitre V – Étude en laboratoire de l'impact d'une exposition au Trier Social Stress Test sur des paramètres de la réponse émotionnelle et physiologique de stress chez des femmes ayant vécu ou non un infarctus du myocarde

The Impact of Myocardial Infarction on Basal and Stress-Induced Heart Rate Variability and Cortisol Secretion in Women: A Pilot Study

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Abstract

Coronary heart disease (CHD), of which myocardial infarction (MI) is a subtype, is the leading cause of death for women. Nonetheless, women remain neglected in CHD research, resulting in treatments and recommendations being primarily based on data collected in men. Pre-clinical and clinical studies have supported dysregulation of the hypothalamic-pituitary-adrenal axis (HPAA) following cardiac arrest and MI to promote the development of mental health disorders (e.g., major depressive disorder, post-traumatic stress disorder). However, studies addressing changes in HPAA activation under basal and stress-induced conditions in women samples have been lacking. Thus, we conducted this study to determine basal and stress-induced changes in heart rate, respiration and cortisol secretion (via 8 saliva samples) in a sample of women with a history of MI (n = 13) and a control group (n = 16). We measured altered stress reactivity through exposure to the Trier Social Stress Test. In addition, participants completed questionnaires assessing perceived stress and mental health status (i.e., anxiety and mood). Overall, our findings indicated comparable assessments of perceived situational stress in both groups. Interestingly, salivary cortisol secretion support reduced stress-induced HPAA activation related to TSST exposure in MI women compared to control counterparts. Our observations are consistent with findings supporting glucocorticoid resistance noted following MI and cardiac arrest. Akin to cardiac arrest survivors, HPAA dysregulation in MI survivors could have an impact on the development of mental health disorders. More studies are needed to address this critical question.

Keywords: myocardial infarction, women, trier social stress test, cortisol, heart rate, perceived stress

Abbreviations

AUC_G	Area under the curve to ground
AUC_I	Area under the curve to increase
CHD	Coronary heart disease
CVD	Coronary vascular disease
HPAA	Hypothalamic-pituitary-adrenal axis
HRV	Heart rate variability
MI	Myocardial Infarction
PANAS	Positive and Negative Affect Schedule
STAI	State-Trait Anxiety Inventory
SCA	Sudden cardiac arrest
TSST	Trier Social Stress Test
RSA	Respiratory sinus arrhythmia

Highlights

- Women have been neglected in coronary heart disease for decades;
- Little is known regarding the impact of myocardial infarction on physiological markers of the HPAA (e.g., cortisol);
- Women with a history of MI perceived similar levels of stress compared to the control group, but CORT secretion was altered;
- Physiological results support MI to affect HPAA function upon stress, which could contribute to increased mental health issues

5.1.0 Introduction

Coronary heart disease (CHD), also known as ischemic heart disease or coronary artery disease, is the leading cause of death and the most prevalent subtype of cardiovascular disease (CVD) worldwide (Virani, Alonso, Benjamin, Bittencourt, Callaway, Carson, Chamberlain, Chang, Cheng, Delling, Djousse, Elkind, Ferguson, Fornage, Khan, Kissela, Knutson, Kwan, Lackland, Lewis, Lichtman, Longenecker, Loop, Lutsey, et al., 2020). A CHD develops from atherosclerosis due to a lack of oxygen-rich blood supply to the heart related to partial or complete occlusion of the arteries' walls. Myocardial Infarction (MI), a subtype of CHD, is amongst the most prevalent CVD, killing one person every 40 seconds in the United States (Virani, Alonso, Benjamin, Bittencourt, Callaway, Carson, Chamberlain, Chang, Cheng, Delling, Djousse, Elkind, Ferguson, Fornage, Khan, Kissela, Knutson, Kwan, Lackland, Lewis, Lichtman, Longenecker, Loop, Lutsey, et al., 2020). Worldwide, MI and stroke account for 85% of all deaths caused by CVD (WHO, 2021a).

Unfortunately, women[5] have been neglected from scientific and medical research for decades (Kim et al., 2010; Zucker & Beery, 2010), and the field of CVD has not been spared (Harris & Douglas, 2000; Kim & Carrigan, 2008; Westerman & Wenger, 2016). Women have been systematically excluded or recruited at lower levels than men (Nature, 2010; Zucker & Beery, 2010). Indeed, two-thirds of heart disease research samples continue to predominately include men (Heart & Stroke, 2018). The lack of women inclusion significantly impacts health care practitioners' levels of knowledge and the development of specific treatment guidelines (Maas et al., 2011; Virani, Alonso, Benjamin, Bittencourt, Callaway, Carson, Chamberlain,

[5] Female and woman are two distinctive terms and not interchangeable. While sex refers to the biological characteristics at birth, gender refers to an individual's expression, identity, and societal roles. Consequently, when the term woman is used in this article, we will refer to the biological characteristics.

Chang, Cheng, Delling, Djousse, Elkind, Ferguson, Fornage, Khan, Kissela, Knutson, Kwan, Lackland, Lewis, Lichtman, Longenecker, Loop, Lutsey, et al., 2020). For example, only 22% of family doctors and 42% of cardiologists report being qualified to assess the risk of heart disease in women (Bairey Merz et al., 2017). Women have a 30% increased likelihood to die from an MI compared to men (Public Health Agency of Canada, 2018), and if the attending physician is a man, the risk of death tends to increase compared with having a woman attending physician (Greenwood et al., 2018). Women tend to experience different symptoms (e.g., back pain, cold sweats) when experiencing an MI (McSweeney et al., 2010), which are considered 'atypical' and are not well known (Kosuge et al., 2006; Mosca et al., 2011). In this context, both the scientific community and the general population remain to be properly educated on sex-specific symptomatology

5.1.1 Psychological Impact of Myocardial Infarction

In women, the risk of mental health disorders such as anxiety and depression increases significantly after an MI (Feng et al., 2016; Mohamed et al., 2019). Importantly, people diagnosed with a major depressive episode following MI are more likely to die (Berkman et al., 2003; Lichtman et al., 2014). The latter is also true for anxiety disorders (Celano et al., 2015; L. L. Watkins et al., 2013). Compared to men, women tend to experience reduced psychological well-being and increased psychological distress following an MI, even five years following the event (Drory et al., 2003). Overall, the levels of perceived stress following an MI are heightened in women (Cohen & Janicki-Deverts, 2012), who tend to present worsened recovery prognostics and report more posttraumatic stress symptoms (Edmonds, 2012; Hari et al., 2010; Vilchinsky et al., 2017). In other words, the impact of MI extends beyond impaired physical capacities.

5.1.2 Physiological Impact of Myocardial Infarction

A bi-directional relationship exists between stress and MI, with stress exposure increasing the risk of CHD and MI occurrence (Bahall et al., 2018; Chi & Kloner, 2003; Georgiades et al., 2009; Jackson et al., 2018; Vujcic et al., 2016). Considering the negative impact of stress on post-infarct recovery (Aboa-Eboulé et al., 2007; Arnold et al., 2012; Georgiades et al., 2009; Orth-Gomér et al., 2000), changes in hypothalamic-pituitary-adrenal axis (HPAA) activation following MI warrant further investigation. Responsible for the body's neuroendocrine response to stress, its response is initiated by the secretion of corticotropin-releasing factor from the hypothalamus, which is followed by the release of the adrenocorticotropic hormone by the anterior pituitary gland, resulting in glucocorticoid release by the adrenal glands, which ultimately acts on cardiovascular functions (Stephens & Wand, 2012). Researchers have found that a sustained increase in endogenous glucocorticoid levels is linked to cardiovascular complications such as systemic arterial hypertension and metabolic syndrome (Isidori et al., 2015; Oakley & Cidlowski, 2015).

The dysregulation of the HPAA following sudden cardiac arrest (SCA) has been studied for years (Houghland, 2009; Q. Zhao et al., 2021). Whereas SCA is described as the sudden malfunctioning of the electrical system of the myocardium (Katritsis et al., 2016), MI is the result of an occluded artery inducing a state of hypoxia and ultimately resulting in different levels of necrosis in the heart muscle (Saleh & Ambrose, 2018). Hypoxia-induced by SCA and MI events acts as a metabolic stressor (e.g., HPAA dysregulation). Research suggests HPAA dysregulation to stem from hippocampal damage and adrenal insufficiency (Chalkias & Xanthos, 2012; Hékimian et al., 2004; Pene et al., 2005). For example, Neigh et al. (2005) demonstrated blunted stress-induced cortisol secretion two weeks following SCA in mice, associated with

hippocampal neuronal damage. Apart from neuronal brain damage, there is evidence that the adrenal gland - a key player in the HPAA - is also impacted. In the event of an SCA, the body becomes suddenly anoxic, and the concentration of epinephrine increases; this can cause varying degrees of necrosis to the adrenal gland (Neigh et al., 2005). As a result, the HPAA integrity is compromised and blunted cortisol concentration is observed in response to stress (Chalkias & Xanthos, 2012; Schultz et al., 1993). The lack of brain oxygenation and nutriments, which characterize MI and SCA, could support common physiological impairments. Supporting this contention, Kaplan et al. (2018) have reported reduced cerebral blood flow up to 30 days post-MI, which renders plausible the contribution of brain injury in MI-induced effects on HPAA and cognitive functions.

There is no doubt that stress impacts both physiological and mental states (Contrada & Baum, 2010). Psychological - measured with tests - and physiological responses - measured with biomarkers such as cortisol - exist as indicators of the stress construct, and a strong association between these two types of reactions is present in healthy individuals (Schlotz et al., 2008), and exemplified in controlled laboratory environments through changes in both affective and physiological states when psychosocial pressures appear (Schlotz et al., 2006). For example, Oldehinkel et al. (2010) found subjective reports of arousal and unpleasantness in a sample of Dutch adolescents (N = 715) to be related to respiratory sinus arrhythmia (RSA) and cortisol responses during the performance of a stressful task. This interaction between psychological and physiological responses coincides with a substantial overlap in their neural pathways (e.g., projections from the hippocampus and amygdala; Herman et al., 2003, 2005; Herman & Cullinan, 1997). Additionally, all regions within this system express glucocorticoid receptors and contribute to HPAA regulation of psychophysiological responses (Ulrich-Lai & Herman, 2009).

In other words, psychological and physiological responses are highly associated, as this is evident through scientific experimentation and the structural cortical supports in the human brain.

5.1.3 Study Objectives

The main goal of this pilot research was to compare HPAA activation in women having experienced an MI and an age-matched control group before and after a stressful task. The physiological response was determined using different biomarkers (i.e., cortisol, heart rate variability). In addition, the levels of perceived stress were evaluated at different time intervals to assess the impact of the stressful task.

5.2.0 Method

5.2.1 Participant Characteristics

Participants were recruited from an online study by indicating their interest in an in-person study. The following information was extracted from the online study to compare the difference between the MI and the control (Non-MI) groups: a) age; b) body mass index (BMI); c) marital status; d) level of education; e) household income; f) employment status; g) ethnic group; h) menopause status; i) status of reproductive organs (i.e., if were removed and when); j) MI information (i.e., number); k) CHD information; l) received diagnoses of high blood pressure, high cholesterol, and diabetes; m) prescribed medication; and n) language of study.

5.2.2 Sampling Procedures

We included participants if: a) aged between 45 and 80; b) no current or past substance use; c) no neurological condition or been diagnosed with dementia; d) no current psychiatric disorder; e) were not taking the contraceptive pill; f) were not following a hormonal replacement therapy; g) if still menstruating, their cycle needed to be regular (between 21 and 35 days); and

h) were not pregnant or breastfeeding at the time. For participants that indicated having a MI condition, the diagnoses needed to be made by a physician. We conducted the study between 9 am and 12 pm. Therefore, to control for possible external factors that could influence the measurement of their HPAA response, after 8 am, participants were instructed to not: a) consume any alcohol and tobacco; b) ingest any food or drink any caffeinated beverage; c) floss or brush their teeth; and d) engage in moderate or high-intensity physical activity.

Participants were from the Ottawa-Gatineau region in Canada and could complete the study in French or English. Free parking was provided in one of the university parking lots, and they were given a choice to pick a 15$ gift card from different stores. When participants were scheduled, only one of the principal investigators (N.F.N.L.) was aware of their status (MI or Non-MI). The ethics board of the University of Ottawa approved the ethical aspect of this study (H-06-18-639).

5.2.3 Sample Size, Power, and Precision

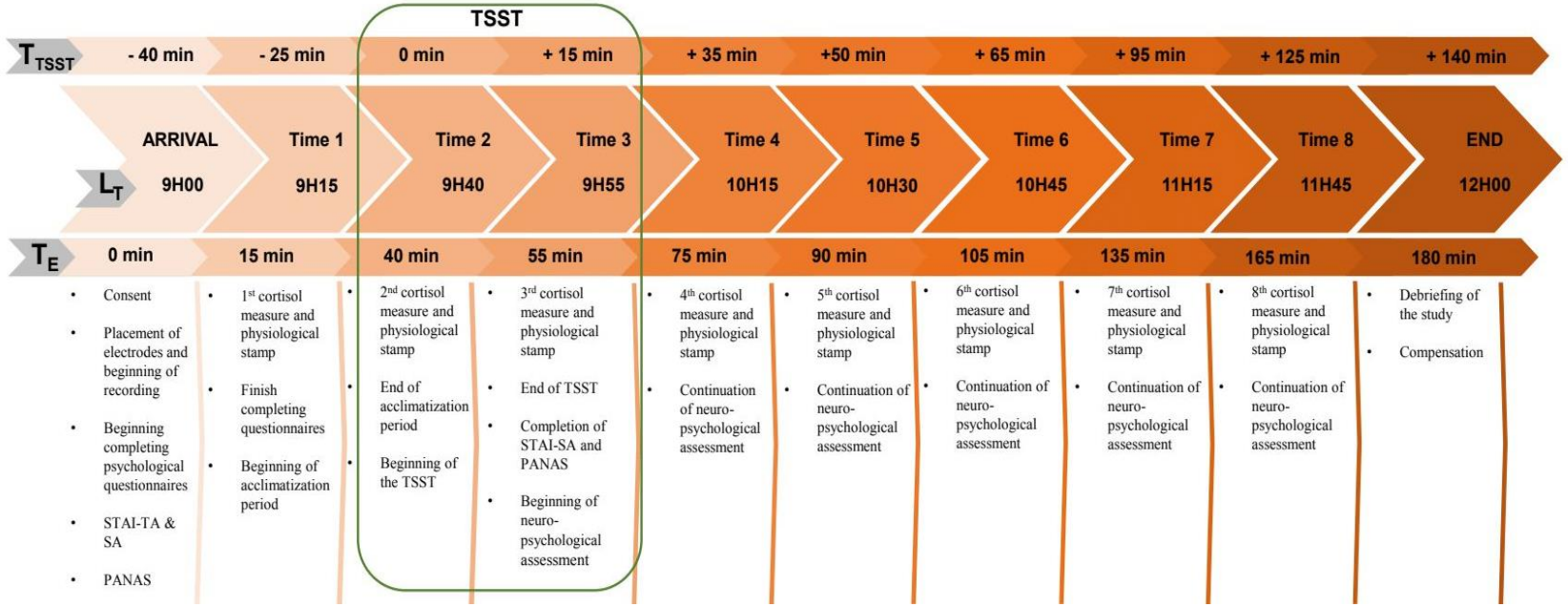
The study initiated in August 2019 ended in March 2020 due to the global pandemic. This led to the recruitment of a limited number of participants, with restricted possibilities to pursue post-pandemic assessments under similar basal conditions. A total of twenty-nine women were tested [N = 29 (n_{MI} = 13; n_{NonMI} = 16)]. Of thirty-four participants initially recruited, 5 were excluded; three participants arrived too late, and we could not take physiological measures, one participant had a major eye surgery less than a year ago, and the software for one participant did not properly record data. We used G*Power 3.1.9.7 (Faul et al., 2009) and found a power of 0.99 to detect a within-between interaction with a sample size of 29 with the following parameters: a) estimated effect size of η_p^2 = .10; b) α = 0.05; c) number of groups = 2; d) number of measurements = 8, e) correlation among repeated measures = .5 (default), and d) nonsphericity

correction = 1 (default).

5.2.4 Data Collection

All participants were invited for a 3-hour study in the Integrated Neurocognitive & Social Psychophysiology Interdisciplinary Research Environment Laboratory at the University of Ottawa. Research assistants in charge of collecting the physiological measures were blind to the assigned participants' group; Figure 1 shows a detailed timeline of the study. In brief, participants were accompanied from the parking lot to the laboratory. Consent to participate was obtained, an explanation of the study was provided, and six electrodes were placed on the upper part of their body to collect physiological measures for the entire study duration.

Figure 5 *(Figure 1 for Chapter V)* Timeline of the study



Note. L_T = Local time; T_{TSST} = Calculated time from the TSST; 0 being the beginning of the TSST; T_E = Time elapsed since the arrival of the participant

Then, participants completed a series of psychological questionnaires. Following this, they were given a choice to read a book they brought – had to be a non-anxiety-provoking book – or watch a safari documentary (Keltner et al., 2017). Participants then completed the Trier Social Stress Test (TSST). Following TSST exposure, two psychological questionnaires assessed the participants' perceived stress, and they completed a series of neuropsychological tests. As the study ended, participants completed the same two psychological tests and received a debriefing. Saliva samples were collected at 8 key experimental intervals using the SalivaBio Passive Drool Method from Salimetrics®. For more details about the measures, please see section 2.5.

5.2.5 Measures

5.2.5.1 Trier Social Stress Test

The TSST was created to objectively study HPAA changes by combining two inducing stressors (Kirschbaum et al., 1993). Since its creation, the TSST has been widely used in more than 1000 peer-reviewed studies (Narvaez Linares et al., 2020) and for most participants (70-80%), there is a rise of salivary cortisol levels up to threefold (Dickerson & Kemeny, 2004). Our laboratory performed an extensive systematic review of TSST methodology because researchers have not applied the method consistently since its creation, which could influence HPAA activation, warranting careful consideration when interpreting findings made with this task (Narvaez Linares et al., 2020). We applied the guidelines provided in this review. For more details about the administration of the TSST, please see the Supplementary Material document.

5.2.5.2 Psychological Tests

5.2.5.2.1 State-Trait Anxiety Inventory (STAI). The STAI is a self-reported measure made of 40 items on a 4-point Likert scale that allows assessing trait (20 items; STAI-TA) – how they feel in general; and state (20 items; STAI-SA) – how they feel in the present moment

(Spielberger et al., 1983). The maximum is 40 on each scale; a higher score indicates higher anxiety levels. The STAI has good reliability and validity and is widely used across studies because it is available in many languages and is simple to administer (Julian, 2011; Spielberger et al., 1983). Our participants completed the STAI-TA at T_1 and the STAI-SA at T_1, T_3, and T_8.

5.2.5.2.2 Positive and Negative Affect Schedule (PANAS).). The PANAS is a self-reported measure made of 10 items, equally divided to measure positive and negative affects. The participant must rate on a 5-point Likert scale to what extent they feel the described emotion at the present moment (Watson et al., 1988). The higher the score, the higher the participant feels this emotion (negative or positive), the maximum score being 50. The PANAS's validity and reliability have been strongly rated (Crawford & Henry, 2004; Watson et al., 1988), and the test has been used in several studies, being simple to administer and available in different languages. Our participants completed the PANAS at T_1, T_3, and T_8.

5.2.5.3 Physiological measures

5.2.5.3.1 Unbound Cortisol. Saliva samples were collected in Eppendorf tubess and placed immediately on ice after collection. Any deviations in a participant's saliva collection time were recorded, accompanied by an explanation. All samples were stored in -80º C freezers until concentrations were later determined. The unbound cortisol concentration was determined using the Salimetrics Expanded Range High Sensitivity Salivary Cortisol Enzyme Immunoassay Kit (ELISA), as recommended by the manufacturer (Salimetrics, 2019). All cortisol samples were run in duplicates. The plates were read at 450 nm using the BioTek PowerWave XS, and BioTek Gen5 was used to determine the coefficients of variability (CV). The inter-assay CV is 8.230, and the intra-assay CV is 5.89, which both meet the acceptable CVs set by Salimetrics (Dickerson & Kemeny, 2004).

5.2.5.3.2 Heart Rate Variability. Heart rate variability (HRV) refers to the fluctuations in cardiac rhythm and is a common measure used to represent the physiological response of the autonomic nervous system (Kim et al., 2018), precisely the sympathovagal balance at the sinoatrial level (Berntson et al., 1997; Sztajzel, 2004). Our study recorded the HRV activity using a non-invasive electrocardiogram technique, and focused on analyzing one type of HRV measure called respiratory sinus arrhythmia (RSA) – defined as the natural logarithm of high-frequency power (Morgan, 2016). The RSA metric represents the change in heart rate as a function of respiration, which falls within the high-frequency range (van Ravenswaaij-Arts et al., 1993). The RSA metric indexes (van Ravenswaaij-Arts et al., 1993). The RSA metric indexes regulation of the parasympathetic system and higher values reflect greater parasympathetic control.

We measured HRV with an electrocardiogram, using pre-gelled Ag/AgCl sensors in a modified lead II configuration. We used Mindware Technologies BioLab v.3.0.13 through a BioNex 8-slot chassis (Model 50-3711-08) with a sampling frequency of 1000 Hz to acquire our data. We analyzed HRV data in Mindware Analysis Application Version 3.2.9, released March 30, 2021. We applied a 60 Hz notch filter and a bandpass filter between 0.25 Hz and 45 Hz to reduce noise due to electrical interference or movement. We derived the respiration signal from the impedance cardiography signal. Noise compromised the accurate identification of B points in the impedance cardiography signal, and these data were not considered further. Please see the Supplementary Material document for more information about how the data were inspected and analyzed.

5.2.6 Statistical Analyses

We carried out ANOVAs and t-tests in IBM SPSS Statistics 28 (IBM, 2021), and repeated measures correlations in R 1.4.1 (R Core Team, 2020) using the rmcorr package

(Bakdash & Marusich, 2017, 2021). We assessed data distribution and assumptions for all variables depending on analysis. A root square transform solved normality issues for cortisol measurement, but PANAS scores could not be converted to normality. All other measures were normally distributed. Due to the small MI group (< 15), we screened for outliers in ungrouped data and defined outliers as z ± 2.00. We replaced outliers with the corresponding value at z ± 2.00. We applied a Greenhouse-Geisser correction (Greenhouse & Geisser, 1959) when repeated measures did not meet the assumption of sphericity. The p-level was set at 0.05 for all analyses, and tests were two-tailed. We elaborated a detailed section for the statistical analyses that can be found in the Supplementary Material document.

5.3.0 Results

5.3.1 Sociodemographic

The characteristics of our participants can be found in table 1, and information related to medication can be found as supplementary material. The average age of our participants was 56.92 (*SD* = 8.59) and 61.44 (*SD* = 9.21) for the MI and NoMI groups, respectively. The average BMI was 27.47 (*SD* = 4.12) and 25.75 (*SD* = 3.27) for the MI and NoMI groups, respectively. Demographic and medical characteristics were compared between women with and without a history of MI to establish a clearer profile of women with and without a history of MI. Welch independent samples *t*-test found women with MI took significantly longer to complete the study than women without a history of MI, $t(17.72) = 3.12$, $p = .006$, $d = 1.23$. Independent samples *t*-test revealed a tendency for women with a history of MI to have a higher BMI than women without a history of MI, $t(25) = 1.91$, $p = .068$, $d = .74$. Women with MI reported more hypertension diagnoses than women without MI [$\chi^2(1) = 3.95$, $p = .047$], and Fisher's exact test

Table 13 *(Table 1 for Chapter V)* Participant characteristics

Characteristics	N	n_{MI}	n_{NoMI}
Language of survey			
English	26	13	13
French	3	0	3
Age group			
35 – 44	0	0	0
45 – 54	11	6	5
55 – 64	5	4	1
65 – 74	13	3	10
75 – 84	0	0	0
Ethnicity			
White	26	11	15
Arab or West Asian	1	1	0
Chinese	1	1	0
Preferred not to answer this question	1	0	1
BMI (Kg/m^2)			
Healthy weight (18.5 - 24.9)	12	4	8
Pre-obesity (25.0 - 29.9)	11	6	5
Obesity class I (30.0 - 34.9)	3	2	1
Obesity class II (35.0 - 39.9)	0	0	0
Obesity class III (> 40)	1	1	0
Preferred not to answer this question	2	0	2
Marital status			
Currently married	18	8	10

Divorced	2	2	0
Common-law or in a relationship	6	3	3
Single	1	0	1
Widowed	2	0	2
Separated	0	0	0
Education level			
No certificate, diploma, or degree	0	0	0
Secondary (high) school diploma or equivalency certificate	3	3	0
Certificate of apprenticeship, certificate of Qualification, or Trades certificate	0	0	0
College, Cégep, or other non-university certificate diploma	9	4	5
University certificate or diploma below bachelor level	1	0	1
Bachelor's degree	8	3	5
Professional degree (e.g., MD)	2	0	2
Master's degree	6	3	3
Earned Doctorate	0	0	0
Household income (CAD $)			
<19,999	0	0	0
20,000 - 29,999	0	0	0
30,000 - 39,999	2	2	0
40,000 - 49,999	1	0	1
50,000 - 59,999	1	0	1
60,000 - 69,999	1	1	0
70,000 - 79,999	2	1	1
80,000 - 89,999	2	1	1
90,000 - 99,999	5	2	3

+100,000	12	6	6
Preferred not to answer the question	3	0	3
Employment			
Full-time employee	6	3	3
Part-time employee	3	2	1
Self-employed	4	3	1
Unemployed or retired	13	4	9
On social welfare	0	0	0
Type of contraception			
No contraceptive	29	13	16
Oral contraceptive pill	0	0	0
Contraceptive patch	0	0	0
Vaginal ring	0	0	0
Intrauterine contraception	0	0	0
Injectable contraception	0	0	0
Hormonal replacement therapy			
No	29	13	16
Yes	0	0	0
Menopause			
No	10	5	5
Yes	19	8	11
Type of surgery (reproductive organs)			
"I had a bilateral oophorectomy"	1	0	1
"I had a hysterectomy, with or without oophorectomy"	3	1	2
No surgery	25	12	13

If surgery			
Before their menopause	2	0	2
During their menopause	1	1	0
After their menopause	1	0	1
Pregnancy			
No	3	1	2
Yes	26	12	14
Number of MI			
1	-	8	-
2	-	4	-
3	-	1	-
Diagnosis of CHD			
No	21	8	13
Yes	8	5	3
Diagnosis of hypertension			
No	17	5	12
Yes	12	8	4
Diagnosis of high cholesterol			
No	19	9	10
Yes	7	4	3
I do not know	3	0	3
Diagnosis of Diabetes types 2			
No	23	8	15
Yes	6	5	1

revealed women with MI tended to report more Type II diabetes, $p = .064$. We did not find other group differences for the remaining demographic variables.

5.3.2 Psychological Impact of Stress

5.3.2.1 PANAS

We entered the PANAS scores in a mixed ANOVA with Valence (positive, negative) as a within-subject factor, Time (T_1, T_3, T_8) as a within-subject factor, and Group as a between-subject factor (NoMI, MI). The main effect of Time was significant, $F(2, 54) = 6.47$, $p = .003$, $\eta_p^2 = .19$, and Valence was significant, $F(1, 27) = 255.44$, $p < .001$, $\eta_p^2 = .90$. The effect of Valence depended on Time, $F(2, 54) = 20.35$, $p < .001$, $\eta_p^2 = .43$.

Positive affect increased from T_1 ($M = 10.90$, $SE = 0.18$) to T_3 ($M = 15.64$, $SE = 0.76$), $p < .001$ (see Figure 2). Positive affect decreased from T_3 to T_8 ($M = 11.96$, $SE = 0.41$), $p < .001$. Positive affect was, nevertheless, still higher at T_8 than T_1, $p = .015$. Negative affect decreased from T_1 ($M = 37.71$, $SE = 1.21$) to T_3 ($M = 33.10$, $SE = 1.52$), $p < .001$, and it was also lower at T_8 ($M = 33.54$, $SE = 1.31$; than T_1), $p = .001$. T_3 and T_8 did not differ in negative affect, $p = .64$. None of these effects depended on Group: Time*Group, $F(2, 54) = 0.80$, $p = .45$, $\eta_p^2 = .03$; Valence*Group, $F(1, 27) = 0.06$, $p = .81$, $\eta_p^2 = .002$, Time*Valence*Group, $F(2, 54) = 0.25$, $p = .78$, $\eta_p^2 = .01$. There was no main effect of Group, $F(1, 27) = 0.60$, $p = .44$, $\eta_p^2 = .02$.

5.3.2.2 STAI

5.3.2.2.1 STAI - SA. The STAI-SA score was entered in a mixed ANOVA with Time (T_1, T_3, T_8) as a within-subject factor and Group (NoMI, MI) as a between-subject factor. The effect of Time was significant, $F(2, 54) = 36.48$, $p < .001$, $\eta_p^2 = .58$, and did not depend on Group, $F(2, 54) = 0.06$, $p = .95$, $\eta_p^2 = .002$. The main effect of Group was also not significant, $F(1, 27) = 0.48$, $p = .49$, $\eta_p^2 = .02$. Participants felt higher levels of increased anxiety from T_1 ($M = 27.38$,

SE = 1.06) to T_3 (*M* = 42.27, SE = 2.15), $p < .001$, and scores were still higher at T_8 compared to T_1 (*M* = 34.05, *SE* = 1.78), $p < .001$ (see Figure 3). Scores decreased from T_3 to theT_8, $p < .001$.

5.3.2.2.2 STAI - TA. An independent samples t-test showed that the NoMI group (*M* = 32.69, *SE* = 1.71) and the MI group (*M* = 33.24, *SE* = 2.43) were not significantly different on the STAI-TA (see figure 4), mean difference of -0.56, BCa 95% [-6.44, 5.05], $t(27) = -0.19$, $p = .85$, Hedges' $g = -0.07$, CI 95% [-0.78, 0.64].

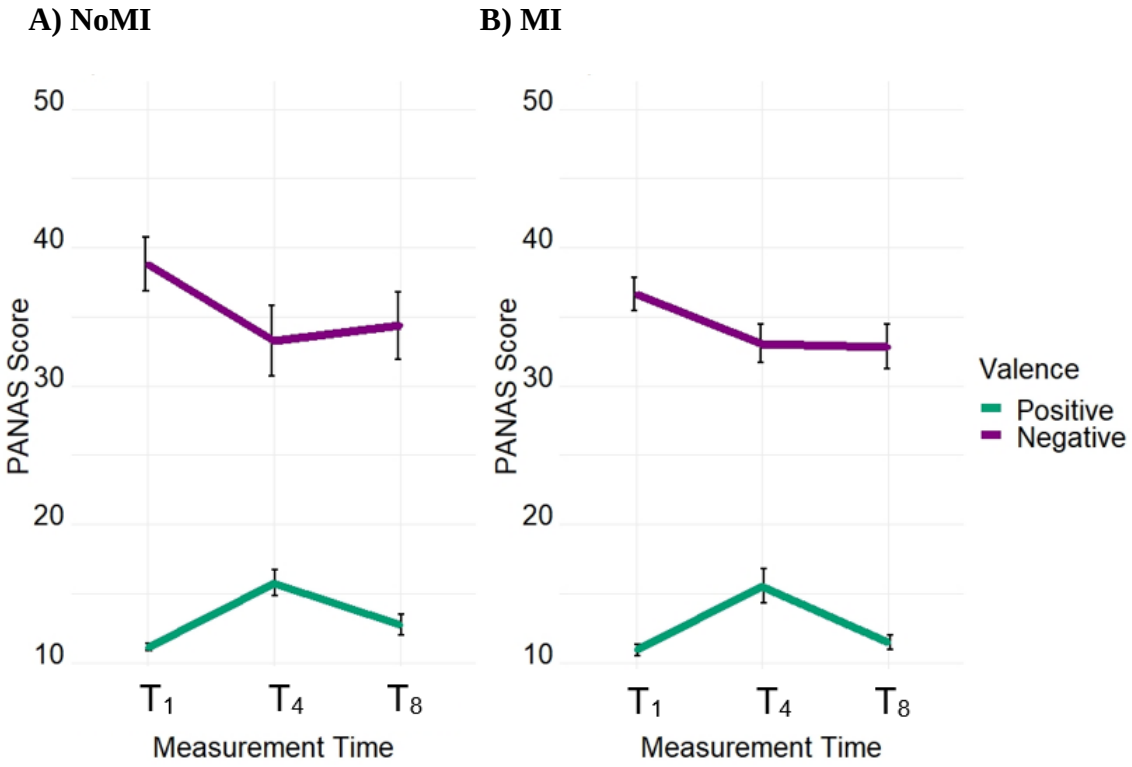
5.3.3 Physiological Reaction to Stress

5.3.3.1 Cortisol

Cortisol values were analysed using a mixed ANOVA with Group (MI, NoMI) as a between-subject factor, and Time (T_1 toT_8) as a within-subject factor. The main effect of Time was significant [$F(4.15, 107.98) = 7.51$, $p < .001$, $\eta_p^2 = 22$]. Specifically, the highest cortisol values were observed at T_1, presumably due to the ongoing acclimatization to the laboratory environment, and at T_4, as expected due to the TSST exposure.

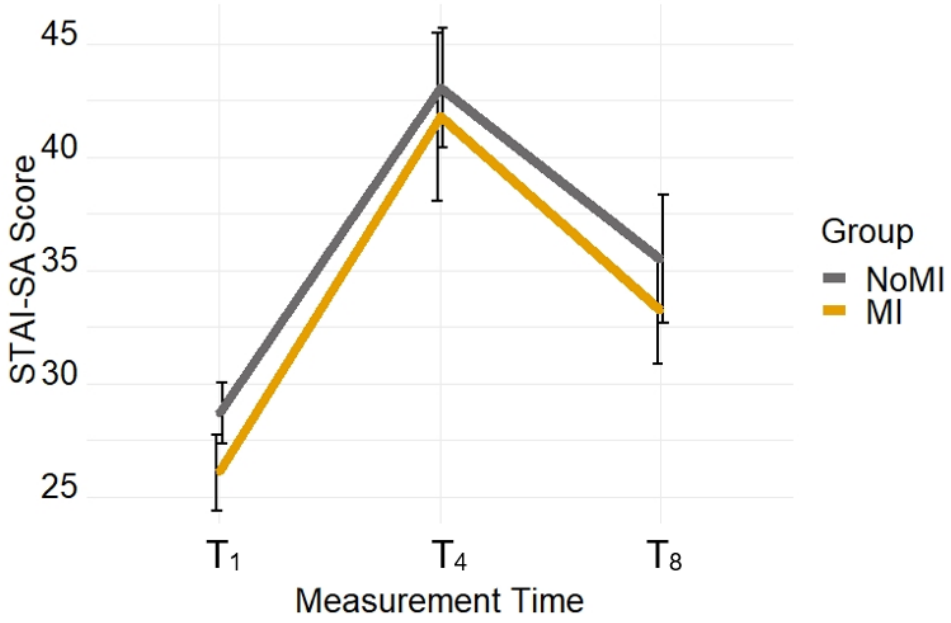
Only significant results are presented; tables 2 provides a summary of all *p*-values. T_1 was significantly higher than T_2 ($p = .016$), T_3 ($p = .017$), T_6 ($p = .001$), T_7 ($p < .001$), T_8 ($p < .001$). T_4 was significantly higher than T_6 ($p < .001$), T_7 ($p < .001$) and T_8 ($p < .001$). Cortisol decreased gradually after T4; hence, T_7 had significant lower cortisol values than T_2 ($p = .016$), T_3 ($p = .018$), and T_5 ($p < .001$). T_8 also had significant lower cortisol values than T_3 ($p = .043$), and T_5 ($p = .002$). Lastly, T_6 had a significant lower cortisol value than T_5 ($p = .002$). Contrary to expectation, the main effect of Group was not significant, $F(1, 26) = 1.78$, $p = .19$, $\eta_p^2 = .06$, and there was no interaction between Group and Time, $F(4.15, 107.98) = 0.93$, $p = .48$, $\eta_p^2 = .04$. To fully characterize the cortisol response profile, targeted analyses of the TSST period were performed using peak reactivity and the area under the curve to ground (AUC_G) and to increase

Figure 6 *(Figure 2 for Chapter V)* Change in PANAS Scores throughout the study period



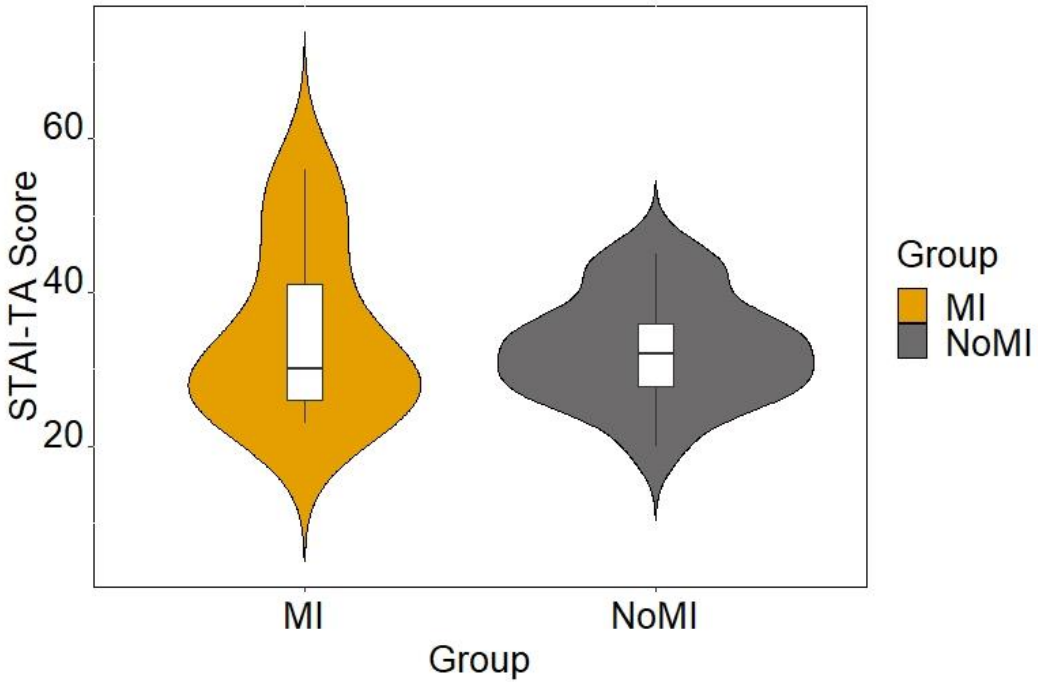
Note. This figure describes the changes in PANAS Scores from the beginning to the end of the study in the A)NoMI Group and the B)MI Group. The PANAS was administered at T_1 (Time 1 prior to the TSST), T_4 (after the TSST) and at T_8 (after all of the assessments).

Figure 7 *(Figure 3 for Chapter V)* Change in STAI-SA Scores throughout the study period



Note. The STAI-SA was administered at T_1 (prior to the TSST), T_4 (after the administration of the TSST and at T_8 (Post-Ax).

Figure 8 *(Figure 4 for Chapter V)* STAI-TA Scores as a function of the study groups



Note. The STAI-TA was administered once at T_1 only.

(AUC_I), comparing the two groups (see Figure 5). No group differences were found on AUC_G, AUC_I, and peak reactivity (see Figure 6). For more details on these analyses, see the Supplementary Material document.

A statistical trend suggests that the difference started emerging earlier: at T_7, the MI group (M = 0.38, SE = 0.02) showed reduced cortisol values compared to the NoMI group (M = 0.45, SE = 0.03); mean difference of 0.07, BCa 95% [0.01, 0.12], $t(26) = 2.00$, $p = .062$, Hedges' g = 0.69, CI 95% [-0.06, 1.44]. We did not find a significant (or near significant) difference for time points prior to T_7.

5.3.3.2 Heart Rate Variability

A mixed ANOVA was conducted with Group (NoMI, MI) and the eight selected time intervals (T_1 to T_8), using RSA as the dependent variable (see Figure 7). Analyses revealed no main effects of Group, $F(1, 24) = 2.21$, $p = .15$, $\eta_p^2 = .08$ and Time, $F(4.50, 108.03) = 1.95$, $p = .10$, $\eta_p^2 = .08$, and also for no Group by Time interaction $F(4.50, 108.03) = 2.10$, $p = .078$, $\eta_p^2 = .08$. See the Supplementary Material Document for more details on this analysis.

5.3.4 Psychological and Physiological Association

5.3.4.1 Cortisol

We performed a repeated-measures correlation between STAI-SA at T_1, T_3, T_8, and cortisol at T_2, T_4, and T_8. Analysis revealed no significant correlation for the whole sample, $r(55) = .20$, $p = .14$, CI 95% [-.07, .44]. When evaluating MI values separately, correlation between these variables was also not significant, $r(23) = .03$, $p = .89$, CI 95% [-.39,.44]. Notably, increased STAI-SA was related to an increase in cortisol in the NoMI group, $r(31) = .37$, $p = .035$, CI 95% [.02, .64] (see figure 8).

Similar repeated-measures correlations established in the complete sample using the

cortisol values and positive affect scores on the PANAS revealed the two measures to be positively correlated, $r(55) = .37$, $p = .004$, CI 95% [.12, .58]. However, group-specific correlations failed to reach significance [MI group, $r(23) = .22$, $p = .29$, CI 95% [-.21, .58]; NoMI group, $r(31) = .53$, $p = .002$, CI 95% [.21, 74]]. As for negative affect on the PANAS, the results of repeated measures correlations were not significant for the whole sample, $r(55) = -.19$, $p = .16$, CI 95% [-.43, .08] nor for the MI group, $r(23) = .05$, $p = .80$, CI 95% [-.37, .45]. A negative correlation was found between cortisol and negative affect in the NoMI group, $r(31) = -.38$, $p = .029$, CI 95% [-.65, -.03].

5.3.4.2 HRV

We tested the possible relationship between subjective emotional response and RSA. Repeated-measures correlations between STAI-SA at T_1, T_3, T_8 and RSA (at 5 minutes pre T_2, at 5 minutes pre T_3, and 5 minutes pre T_8), making the RSA assessments coincident with the time at which participants filled the STAI and PANAS questionnaires. The correlation was not significant between STAI-SA and RSA in the whole sample, $r(51) = -.15$, $p = .30$, CI 95% [-.41, .13], nor the NoMI group, $r(27) = .06$, $p = .76$, CI 95% [-.33, .43], but close to significance for the MI group, $r(23) = -.39$, $p = .053$, CI 95% [-.69, .02] (see figure 8). A negative correlation would follow the expected pattern: Increased subjective stress co-occurring with reduced parasympathetic control. No other significant correlations were found.

Figure 9 *(Figure 5 for Chapter V)* Salivary Cortisol Concentration throughout the study

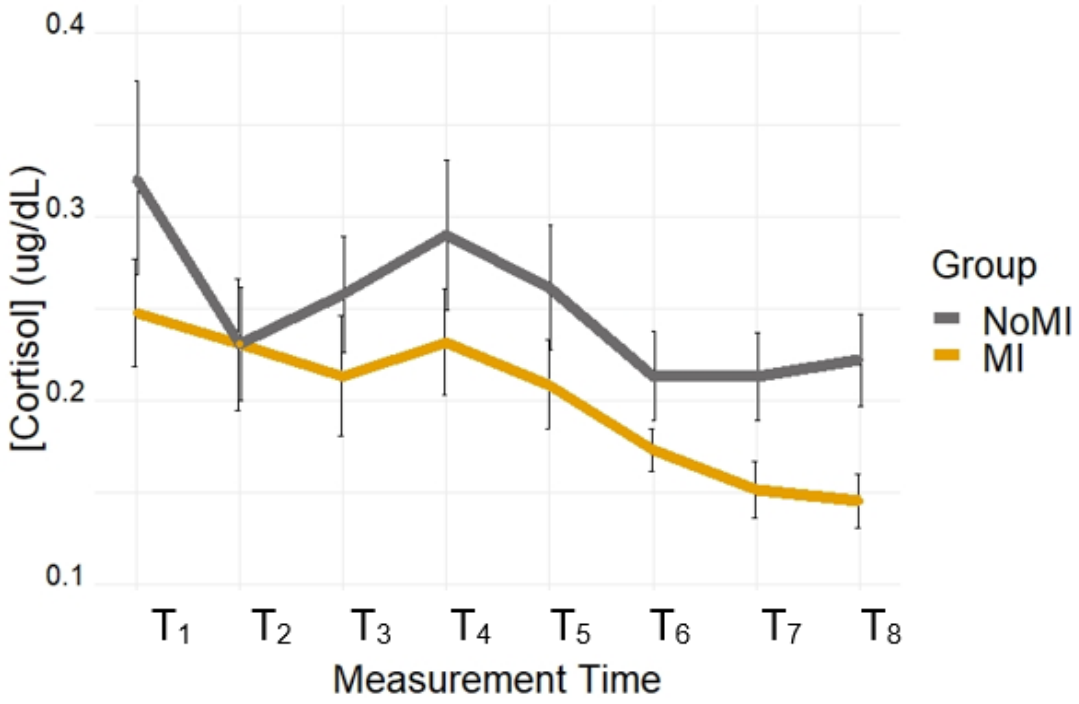

0.4
0.3
0.2
0.1
[Cortisol] (ug/dL)
T1
T2
T3
T4
T5
T6
T7
T8
Measurement Time
Group
NoMI
MI

Figure 10 *(Figure 6 for Chapter V)* A)AUC_G, B) AUC_I, and C) Peak Reactivity compared between the study groups

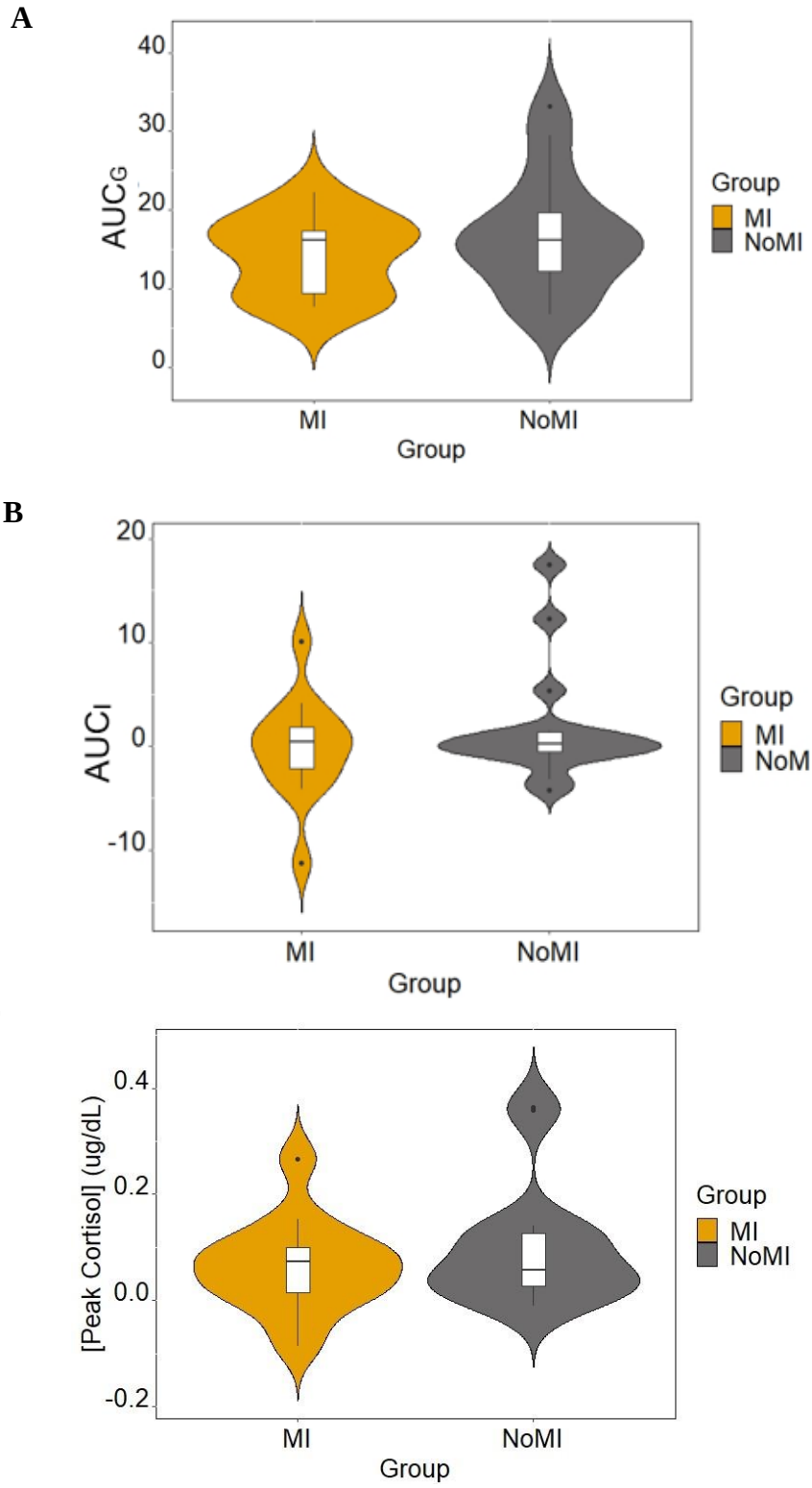
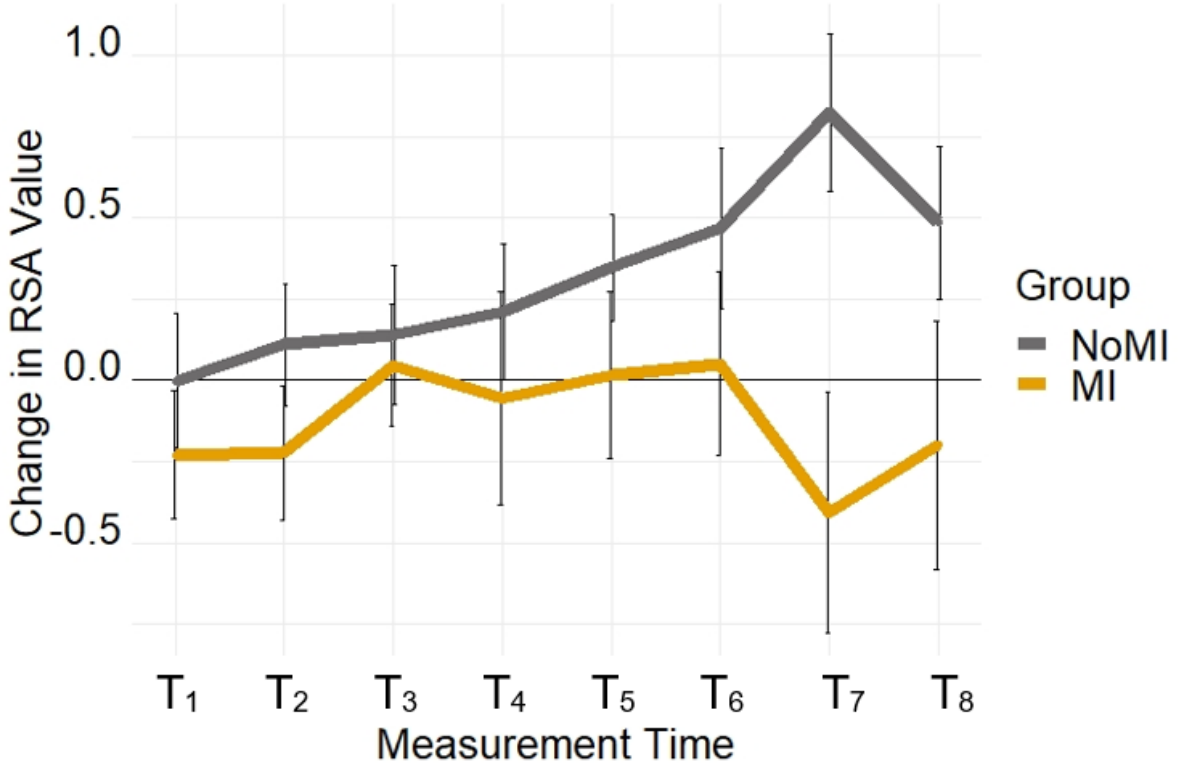
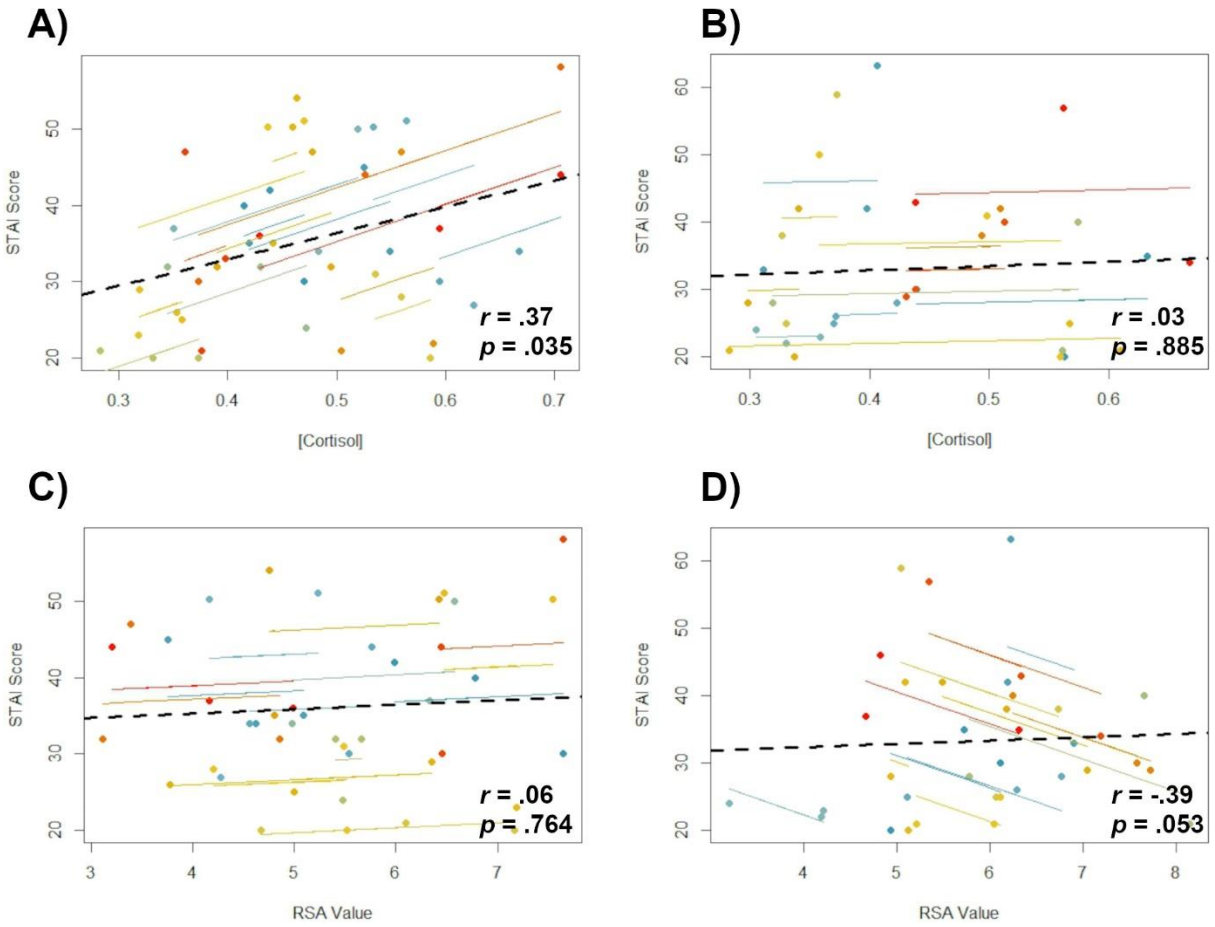


Figure 11 *(Figure 7 for Chapter V)* Change in RSA Value throughout the study period



Note. All RSA values were corrected using the recognized acclimatization period (T_2)

Figure 12 *(Figure 8 for Chapter V)* Repeated-measure correlations between STAI-SA at T_1, T_3, T_8 and cortisol concentration at T_2, T_4, T_8 for A) the NoMI group and B) the MI group and repeated-measure correlation between STAI-SA at T_1, T_3, T_8 and RSA at T_2, T_4, T_8



5.4.0 Discussion

This pilot study aimed to characterize and compare various physiological outcomes (i.e., cortisol, HRV) measured during basal and stress-induced conditions and characterize psychological response profiles (using STAI-SA and PANAS) of MI women and a matched control group. At present, no research has monitored in vivo the acute changes in stress-related physiological outcomes associated with social stress exposure in women with a history of MI using the TSST.

5.4.1 Psychological Changes

We used the STAI-TA and -SA versions to measure trait and state anxiety, respectively (Spielberger et al., 1983), and the PANAS to measure positive and negative affect (Watson et al., 1988). Participants completed the STAI-SA and PANAS at three critical intervals during the study (i.e., arrival to the laboratory [T_1], after the TSST [T_3], and at the end of the study [T_8]). We found no difference between the MI and NoMI groups for the STAI-Trait Anxiety (STAI-TA), which indicates similar daily life anxiety profiles in both groups. However, participants' scores on the STAI-SA support an effect of the TSST to increase anxiety levels in both groups. Specifically, anxiety levels increased significantly at T_3 and T_8 compared to T_1, and a significant decrease is noted between T_3 and T_8. In addition to increased anxiety related to TSST exposure, participants' affect gained in positivity as the experiment progressed from pre- to post- TSST, with negative affect decreasing over the same period. Specifically, we found the T_3 measure, collected post TSST, to be associated with scores supporting increased positive affect compared to measures taken at T_1. Consistent with this, as participants recovered from TSST exposure, scores indicated significantly reduced negative affect at both T_3 and T_8 compared to T_1. Overall, these results suggest that participants entered the study with elevated anxiety levels, which levels

gradually decreased throughout the study, with a peak negative emotionality related to TSST exposure. Considering that participants had to complete a battery of neuropsychological tests after the TSST, which can be stressful, our findings support participants to have acclimatized to the anxiety-provoking environment. Our observations are consistent with the TSST being a validated stressful paradigm that significantly activates the endocrine secretion of cortisol (Allen et al., 2014, 2017; Narvaez Linares et al., 2020). Our study also suggests that performing neuropsychological assessments, possibly due to individual test completion, likely made participants feel an increased control compared to the TSST.

5.4.2 Physiological Changes

Eight cortisol samples were collected at key intervals during the study (Narvaez Linares et al., 2020), and HRV was continuously recorded. We did not find significant between-group alteration in HRV; however, *p*-values and effect sizes suggest that this could be attributable to statistical power related to a small sample. Although the cortisol response of the MI group appeared on average tempered compared to measures of the NoMI group, no significant group differences were detected. Follow-up analyses on individual time intervals, enabled by priory hypotheses, revealed lower cortisol levels in MI compared to NoMI participants at T_8, with a trend emerging at T_7.

We expected greater differences in cortisol secretion between MI and NoMI participants following TSST exposure. Indeed, the impact of cardiac arrest and associated hypoxic state on HPAA reactivity has been long recognized (Hékimian et al., 2004; Lindner et al., 1992; Pene et al., 2005; Schultz et al., 1993f; Tavakoli et al., 2012), as well as the impact on brain tissues and systems associated with this response (de la Tremblaye et al., 2014; Neigh et al., 2009; Neigh, Glasper, et al., 2004; Neigh, Kofler, et al., 2004; Okuma et al., 2021; Q. Zhao et al., 2021). In

this context, Zhao et al. (2021) recently demonstrated resuscitation from cardiac arrest in mice to significantly increase pro-inflammatory cytokines secretion, promoting elevated HPAA activation and glucocorticoid secretion upon stress exposure. The authors also noted significant atrophy of lymphoid organs dimensions, which further impacted HPAA function. Although of reduced magnitude, MI impacts brain oxygenation and induces damage to the hippocampus, which regulates HPAA activation (Dimsdale, 2008; Malick et al., 2018). Thus, MI represents a potent metabolic stressor, likely to have repercussions on stress-induced physiological (i.e., heart rate and cortisol secretion) and emotional reactivity.

Our study is the first to examine how MI in women impacts HPAA response upon exposure to a social stressor. Jackson et al. (2018) characterized 221,677 individuals' levels of psychological distress and risk for MI over 5 years. Authors found that participants who experienced an MI were those who reported high/very high psychological distress, and that this factor increased the risk of experiencing a second MI by 20.0%. Similarly, Roest et al. (2010) reported that individuals experiencing high levels of post-MI anxiety were 36.0% more likely to have cardiac complications (e.g., mortality, risk of having another MI). Considering that SCA and MI have a similar impact on the brain (i.e., lack of oxygen and nutrients), although, at a different degree, the effect of MI on brain functions may be more subtle. Nevertheless, with an increased occurrence of mental health disorders post-MI related to heightened mortality rate, MI may play a significant role in HPAA functionality of individuals showing elevated psychological distress post-MI (Dimsdale, 2008; Jackson et al., 2018; Roest et al., 2010). Nonetheless, our findings suggest that MI could be associated with reduced flexibility in the stress response over a long period. Follow-up studies will need to investigate this in larger sample sizes, where psychological distress would act as a covariate.

5.4.3 Relation between Physiological and Psychological Changes

Despite a small sample, our findings partially support the idea that there is a disconnect between subjective (e.g., how I feel) and objective experience for MI participants, particularly for cortisol response. At a group level, this is illustrated by the fact that even though the MI and NoMI groups perceived the TSST as a stressful experience, the physiological response to stress tended to be slightly larger for the NoMI than MI group overall and significantly so towards the end of the experiment for cortisol. At the individual level, we observed strong and significant correlations between changes in subjective experience (e.g., anxiety, positive and negative affect) and cortisol levels only in the NoMI group and not in the MI group. These findings support that the HPAA is not properly adapting in its response to stressful events, particularly when prolonged, possibly due to an altered negative feedback mechanism (Gjerstad et al., 2018; Lightman & Conway-Campbell, 2010). Future studies should include more than one marker of stress, as women with a MI history might be more attuned to cardiovascular indices of stress, as suggested by the repeated correlations between subjective anxiety and RSA. In addition, it is essential to highlight that psychophysiological response depends on sex, and it is, therefore, necessary to consider this factor in the analyses and interpretations of the collected findings (Schmaus et al., 2008).

5.5.0 Limits of the Study

The global pandemic did not allow the recruitment of additional participants, which could be tested under similar basal conditions. Our sample size did not enable accounting the effect of diabetes on our physiological data (i.e., CORT and HRV). However, future studies should consider this condition as it is known to impact HRV data (for more information, see Ernst,

2014). In addition, the sample size of our study prevented addressing possible effects of the participants' prescribed medication on the measured physiological responses. Therefore, one cannot rule out the impact of post MI medication on some responses. Such effects however remain difficult to determine as influence of medical treatments likely depend on post MI recovery period.

Considering our observations, we believe that replicating our study with a bigger sample would refine our findings and statistical tendencies observed to be validated. It also appears necessary to assess multiple correlates of stress (e.g., cortisol, electrodermal activity, heart rate), especially in women, because their reaction is different than men, and not all tools may be sensitive enough to capture these differences (Bari, 2020; Lash et al., 1995; Reschke-Hernández et al., 2017). In addition, adding two supplementary groups that would use the friendly-TSST to compare the difference between stress (TSST) and non-stress (friendly-TSST) would allow capturing a global picture of the effect of the HPAA. Indeed the non-stressful situation would allow researchers to compare how stress impacts physiological activation (i.e. HPAA) and perception of stress with the stressful situation. Without a doubt, studies also need to include participants from different racial/ethnic background as the HPAA respond differently in BIPOC population (Allen et al., 2019; Berger et al., 2017; Chong et al., 2008; Suglia et al., 2010; Yanovski et al., 1993, 1993, 1996). Finally, future studies should also include measures of Type D personality - disposition to repress emotional distress (Denollet et al., 1996) - as it has been shown that individuals with CHD are more prone to have this type of presentation, which could potentially explain the differences in perceived stress (e.g., mental distress; Gecaite, Burkauskas, Brozaitiene, et al., 2019; Gecaite, Burkauskas, Bunevicius, et al., 2019; Kupper et al., 2013; Williams et al., 2009), and might impact the prognosis in MI individuals (Denollet et al., 2009;

Kazukauskiene et al., 2021).

5.6.0 Conclusion

This pilot research is the first to characterize stress-induced changes in HPAA activation via cortisol secretion in women with MI history. Despite a small sample, we found that women with MI reported similar levels of perceived stress compared to the control group; however, the different physiological measures collected indicated a psychophysical dissonance in the response profile of MI women, especially as it pertained to RSA and cortisol secretion, which appeared attenuated post-stress in MI women. Our findings open the door to a more in-depth examination of the parameters of MI recovery that are most closely associated with altered cardiovascular and HPAA responses, since dysregulation of such responses could explain why some people present an increased risk of developing mental health disorders following MI.

5.7.0 Acknowledgements

We acknowledge that our research was conducted in the traditional unceded territory of the Algonquin Anishnaabeg People. We declare no conflict of interest. N.F.N.L. was supported by a doctoral scholarship from the Québec Research Funds in Nature and Technologies (FRQNT). A discovery grant supported this work to H.P. from the Natural Sciences and Engineering Research Council of Canada (RG203596-13). We would also want to thank our participants for having participated in this study. Finally, we would like to thank Zoey Burr, Kathel Dongnang, Yassine Hmidni, Zachery Verret-Borsos, Jeremy Oueis, and Eva Fernandes for their assistance in data collection.

Supplementary Material

Check List laboratory study

Before participant arrival

☐Package is ready (make sure to pick the right language)

☐Every document is identified with participant's ID

☐Are the tubes (cortisol) identified?

☐Is the cooler filled with ice?

☐Is the TSST room ready (camera and microphone) ?

☐Do you have the lab coats ?

☐Is the testing room ready (table, chairs and computer) ?

Pre TSST

☐Consent if signed

☐GHQ-12 completed

☐STAY-Y-SA completed

☐I-PANAS-SF completed

☐CESD-R completed

Post TSST

☐STAY-Y-SA completed

☐I-PANAS-SF completed

☐Moca Completed

☐COWA completed

☐CBS

☐RCFT copy and immediate

☐Trails A and B

☐ACC

☐RCFT copy and immediate

☐Feedback (consent + gift card + parking pass)
☐Relaxation

Physiological measures

Times	**Physiological measure**	**Did you write the time on the cortisol tube?**	**Did you check if the heart rate monitor was functioning**
15 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
40 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
55 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
75 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
90 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
105 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
135 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____
165 minutes	☐Cortisol ☐Physiological measures	☐ Yes: _____	☐ Yes: _____

Who participated in the session

1. Female TSST judge: _____
2. Male TSST judge: _____
3. Research Assistant: _____
4. Assessor: _____

5.2.5.1 Trier Social Stress Test

As for the TSST protocol, participants had 5 minutes to prepare for a speech task and were given a piece of paper to write their thoughts. However, they were instructed that their notes could not be used during the speech delivery. Then, participants had to stand up and deliver a 5-minute oral presentation telling the jury why they would be the best candidate for their dream job. Participants were encouraged to continue presenting, and if they experienced difficulties, a series of standardized questions were asked to enhance continued speech. Finally, participants completed the arithmetic task for 5 minutes which entailed subtracting 17 from 2040 until 0. Every time the participant made a mistake, she was instructed to start from the beginning. The panel was composed of two undergraduate students (a woman and a man) trained to deliver the TSST protocol. These judges wore lab coats and maintained a neutral expression through the duration of the TSST. Before initiating the speech task, one judge (man) stated to the participant that three cameras – he pointed to them - were going to record their performance since both judges were 'behavioural analysis' experts; the judge also indicated that they were there going to take notes. During the debriefing, N.F.N.L. shared that no recording was performed, but that such mention participated in creating a stressful environment.

5.5.3.2 Heart Rate Variability

We visually inspected all data for incorrectly identified peaks, missing heartbeats, and any portion of data that would be unusable due to excessive noise. We interpolated up to two beats when beats were missing or diverged substantially from their expected time. We removed incorrect R peaks and inserted the correct R peaks manually when these were clear. Additionally, we discarded data portions with excessive noise, but all included segments contained at least 30 seconds of continuous data. After cleaning, we excluded the data of one MI and one NoMI

participants from HRV analyses because they retained a low percentage of normal peaks (i.e., not estimated, not ectopic; mean of 82.04% and 87.61%, respectively). All other participants had more than 90% of normal R peaks in each segment (sample mean of 99.29%, *SD* = 1.58). The respiratory peak frequency of all segments was within the RSA frequency band, which was defined as 0.15 to 0.40 Hz.

Portions of the collected data were selected for analysis. Thus, segments of 5 minutes heart rate recordings were analyzed related to each of the collection intervals T_1 to T_7. Further, as changes related to stress induction was of importance, the entirety of the TSST was analyzed by segmenting the data between T_2 (beginning of TSST) and T_3 (end of TSST). Lastly, HRV reported for T_8 represents the 300-second preceding initiation of this time interval (this period corresponds to the end of neuropsychological testing). Similarly, T_2 represents HRV measured 300-second before initiation of this time interval and evaluate baseline.

5.2.6 Statistical Analyses

The first set of analyses compared the NoMI and MI groups on psychological tests (i.e., STAI and PANAS) using mixed ANOVAs. The two groups were further compared on trait anxiety with independent samples t-test, 5000 bootstraps, and bias-corrected accelerated confidence intervals, like all other t-tests reported here.

The second set of analyses compared the NoMI and MI groups on objective measures of stress, first cortisol and then respiratory sinus arrhythmia (RSA), using mixed ANOVAs and independent samples t-tests. In addition to comparing cortisol throughout the experiment, we also compared the response to the TSST, using the area under the curve to ground (AUC_G) and to increase (AUC_I; Pruessner et al., 2003), and peak reactivity (Khoury et al., 2015). We considered T_2 the 'baseline' for AUC_G, AUC_I, and peak reactivity because it was collected after the

habituation period and before the TSST (similar to RSA analyses, described below). We selected this period as the baseline as it represented when the participants were most relaxed (i.e., they relaxed by sitting down and reading a text of their choice or watching a calming video). To calculate $AUC_{G,}$ we obtained the sum of the mean cortisol of two subsequent periods (T_2 and T_3, T_3 and T_4, T_4 and T_5, T_5 and T_6), with each means being multiplied by that period's duration in minutes (Pruessner et al., 2003). AUC_I was identical to AUC_G but entailed subtracting the T_2 value multiplied by the total time between T_2 and T_6 (Pruessner et al., 2003). Peak reactivity was defined as each participants' highest cortisol value from T_3 to T_6 subtracted from their own T_2 value (Khoury et al., 2015).

We ran separate mixed ANOVAs to compare the two groups on RSA values extracted over the experiment and over the entire TSST period. Participants' RSA value for the 'baseline' period (5 minutes pre T2) was subtracted from each of these segments. Hence, a negative value reflects reduced parasympathetic control relative to baseline – consistent with a stress response from the parasympathetic system – and positive values represent higher parasympathetic control relative to baseline.

Lastly, we performed repeated-measures correlations (Bakdash & Marusich, 2017) to test the within-subject relation between subjective (i.e., STAI, PANAS) and objective measures (i.e., cortisol, RSA) across three timestamps during the experiment. These correlations included the whole sample in a first step and were repeated in each group as we anticipated that subjective experience would align less well to objective experience in the MI than the NoMI group.

One participant from the MI group missed a cortisol value for T_1, and another participant missed a T_1 segment for RSA analyses. They were excluded whenever that particular T_1 measurement was included in the analyses. For the questionnaires, the mean value for each item

of the whole sample was given if a participant forgot to fill out an item (STAI-SA_{T1} = 4; STAI-SA_{T3} = 1; STAI-TA = 1; $PANAS_{T8}$ = 4 participants).

5.3.3.1 Cortisol

The AUC_G was not significantly reduced in MI (*M* = 14.23, *SE* = 1.36) compared to NoMI (*M* = 16.24, *SE* = 1.56) group. A between group mean difference of 2.02, BCa 95% [-2.09, 6.25], *t*(27) = 0.98, *p* = .34, Hedges' *g* = 0.36, CI 95% [-0.39, 1.09] was detected. Similarly, the AUC_I was not significantly reduced in the MI (*M* = -0.05, *SE* = 0.97) compared to NoMI (*M* = 0.80, *SE* = 0.76) group. A between group mean difference of 0.84, BCa 95% [-1.44, 3.23], *t*(27) = 0.70, *p* = .49, Hedges' *g* = 0.25, CI 95% [-0.47, 0.96] was detected. Finally, the MI (*M* = 0.06, *SE* = 0.02) and NoMI group (*M* = 0.08, *SE* = 0.02) groups showed comparable peak reactivity, with mean difference of 0.02, BCa 95% [-0.03, .07], *t*(27) = 0.73, *p* = .48, Hedges' *g* = 0.26, CI 95% [-0.46, 0.97].

5.3.3.2 Heart Rate Variability

We expected the TSST to induce differential impact on heart rate stress-related response. The initial analysis only included a portion of the TSST (i.e., speech preparation). Our follow up analysis included the complete TSST exposure period. The mixed ANOVA included Group (MI, NoMI) as a between-subject factor and three periods of 5 minutes for Time (speech preparation, speech delivery, arithmetic task) as a within-subject factor. Neither the main effects nor the interaction were significant: Time, *F*(2, 50) = 1.90, *p* = .16, η_p^2 = .07; Group, *F*(1, 25) = 0.93, *p* = .344, η_p^2 = .04, Time*Group, *F*(2, 50) = 2.23, *p* = .12, η_p^2 = .08.

Table 14 (Table 2 for Chapter V) *Difference between time for cortisol measures (p-values)*

	T_2	T_3	T_4	T_5	T_6	T_7	T_8
T_1	**.16**	**.017**	.38	.055	**.001**	< **.001**	< **.001**
T_2		.91	.13	.67	.11	**.016**	.058
T_3			.10	.64	.086	**.018**	**.043**
T_4				.12	< **.001**	< **.001**	< **.001**
T_5					**.002**	< **.001**	**.002**
T_6						.16	.33
T_7							.92

Note. Bold p-values indicates a significant result (< .05).

References

See Chapter 8 – Références de la thèse for the references. The specific references for this article are available in the published format (see online publication)

5.8.0 References

See Chapter 8 – Références de la thèse for the references. The specific references for this article are available in the published format (see online publication)

Chapitre VI – Discussion générale de la thèse

6.0 Discussion générale

Les recherches effectuées dans le cadre de cette thèse ont permis de mieux comprendre et caractériser certaines des répercussions émotionnelles et physiologiques associées à un historique d'IM chez la femme, dans un contexte où elles sont exposées en laboratoire à une situation de stress. Ce projet doctoral comporte quatre composantes principales, deux revues systématiques (chapitre II et III), une étude transversale ayant utilisé une enquête par questionnaire (chapitre IV) et une étude transversale quasi-expérimentale (chapitre V).

Le but principal du premier article scientifique visait à établir un protocole et une méthodologie pour le TSST basé sur une revue systématique des études publiées ayant utilisé ce paradigme auprès d'une population adulte. Une telle démarche visait à créer un protocole rigoureux afin d'en maximiser la validité lors de son utilisation auprès d'un échantillon de femmes dans le quatrième article de la thèse (chapitre V). Cette recension nous a permis d'élaborer deux documents soulignant les facteurs et variables importants à prendre en considération lors de la passation d'un TSST. Ces documents permettront aux recherches futures utilisant ce paradigme d'utiliser les recommandations fournies afin d'établir un protocole et une méthodologie basés sur des données probantes (Narvaez Linares et al., 2020).

La deuxième revue systématique de cette thèse visait à établir l'état des connaissances concernant les altérations cognitives associées aux sous-types de MC, avec un accent sur les répercussions cognitives associées à l'IM chez les femmes (Narvaez Linares et al., 2021). Cet article a permis de mettre en lumière le manque de standardisation dans l'opérationnalisation des variables (p.ex., nous avons noté une disparité dans les types de conditions médicales regroupées comme des MC) ce qui apporte un éclairage sur la discordance des constats cliniques dans ce domaine.

Deux études de terrain complètent cette thèse; elles ont pu bénéficier des connaissances acquises via les revues systématiques préalables. Une enquête par questionnaire en ligne fut créée visant à étudier la prévalence au sein d'échantillon de femmes canadiennes de certains facteurs (p.ex., hypertension artérielle, diabète) connus pour leur association à un historique d'IM. Nous désirions également documenter les symptômes ressentis lors d'un IM et comparer nos résultats à ceux d'études venant des États-Unis et de l'Europe. Finalement, l'étude en laboratoire désirait mesurer certains changements physiologiques et émotionnels, incluant les niveaux de CORT, la variabilité du rythme cardiaque, ainsi que la perception d'adaptabilité au stress, associés à l'exposition au TSST.

La discussion qui suit propose une discussion par thème des informations liées aux différentes études accomplies. Cette disposition permet une intégration globale optimale des connaissances acquises.

6.1 Les femmes dans la recherche scientifique

La recension des écrits utilisant le TSST a offert une validation additionnelle de l'absence des femmes dans la recherche contemporaine. Au sein des études incluses dans l'analyse systématique (N = 35; Narvaez Linares et al., 2020), cinq études comprenaient des échantillons composés exclusivement de femmes contre douze ayant des échantillons exclusivement d'hommes. De plus, les dix-sept études présentant des échantillons mixtes comportaient en moyenne 70,7 % (± 25,9) d'hommes contre 59,8 % (± 23,9) de femmes. De façon similaire, notre deuxième revue systématique (Narvaez Linares et al., 2021) établit le même constat d'une sous-représentation de femmes en recherche sur les MCV et MC (Wenger, 2012; Woodward, 2019). Une sous-représentation des femmes au sein de ce type de recherche est injustifiée considérant une prévalence similaire des MCV chez les deux sexes, et nuit indéniablement à la

recherche de traitements mieux adaptés (Söderström, 2001). Les essais cliniques chez l'humain et précliniques chez l'animal continuent d'inclure majoritairement des participants/sujets mâles, ce qui a des répercussions désastreuses sur la santé des femmes (de Vries et al., 2019; Zucker & Prendergast, 2020).

Les raisons sous-jacentes à l'exclusion des femmes sont multiples. De façon générale, les hommes ont été considérés comme la norme dans les études sur les populations puisque la fluctuation hormonale des femmes liée au cycle reproducteur s'avérait trop compliquée et coûteuse (Liu & Mager, 2016). Des initiatives aux États-Unis (Kim et al., 2010) et au Canada (Yakerson, 2019) visant à augmenter le nombre de femmes dans les études scientifiques et essais cliniques engendrent des effets positifs qui demeurent toutefois insatisfaisants (Feldman et al., 2019). Au Canada, la stratégie nationale visant la santé des femmes s'est engagée à surveiller l'inclusion des femmes dans les essais cliniques et les trois conseils nationaux de subvention prônent à même leurs politiques de soutien à la recherche la non-exclusion de sujets basé sur le sexe ou lié au statut de reproduction des femmes. Toutefois, le suivi quant aux applications de ces principes n'est pas instauré de manière systématique (Yakerson, 2019).

L'exclusion des femmes continue d'avoir des conséquences néfastes sur différents aspects du suivi médical des femmes, incluant : a) la perception des professionnels de la santé des affectations et de la symptomatologie spécifiques chez les femmes; b) les résultats différentiels à la suite de traitements selon les sexes; c) les modalités de traitement et de diagnostic; d) ainsi que la morbidité associée aux maladies selon le sexe (Institute of Medicine [US] Committee on the Ethical and Legal Issues Relating to the Inclusion of Women in Clinical Studies, 1999). En dépit de la reconnaissance de ces lacunes, les femmes ont continué d'être exclues dans l'étude des MCV et des MC (Dougherty, 2011; Kim & Menon, 2009; Thomas &

Braus, 1998). Par exemple, en analysant le recrutement des femmes au sein de 36 essais cliniques pour des médicaments traitant diverses conditions cardiovasculaires, Scott et al. (2018) ont trouvé que les femmes représentaient en moyenne 46,0 % de l'échantillon total (étendu : 22,0 – 81,0 %). De plus, ces derniers ont remarqué que les femmes étaient bien représentées dans les essais de médicaments liés au traitement de l'hypertension et la fibrillation auriculaire, mais sous-représentée dans les essais de médicaments liés au traitement de l'insuffisance cardiaque, les MC et IM (Scott et al., 2018). Bien que ces maladies soient celles qui affichent un taux de mortalité plus élevé chez les femmes, l'inclusion de ces dernières au sein de ces études n'est malheureusement pas systématique.

Malgré des proportions inégales, les résultats des recherches soulignent que la simple inclusion de femmes au sein des échantillons a des répercussions positives en ce qui a trait au développement de traitements prometteurs destinés spécifiquement aux femmes (Aggarwal et al., 2018; Geraghty et al., 2021; Sarma & Scott, 2017). Par exemple, l'augmentation du nombre de femmes dans les recherches sur les MCV a permis une réduction de près de 30,0 % du taux de mortalité entre 1984 et 2004 (Benjamin et al., 2017). L'inclusion des femmes est liée au développement d'une sensibilité accentuée de leur situation particulière, mettant l'accent sur une plus grande prévalence des MC chez les femmes ainsi que soutenant l'application de traitements fondés sur données probantes pour traiter ces maladies (Aggarwal et al., 2018). Toutefois, le pronostic des femmes ayant une MC demeure défavorable en comparaison à celui des hommes, particulièrement pour celles qui sont plus jeunes (<55 ans), appartiennent à certains groupes ethniques/races, ou présentent un statut socioéconomique et/ou niveau d'éducation inférieur (Benjamin et al., 2017; McSweeney et al., 2016). En somme, malgré des améliorations importantes de l'inclusion et une augmentation des femmes dans les recherches sur les MCV et

les MC au courant de la dernière décennie, il reste plusieurs enjeux à adresser; incluant celui de l'imputabilité quant à la réalisation des recherches auxquelles des fonds publics sont attribués (Jin et al., 2020).

6.1.1 L'infarctus du myocarde chez la femme

Vers la fin du 20^{e}, plusieurs recherches ont suggéré la manifestation de symptômes distincts associés à un IM chez les femmes et les hommes (Canto et al., 2000; Dempsey et al., 1995; Everts et al., 1996; McSweeney, 1998; McSweeney Jean C. et al., 2003; Milner et al., 1999). Comparativement aux hommes, les femmes sont moins enclines à ressentir une douleur à la poitrine (Canto et al., 2012; N. A. Khan et al., 2013), ayant davantage tendance à ressentir des symptômes plus diffus comme de l'indigestion, des nausées et/ou vomissements, une douleur de dos et/ou à la mâchoire (DeVon et al., 2008). Malgré l'évidence de l'intérêt d'une communication générale de cette information cruciale d'un point de vue de la santé des populations, ces différences entre les sexes ont tardé à être rendues publiques et n'ont pas été transmises efficacement. À ce jour, moins de 50,0 % des femmes savent que les symptômes d'un IM chez elles sont différents de ceux vécus par les hommes, une méconnaissance en partie liée à la croyance populaire que les hommes demeurent principalement affectés par l'IM (Clayton & Arnegard, 2018; McDonnell et al., 2014). Il n'est donc pas étonnant que les femmes tendent à négliger les symptômes reliés à un IM et attendent plus longtemps que les hommes avant de consulter et d'avoir recours au système de santé pour obtenir de l'aide (Canto et al., 2007; Lefler & Bondy, 2004). Meyer et al. (2019) se sont intéressé à ce phénomène sur une période de 16 ans. Leur étude auprès de N = 4360 individus (n_{femmes} = 967; 22,2 %) ont souligné que : a) pour la même période, le temps avant de consulter a diminué pour les hommes alors qu'il est demeuré le même pour les femmes; b) les femmes attendent environ 37 minutes de plus avant d'avoir

recours à des services médicaux; c) contrairement aux hommes, les femmes qui ont une douleur thoracique sont moins enclines à attribuer leurs symptômes à une condition médicale qui nécessite une prise en charge urgente; et d) le taux de mortalité à l'hôpital est significativement plus élevé pour les femmes (5,9 %) en comparaison aux hommes (4,5 %).

De plus, bien que plusieurs groupes de recherche canadiens soient actifs dans l'étude des MCV, MC et de l'IM chez la femme, il continue d'exister un écart de connaissances relatif à l'examen de ces pathologies dans un contexte canadien (Heart & Stroke, 2018; Izadnegahdar et al., 2014; Norris, Yip, Nerenberg, Clavel, et al., 2020; Norris, Yip, Nerenberg, Jaffer, et al., 2020). À ce jour, la recherche de McDonnell et al. (2014) est la seule à avoir étudié le risque perçu de différents facteurs de risque sur la santé cardiovasculaire (p. ex., hypertension) ainsi que les symptômes d'un IM chez des femmes n'ayant jamais eu d'IM dans un contexte canadien. Ces chercheurs ont trouvé parmi les N = 1654 femmes de 25 ans et plus interviewés que : a) moins de la moitié étaient capable d'identifier le tabagisme comme facteur de risque; b) moins d'un quart savaient que le cholestérol ou l'hypertension sont des facteurs de risque majeurs; c) moins de la moitié connaissaient les symptômes prédominants des MC chez leur sexe; et d) malgré que la majorité préfère être éduquée sur le sujet par leurs médecins, seulement un peu plus de la moitié des femmes sondées rapportent avoir eu une discussion avec leur médecin quant à la prévention et le mode de vie à adopter lors de leur consultation. Incidemment, bien que cela puisse sembler invraisemblable, l'enquête par questionnaire en ligne effectuée dans cette thèse représente la première étude canadienne qui se soit consacrée à documenter les symptômes ressentis lors d'un IM par les femmes ayant un historique d'IM et étudier la prépondérance des différents facteurs connus (p.ex. hypertension) simultanément.

Nos résultats indiquent que les femmes canadiennes de notre échantillon se comparent en

matière du nombre et de la particularité des symptômes ressentis à ceux répertoriés par les études auprès des femmes américaines (Brush et al., 2020; Virani, et al., 2020). Tout comme ces dernières, elles rapportent des symptômes distincts associés à un IM de ceux typiquement nommés par les hommes. À cet effet, les femmes de notre échantillon rapportent : a) des signes d'anxiété; b) une fatigue inhabituelle; c) des nausées et des vomissements; d) une douleur ou un malaise dans la partie supérieure de l'abdomen; e) des sueurs froides. Par conséquent, ces symptômes étiquetés comme « atypiques » par les études ciblant des populations masculines, représentent en fait des symptômes typiques ressentis par les femmes lors d'un IM. Ces résultats sont essentiels, car ils soulignent que l'inclusion des femmes est susceptible de redéfinir les paramètres de différentes pathologies et de conférer des chances équivalentes de prise en charge rapide des traitements assurant une meilleure survie des femmes. Par exemple, Mozaffarian et al. (2015) ont souligné dans le rapport du American Heart Association que peu importe l'âge, les femmes meurent en un plus grand nombre en comparaison aux hommes (26,0 % *vs* 19,0 %) dans l'année qui suit leur IM. De plus, les auteurs ont également rapporté que les femmes meurent d'autres MCV, comme l'insuffisance cardiaque ou un accident vasculaire cérébral, en comparaison aux hommes (47,0 % *vs* 36,0 %) dans les cinq ans qui suivent leur premier IM.

Les résultats découlant de l'enquête par questionnaire en ligne soulignent une plus grande prévalence d'hypertension artérielle (Ouyang et al., 2006) et d'hypercholestérolémie (Wei et al., 2017) chez les femmes qui ont un historique d'IM. Ces facteurs sont souvent présents bien avant le premier IM chez les femmes – ce qui fut également le cas pour notre échantillon ; agissant comme catalyseurs dans le processus de développement d'un premier IM chez la femme (Meagher, 2004; Nakanishi et al., 2017; Rakugi et al., 1996). En ce qui concerne les niveaux de cholestérol sanguin, l'œstrogène favorise leur régulation (Parini et al., 1997). De ce fait, la baisse

du niveau d'œstrogène associée à la transition vers la ménopause engendre un dérèglement de la régulation des différents types de cholestérol sanguin : certains augmentent et tendent même à excéder ceux des hommes (Abbey et al., 1999; Brown et al., 1993; Davis et al., 1994; Trémollières et al., 1999). En effet, durant la ménopause il y a habituellement une augmentation progressive du cholestérol total, en particulier une augmentation des lipoprotéines de basse densité – communément appelé le « mauvais cholestérol » et une diminution des lipoprotéines de haute densité – communément appelé le « bon cholestérol ». Dès lors, ceci permet d'expliquer pourquoi les femmes ménopausées ont un profil lipidique plus athérogène (Schnatz & Schnatz, 2006) comparativement aux femmes préménopauses et qu'elles sont plus à risque d'avoir un IM (Maas & Appelman, 2010). Par conséquent, l'atténuation du rôle protecteur de l'œstrogène associé à la ménopause est en partie liée à un dérèglement de la composition du cholestérol sanguin, contribuant ainsi à une augmentation de l'incidence des MC et des IM chez les femmes post-ménopausées (Maas & Appelman, 2010; Stensvold et al., 1992). La diminution de l'œstrogène à la ménopause mène également à une perte de l'élasticité artérielle et la prévalence de l'hypertension tend aussi à augmenter avec l'âge (Staessen et al., 1991), particulièrement chez les femmes (Kannel et al., 1980). En d'autres termes, l'hypertension augmente les risques de MC et de la mortalité, toutes causes confondues, chez les deux sexes, et ce, indépendamment des autres facteurs de risque; il est même suggéré que l'hypertension constitue le principal facteur de risque pour développer une MC (Antikainen et al., 1998; Jonsdóttir et al., 2002).

6.2 Impact cognitif et physiologique de l'infarctus du myocarde

6.2.1 Le Trier Social Stress Test

La création du TSST à la fin du 20^{e} siècle (Kirschbaum et al., 1993) a révolutionné l'étude empirique des effets de l'exposition au stress chez l'humain sur les réactions

psychoneuroendocrinologiques des individus. Ce paradigme est utilisé pour sa validité et sa fidélité à stimuler l'activation de l'axe HHS lors de sa passation; suscite en moyenne une sécrétion trois fois plus élevée de cortisol chez 70,0 à 80,0 % des participants (Dickerson & Kemeny, 2004; Frisch et al., 2015). Il n'est donc pas étonnant que Kudielka et al. (2007) au début du 21e siècle ont trouvé près de 4000 publications ayant utilisé le TSST. Au fil des ans, les études scientifiques ont toutefois permis de raffiner la compréhension de l'apport singulier de différentes variables dans l'activation de l'axe HHS, rendant l'application du TSST comme initialement prescrite susceptible de conduire à des interprétations fautives des changements observés (Goodman et al., 2017; Labuschagne et al., 2019). Notre revue systématique du TSST a voulu établir la validité des procédures méthodologiques du TSST rapportées afin d'en standardiser sa livraison dans les futures études; considérant le rôle établi de certaines variables susceptibles d'influencer les réponses endocrines produites lors de sa passation. Cette revue s'avérait appropriée considérant notre intention d'utiliser nous-mêmes ce paradigme auprès d'une population de femmes.

L'examen systématique effectué a permis de confirmer qu'en dépit de sa création il y a près de trois décennies, le TSST continue d'être largement inclus comme agent stressant dans les études psychoneuroendocrinologiques, avec plus de 1000 articles scientifiques publiés par les pairs ayant utilisé ce paradigme entre 1993 et 2020 (Narvaez Linares et al., 2020). L'analyse systématique des données scientifiques retenues a permis : a) de proposer des critères permettant de normaliser la méthodologie relative à la passation du TSST et d'augmenter ainsi les comparaisons interétudes (en contrôlant les variables qui influencent la réponse du stress [p. ex., consommation de caféine, cycle menstruel]); b) de promouvoir l'utilisation systématique de paramètres/variables précis lors de l'utilisation de ce protocole (p. ex., valider l'utilisation du

nombre le plus communément utilisé pour effectuer les soustractions, recommander la collection de prises de sang à intervalles fixes et en nombre constant). Cette analyse systématique permet aux futures recherches de considérer l'utilisation d'un protocole rigoureux et comparable. Cet exercice compréhensif et laborieux n'est pas à la portée de la majorité des équipes de recherche actives désireuses d'opter pour un outil expérimental valide et un protocole maximisant les possibilités de comparaisons adéquates des résultats obtenus par leur équipe avec ceux recueillis auprès de populations comparables par d'autres groupes de recherche.

Tel qu'anticipé, au fil des ans les chercheurs n'ont pas toujours utilisé le TSST de la même manière, y compris les aspects centraux du paradigme expérimental tels que le discours oral et la tâche mathématique. Ces divergences ont, de manière non intentionnelle, affecté la possibilité de comparaisons directes entre les études évaluant les mêmes variables, ce qui a contribué à l'observation de résultats divergents chez des populations autrement comparables. Également, bien que le TSST soit un outil grandement utilisé dans le domaine de la psychoneuroendocrinologie pour étudier les effets du stress sur différentes variables, la validité écologique de ce paradigme n'a pas été étudiée aussi exhaustivement que les autres variables et facteurs qui doivent être pris en considération lors de l'utilisation du TSST. Dans un tel contexte, des études de la validité écologique du TSST permettraient d'établir si les résultats à ce test peuvent être généralisés à la réaction des participants à des situations réelles présentant des similitudes (Lewkowicz, 2010). À ce jour, seulement deux études se sont intéressées à la validité écologique du TSST. Wolfram et al. (2013) ont comparé le profil de sécrétion de CORT de N = 21 étudiants stagiaires pendant l'enseignement, alors que Henze et al. (2017) ont regardé le profil chez N = 31 étudiants universitaires précédents un examen oral au profil de sécrétion de CORT mesuré lors du TSST. Les 9 femmes de l'étude de Wolfram et al. (2013) étaient jeunes et

devaient prendre un type de contraception hormonale pour être admisse dans l'étude, alors qu'Henze et al. (2017) ont testé un groupe mixte, comprenant 14 femmes prenant une contraception orale et 10 autres n'en prenant aucune; par ailleurs, ces chercheurs n'ont pas rapporté d'analyses distinctives pour les deux groupes. Seul Henze et al. (2017) ont trouvé des résultats significatifs indiquant une similitude entre la sécrétion de CORT associée au TSST et celle observée face à un stresseur expérimenté dans un contexte de leur vie quotidienne. Ces deux études démontrent l'importance d'établir une validation plus complète des situations sociales pouvant exercer un impact similaire sur la réponse de stress que celui noté avec le TSST. À ce stade, une validation écologique est nécessaire pour faire des comparaisons plus adéquates au niveau de stress de la vie réelle avec celui que représente une exposition au TSST.

La reproductibilité « *replicability* » des études demeure une préoccupation importante en sciences. Ainsi, nous espérons que les recommandations qui ont découlé de cette revue systématique permettront des contrôles plus rigoureux entourant la passation de ce paradigme. Ces contrôles sont garants d'une validité accrue des mesures physiologiques recueillis dans des contextes spécifiques, dont dépend la généralisation des résultats obtenus à partir d'études multiples sur des populations données. En psychologie, une « crise de reproductibilité » a fait les manchettes à l'automne 2015 lorsque plusieurs groupes de recherche ayant collaboré afin de répliquer 100 études publiées dans des journaux de psychologie obtinrent un taux de succès de 36,0 % (Open Science Collaboration, 2015). Bien que cette étude ait eu l'effet d'un cyclone au sein de la communauté scientifique, Ioannidis (2005) étant l'un des premiers à documenter l'étendue de ce problème, d'autres ont suivi et appuyé le constat de non-reproductibilité (Camerer et al., 2016). Ainsi, plusieurs recommandations ont été émises pour contrer ce problème, dont la soumission et l'enregistrement de son protocole et de sa méthodologie de

recherche (Nosek et al., 2018). Cette recommandation fut suivie avec les deux revues systématiques de cette thèse enregistrée dans PROSPERO. En somme, tel qu'indiqué par Munafò et al. (2017), il est important que les chercheurs, les journaux scientifiques et les environnements de recherche adoptent des mesures permettant de maximiser le partage des éléments essentiels du processus scientifique tels qu'une méthodologie claire et complète, incluant l'ensemble des détails permettant de répliquer l'étude en question. Enfin, il est important de souligner que les enjeux de la reproductibilité sont également liés à des facteurs externes. Parmi ces facteurs, ceux liés aux conditions de vie et aux demandes associées à l'emploi du temps, au moment ou un test spécifique est effectué sur des populations cliniques (p. ex., l'intervalle de temps entre l'IM et une évaluation), la récurrence et le degré d'intensité de l'IM – ces facteurs souvent non rapportés et variant au sein de la population étudiée affecteront eux aussi la possibilité de comparer directement des résultats scientifiques.

6.2.2 La réponse physiologique des femmes ayant un infarctus du myocarde

Depuis longtemps, les recherches ont soutenu un rôle déterminant de l'exposition au stress comme facteur de risque étroitement lié à l'apparition d'un IM (Dimsdale, 2008; Jackson et al., 2018; Yusuf et al., 2004). Par exemple, Song et al. (2019) ont étudié des fratries et ont trouvé que ceux ayant un trouble lié au stress (*stress-related disorder*) encouraient un risque plus grand d'avoir une MCV (entre 1.24 et 1.40 dépendamment de l'âge), dont un IM, peu importe le sexe ou les antécédents familiaux. De plus, ces chercheurs ont trouvé que durant les six premiers mois suivants l'IM il existe un risque accru d'être affecté d'un autre événement cardiaque. Cette disposition est possiblement engendrée par la cascade traumatique et la puissante réaction physiologique induite par l'IM. Bien que ces informations soient disponibles, l'étude de l'impact de l'IM sur l'activation de l'axe HHS est un sujet ayant à ce jour reçu peu d'attention dans la

littérature scientifique. Néanmoins, les auteurs de plusieurs études recommandent une sensibilisation accrue à cet effet auprès des professionnels et les patients permettant d'accroître la connaissance des conditions favorisant une récidive (Edmondson et al., 2013; Gradus et al., 2015; Jacquet-Smailovic et al., 2020). Dans ce contexte, les recherches indiquent qu'une personne présentant un trouble de santé mentale telles une dépression clinique (Berkman et al., 2003; Lichtman et al., 2014) ou de l'anxiété clinique (Celano et al., 2015; D. C. Watkins & Jefferson, 2013) est plus susceptible de séquelles ou de mort suivant un IM. La littérature scientifique permet de mettre en lumière également que les individus qui ont subi un IM et ont développé un trouble de santé mentale à la suite de l'IM sont davantage à risque de décès d'un second IM, en raison d'un axe HHS possiblement dysfonctionnel (Carney et al., 2005; Grippo & Johnson, 2009).

6.2.3 Infarctus du myocarde, arrêt cardiaque et altération de la réponse au stress

L'arrêt cardiaque soudain (ARS) est une MCO liée à une affectation de l'activité électrique du cœur. En comparaison, l'IM est lié à une affectation des vaisseaux sanguins alimentant le cœur. Toutefois, l'état d'hypoxie occasionné dans ces deux conditions agit comme un facteur de stress métabolique, qui entraine des répercussions sur la régulation de l'axe HHS. Le dérèglement de la réponse de l'axe HHS suivant un ARS est bien documenté chez les humains (Hékimian et al., 2004; Lindner et al., 1992; Pene et al., 2005; Schultz et al., 1993; Tavakoli et al., 2012) et les animaux (de la Tremblaye et al., 2014; Neigh et al., 2009; Neigh, Glasper, et al., 2004; Neigh, Kofler, et al., 2004; Okuma et al., 2021; Q. Zhao et al., 2021). Ceci n'est pas le cas des gens ayant eu un IM, bien que considérant des similarités physiologiques, ces derniers sont utilisés comme groupes contrôles dans certaines études sur les ARS. Au sein de cette thèse, un des objectifs a donc visé l'examen de l'axe HHS (via le cortisol) et du système

parasympathique (via la variabilité du rythme cardiaque) suivant un IM chez les femmes. À ce jour, cette étude est la première à s'intéresser aux effets d'un agent stressant social sur la réponse physiologique (c.-à-d.., CORT et variabilité du rythme cardiaque) chez des participantes ayant un historique d'IM.

Les résultats de l'analyse de CORT salivaire et de la variabilité du rythme cardiaque, de façon générale, n'indiquent pas de différences significatives entre les groupes. Toutefois, les *p-values* et les tailles d'effet suggèrent que cela semble être attribuable à la puissance statistique liée à la grandeur de notre échantillon. D'abord, la variabilité du rythme cardiaque pour le groupe MI est restée plutôt stable au travers de l'étude, incluant lors de la passation du TSST, et il a diminué au temps 7 pour ensuite revenir aux valeurs moyennes du groupe. Pour ce qui est du groupe NonIM, la variabilité du rythme cardiaque a augmenté graduellement durant l'étude sauf à l'étape 7 où on note une augmentation abrupte avant un retour aux valeurs typiques. À l'étape 7, les participantes devaient effectuer une tâche mathématique complexe impliquant la mémoire de travail. Ainsi, l'augmentation de la variabilité du rythme cardiaque des participantes du groupe NonIM associées à cet ajout est appropriée, puisque cette tâche procure un niveau de stress additionnel (c.-à-d., tâche d'arithmétique similaire à celle du TSST). On pourrait s'attendre dans une telle situation à une diminution de l'activation du système parasympathique, ce que nos résultats ne démontrent pas. Toutefois, Goldberger et al. (2001) ont montré que l'augmentation graduelle d'une dose de phenylephrine (un agoniste de récepteur adrénergique alpha-1) ne conduit pas à l'établissement d'une relation linéaire entre la variabilité du rythme cardiaque et l'activité du système parasympathique; la courbe atteint plutôt un plateau à l'apogée duquel la variabilité du rythme cardiaque décroit nonobstant une l'augmentation concurrente de l'activité parasympathique. Les auteurs notent une importante variabilité interpersonnelle dans cette

relation entre variabilité du rythme cardiaque et activité autonomique. Une revue systématique effectuée par Forte et al. (2019) indique pour sa part qu'une diminution de l'activité du système parasympathique en l'absence de démence, MCV, ou de maladies psychologiques ou médicales chez les participants est associée avec une diminution des performances cognitives. Dès lors, le maintien d'une activation parasympathique élevée chez nos participantes n'ayant pas eu d'IM a possiblement contribué à maintenir chez elles des performances optimales (Eysenck, 2010; Eysenck & Calvo, 1992; Yerkes & Dodson, 1908). D'autres études sont nécessaires afin de valider l'influence du niveau de stress ressenti sur la régulation de la variabilité du rythme cardiaque via le système parasympathique.

Pour ce qui est du CORT, le groupe NonIM a eu une réaction typique face au TSST qui est comparable à celle démontrée par d'autres groupes contrôles dans la littérature (Allen et al., 2014; Kirschbaum et al., 1993; Kudielka et al., 2007; Narvaez Linares et al., 2020). Toutefois, les données du groupe IM montrent qu'il y a diminution du CORT avec le passage du temps. Par exemple, à l'étape 7 et 8, on note une différence significative liée à la diminution de la sécrétion de CORT par les participantes du groupe IM, qui contraste avec la réponse endocrine au TSST du groupe NonIM. Toutefois, en raison de la taille de l'échantillon, il est difficile d'expliquer pourquoi le groupe IM n'a pas eu une réaction typique face au TSST, surtout lorsqu'on prend en considération certaines limites de l'étude. Par exemple, bien que nous ayons la liste de médicaments et leur posologie, nous n'avons pu contrôler pour cette variable lors de nos analyses. Ainsi, il est possible que les médicaments (p. ex., psychotropes [Subramaniam et al., 2019], statines [Sahebkar et al., 2016]) que nos participantes IM ont pris aient affecté la sécrétion de CORT.

En somme, les résultats de l'analyse de CORT salivaire et de la variabilité du rythme cardiaque de notre étude en laboratoire ne nous permettent pas de tirer des conclusions claires. Néanmoins, comme mentionné, les analyses de plusieurs résultats indiquaient des résultats approchant des effets significatifs. Ainsi, les niveaux moins élevés de ces deux marqueurs physiologiques pour le groupe IM en comparaison au groupe NonIM, soulignent l'intérêt de continuer une analyse approfondie de ces variables sur un échantillon plus grand. Cette recherche permettra de confirmer l'existence d'un dérèglement de l'activation de l'axe HHS lors d'un stress, ce que des études animales et humaines observent suivant un arrêt cardiaque. Par ailleurs, les participantes du groupe IM et NonIM ont rapporté des niveaux de stress subjectifs comparables. En effet, les questionnaires administrés afin d'évaluer les effets du stress au travers de l'étude ainsi que sur leurs affects positifs et négatifs n'indiquent pas de différences significatives entre les groupes. Dès lors, ces observations suggèrent une possible déconnexion entre l'état psychologique et la réponse physiologique suivant un IM. Dans cette optique, tel que nous avons mentionné dans la section 1.3, la dépression et l'anxiété clinique sont intimement liées à un dérèglement de l'axe HHS (Feng et al., 2016; Grippo & Johnson, 2009). Ainsi, s'il existe une atteinte de l'axe HHS suivant un IM et sachant que ces deux maladies augmentent le taux de mortalité chez les femmes ayant un IM dans les mois suivants leur évènement, il devient crucial de mieux étudier ces liens.

6.2.3 L'impact cognitif

L'impact cognitif des MCV a fait l'objet d'études depuis plusieurs décennies (Breteler et al., 1994; Hammeke & Hastings, 1988; Hertzog et al., 1978; Light, 1978; Waldstein et al., 2001). Nous connaissons également l'impact de plusieurs facteurs de risque associés aux MCV sur les fonctions cognitives (Harrison et al., 2014; Sexton et al., 2019). Par ailleurs, l'impact des MC,

plus particulièrement de l'IM, sur les fonctions cognitives a reçu peu d'attention. Bien que les premières études sur le sujet ont révélé des incongruences (Arntzen et al., 2011; Bursi et al., 2006), la fin de la dernière décennie a vu émerger des résultats plus concluants quant aux liens entre les MC et une accentuation du déclin cognitif, des troubles cognitifs et du rôle précurseur des MC dans l'apparition d'une démence (Deckers et al., 2017; Xie et al., 2019).

La revue systématique effectuée au sein de cette thèse constitue le premier article scientifique résumant la connaissance actuelle concernant l'impact des MC sur les fonctions cognitives exclusivement chez les femmes. Ce travail de recension scientifique a permis d'établir un sommaire exhaustif des découvertes quant aux atteintes cognitives spécifiques observées chez les femmes atteintes d'un IM ou d'une MC. Notamment, la colligation des écrits scientifiques a permis de déterminer un profil plus spécifique des atteintes cognitives observées chez les femmes ayant un historique d'IM. Ces dernières : a) ont davantage de difficulté à se rappeler de mots entendus (« *word retrieval* »); b) requièrent plus de temps pour compléter des tests visuospatiaux et moteurs; c) éprouvent des difficultés à se rappeler d'informations verbales apprises dans le passé; et d) montrent des difficultés à compléter des exercices reliés au raisonnement et à la résolution de problèmes. De plus, nous avons observé que lorsque le nombre de femmes avec une MC dans les études était plus grand, les données montraient des pertes cognitives significatives ou des résultats qui soulignaient des tendances vers de telles différences. À ce jour, seul Haring et al. (2013) ont étudié l'impact des MCV, incluant l'IM, chez les femmes exclusivement. Cette équipe de recherche a trouvé que les femmes plus âgées et ménopausées présentaient un risque accru de déclin cognitif associé aux MCV; ce lien étant encore plus grand lorsque ces dernières faisaient de l'hypertension et du diabète. Les résultats de Haring et al. (2013) combinés aux observations de notre recension (Narvaez Linares et al., 2021) renforcent la

proposition selon laquelle les MC, en lien avec des facteurs prédisposants, affectent des sphères spécifiques du fonctionnement cognitif. Les recherches mixtes soutiennent de plus l'importance de l'étude spécifique des femmes qui présentent un profil de recouvrement distinct de celui observé chez les hommes.

6.2.4 Synthèse de l'information

Les quatre composantes de cette thèse auront à terme permis l'élaboration de quatre articles scientifiques présentés au cœur de cette thèse. Les chapitres II, III et IV ont servi de base à l'élaboration de l'étude en laboratoire (chapitre V). La contribution de l'ensemble de cette recherche est observable à différents niveaux. Ces travaux ont permis de : a) standardiser l'application du protocole du TSST; b) de constater que la littérature dans son ensemble rapporte des problèmes cognitifs chez les femmes atteintes d'une MC; c) de réitérer la description de symptômes différents lors d'un IM chez les femmes en comparaison aux hommes, en plus de mettre l'accent sur différents facteurs qui jouent également un rôle primordial dans l'apparition des IM dans un échantillon canadien; et d) de montrer que les femmes ayant un historique d'IM rapportent des niveaux similaires de stress en comparaison à un groupe contrôle, malgré une tendance pour le groupe IM d'avoir une activation physiologique (déterminée par la sécrétion de CORT et la variabilité du rythme cardiaque) diminuée en réaction à un stress.

6.3 Limites et pistes futures

Ce projet doctoral a permis d'explorer différentes variables associées à l'IM chez la femme. Nous reconnaissons toutefois les limites de nos travaux scientifiques et analyses. D'abord, il est important de souligner que certaines informations obtenues sont autodéclarées. Certaines problématiques sont liées à ce type d'informations puisqu'elles sont sujettes à certains biais (p. ex., désirabilité sociale) qui peuvent affecter la validité des résultats. La taille des

échantillons présentés dans les chapitres IV et V de la thèse sont plus petits qu'il n'était prévu dû à la pandémie. Bien que des résultats significatifs et des tendances émergent à partir des données recueillies, nous croyons fortement qu'avec des échantillons plus grands, les tendances observées se seraient transformées en résultats significatifs, principalement pour l'étude en laboratoire. Au moment où la pandémie a forcé la fermeture des laboratoires en mars 2020, nous venions de commencer à recruter de manière plus active des femmes avec différents profils ethniques. Les études 3 et 4 sont majoritairement composées de femmes blanches, ce qui n'est pas représentatif de la population canadienne au niveau de la diversité. Aussi, l'étude 4 bénéficierait de l'ajout de groupes non exposés au TSST ayant ou non un historique d'IM. En ajoutant ces deux groupes, il serait possible de mesurer plus adéquatement l'impact de l'activation de l'axe HHS sur les performances cognitives (avec et sans stress préalable). De plus, la durée de notre étude empirique avec le TSST (près de 3 h) n'a pas permis de recueillir des commentaires quant à leur expérience; ce qui aurait ajouté de l'information qualitative intéressante qui manque à beaucoup d'études. Une deuxième rencontre ou une discussion téléphonique aurait permis d'ajouter une appréciation qualitative aux réponses physiologiques et au profil cognitif de ces femmes et enrichir l'interprétation des résultats par des commentaires davantage reliés au vécu de ces groupes de femmes et aux changements plus généraux qu'elles ont pu noter suivant leur IM. Enfin, un nombre d'analyses statistiques a été effectué pour les deux études et l'utilisation d'une correction de Bonferroni aurait permis de contrôler l'augmentation du risque d'erreur de type I (Armstrong, 2014).

Incidemment, au courant de la dernière décennie, certains chercheurs ont noté que des traits de personnalité prévalent chez les individus ayant une MC, comme des traits associés à la personnalité de type D (Burkauskas, et al., 2016; Gecaite, Burkauskas, Brozaitiene, et al., 2019;

Kupper & Denollet, 2018; Staniute et al., 2015). Les individus présentant ce type de personnalité se distinguent au niveau de deux traits particuliers, soit une inhibition sociale et une affectivité négative. De par ses caractéristiques, ces personnes ont une tendance à ressentir des émotions plus fortes (p. ex. colère, hostilité, perception négative de soi) et se plaignent également davantage de troubles psychosomatiques (Denollet et al., 1996). Au sein des recherches futures, la validation de l'influence de variables personnelles lors d'études empiriques ou de questionnaires effectués auprès de femmes représente une avenue de recherche susceptible de proposer des approches prometteuses et novatrices, impliquant des modifications cognitivocomportementales personnalisées.

7.0 Conclusion

Les femmes ont été négligées dans plusieurs sphères de la recherche, autant dans un contexte humain qu'animalier. L'étude des MC n'a pas été épargnée par un tel biais, bien que ce groupe de maladies affiche un taux mortalité parmi les plus élevés. L'IM, tout comme les accidents vasculaires cérébraux, représentent une des causes principales de décès pour les femmes à travers le monde. Dès lors, une accentuation de la recherche scientifique inclusive représente un avantage important pour l'avancement des connaissances, entre autres concernant la présentation clinique et le développement de traitements et programmes de réadaptation plus spécifiques et prometteurs pour le rétablissement des femmes. La recherche future doit également prendre en compte la représentation ethnique/raciale au sein des populations étudiées, permettant de baser les recommandations sur des échantillons multiethniques et non majoritairement composés d'individus blancs. Une telle inclusion permettrait 1) une meilleure équité dans la représentation sociale et une extrapolation optimalisée des résultats à l'ensemble des populations; et 2) une meilleure considération des inégalités culturelles et sociales présentes dans nos sociétés qui ont des répercussions indéniables sur la santé des populations. Une plus grande équité dans la représentation des populations étudiées en employant une approche scientifique pluridisciplinaire permettra des mieux comprendre les problématiques étudiées. Dans cette optique, la dernière décennie a permis de souligner un accroissement de l'incidence des IM au sein de populations de femmes plus jeunes. L'étude à long-terme de ces individus représente une avenue de recherche susceptible de permettre une meilleure compréhension de variables déterminantes associées à la prévention et au développement de traitements adaptés aux populations affectées par un IM ou susceptibles de l'être.

8.0 Références de la thèse

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