Family History in the Assessment of Risk for Common Complex Diseases: Current State of Evidence

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Thesis submitted to the Faculty of Graduate and Postdoctoral Studies in partial fulfillment of the requirements for the M.Sc. degree in Epidemiology.

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ABSTRACT

Family history (FH) is a risk factor for many diseases. Disease guidelines often include family history as important in assessing chronic disease risks, but the empirical evidence base to inform the routine use of family history in primary care in practice appears largely lacking. An environmental scan of how family history is represented in prevention guidelines for five conditions showed that, while family history is often included in guidelines, there is variation in the definition used, recommendation given and evidence cited. A dataset on cardiovascular health in women was analyzed to examine whether family history offers useful discrimination value above standard risk factors. Regression results showed that family history is an independent risk predictor for coronary heart disease which improves discrimination beyond classical clinical factors. However, the absolute amount of discriminatory ability alone or with other factors is moderate at best, raising issues regarding clinical utility.

ACKNOWLEDGEMENTS

I would like to express my genuine gratitude to the following people who have helped make this thesis possible.

Dr. Brenda Wilson, my supervisor, for her ongoing support, availability, knowledge, patience, guidance and friendship throughout my thesis project.

Dr. Julian Little, my co-supervisor, for his expertise and relevant comments.

Dr. Zahra Montazeri for her help with statistical analysis and being generous with her time.

Silvia Visentin and Samantha Craigie for their help with word processing and for being wonderful friends and co-workers.

Dr. Elizabeth Potter for her advice and opinion when needed.

Diana Fox for her cheerful visits.

Dr. Gordon J. Prescott for access to the ASCHW dataset and prompt replies to inquiries.

Lee-Anne Ufholz for her help with library services.

And last but not least, my FAMILY for their continued love, support and encouragement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

FH-Family history
FDR-First degree relative
CHD-Coronary heart disease
CRC-Colorectal cancer
AUC-Area under the curve
CVD- Cardiovascular disease
NIH-National Institutes of Health
BMI-Body mass index
NRI-Net reclassification index
ROC-Receiver operating curve
ASCHW-Aberdeen Study of cardiovascular health in women
AMND-Aberdeen maternity and neonatal databank
BP-Blood pressure
HDL-High density lipoprotein
WHO-World Health Organization
ECG-Electrocardiogram
LOESS- Locally weighted scatterplot smoothing
JBS 2-Joint British Society' Guidelines on cardiovascular disease prevention in clinical practice
HTA-Health Technology Assessment

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EXECUTIVE SUMMARY

Introduction: A positive family history (FH) is strongly associated with risk of many common complex diseases. FH is a unique risk factor which can provide insights into shared disease susceptibilities arising from genomic susceptibility, shared environments, and common behaviors. Disease guidelines include FH as an item important in assessing disease risks. However, the empirical evidence base to inform the routine use of FH in primary care practice is largely lacking. The 2009 NIH State-of-the-Science panel on Family History and Improving Health concluded that, for FH to be established as an evidence-based tool, there is a need to evaluate its predictive ability and prognostic value in combination with traditional risk factors.

Objectives

1) To identify (a) how closely 'positive FH', as defined in disease-specific guidelines, reflects current evidence on its predictive accuracy in clinical practice, (b) how a positive FH translates into preventive recommendations and (c) to determine the quality of the guidelines currently in use
2) To assess the incremental improvements in individual risk prediction which is gained by adding FH to other clinical information recommended in guidelines, and its potential impact on patient classification and management.

Methods: To address objective 1, an environmental scan of chronic disease guidelines currently in use in North America using standard systematic review methods was performed. Data were extracted on (1) the definitions of 'positive FH' which were used (if any) and compared with a recently published systematic review, and (2) the way in which preventive

recommendations were altered according to presence of positive FH. Quality of included guidelines was evaluated using the AGREE instrument. To address objective 2, a secondary analysis of data from the Aberdeen Study of Cardiovascular Health in Women (ASCHW) was conducted to determine the predictive ability of FH alone and in addition to classical risk factors from a specific guideline applicable to the study population (Joint British Society Guidelines' on cardiovascular disease prevention in clinical practice 'JBS 2') using regression modeling.

Results: Regarding the environmental scan, there was no consistency of definitions of 'positive FH' between guidelines for the same condition and there was a wide range in how preventive recommendations are modified in response. Furthermore, there is a significant lack of consistency in reporting of guidelines and most FH definitions used in current guidelines are not evidence based. Regarding the risk prediction study, regression results showed that FH is an independent risk predictor for CHD which improves discrimination beyond classical clinical factors (OR 1.7). However, its predictive ability on its own (AUC 0.56) and with other factors (AUC 0.63) is moderate at best.

Conclusion: Most current guidelines include FH in their risk assessment algorithms; however the definitions of positive FH used are inconsistent and do not seem to reflect a clear assessment of the evidence. FH is strongly associated with CHD risk, but its ability to accurately discriminate between individuals who do and do not have CHD is modest. It offers a statistically significant incremental improvement in discriminatory accuracy when added to other standard clinical risk factors, but the clinical relevance of this gain is marginal. These analyses should be replicated in other datasets, along with a fuller

consideration of the impact on patients in terms of benefits, harms and costs associated with changes in recommended interventions which flow from risk reclassification.

CHAPTER I

INTRODUCTION

The completion of the Human Genome Project and advances in related technologies has begun to change our understanding of the genetic basis of diseases.[1-3] There has been a gradual shift[4] from traditional genetics, defined as "the study of single genes and their effects"[2] to genomics, which is "the study not just of single genes, but of the functions and interactions of all the genes in the genome."[2;4] The shift is not dichotomous, rather it may better be described as "a continuum"[4] which ranges from "single gene disorders with a high penetrance to genetic information obtained from multiple loci of somatic cells."[4] (Table 1) In genomics, the emphasis is not limited to monogenic diseases such as the Huntington's disease or phenylketonuria, but also includes common complex diseases such as breast cancer, coronary heart disease and type II diabetes, which result from the interaction of heredity and environmental factors.[2;5;6] However, despite the advances in our understanding of the genetic basis of disease, we are far from elucidating the mechanisms by which multiple genes interact with environmental factors to produce disease.[5]

The arrival of the 'genomics era'[5] has so far only provided us with a few useful genomic tests.[4;6] In fact, most observers now agree that much of the genomics research promise for improved health was premature and there will be some time before it translates into better health.[7-9] Perhaps in reaction, family history is gaining increased attention as a risk assessment tool for common complex diseases.[3;4;6;10] Family history has been shown to be a risk factor for many common complex diseases reflecting "the consequences of genetic susceptibilities, shared environment, and common behaviors."[6] In clinical genetics, family history information is used as a principal tool for risk assessment of patients, with most

attention historically, and currently, on monogenic diseases. However, recently, it is increasingly being discussed in terms of being a potential *genomic tool*[5] and associated with notions of 'personalized' disease prevention[5] as part of the new trend toward 'personalized health care.' The latter has been described as care which is patient-oriented and takes into consideration the patient's preferences, culture, behavior, family history and genetic/genomic profile to customize all aspects of care.[11]

Table 1. Continuum from genetics to genomics in practice[4]

Type of genetic variation	Examples	Practice Model
Single gene disorders, High penetrance; No effective interventions	Huntington disease	Genetic services; nondirective counseling
Single gene disorders; High penetrance; Effective interventions	Phenylketonuria	Population screening (e.g., newborn screening)
Single gene disorders; Low or variable penetrance; Intervention: variable	Hereditary breast/ovarian cancer, hemochromatosis	Genetic services; counselling may or may not be directive
Genetic variation at one or multiple loci	Pharmacogenetic traits; factor V Leiden, MTHRF	Communicating genetic information re: future risk of disease and intervention; counselling may be directive
Genetic variation at multiple loci in somatic cells (e.g., tumours)	Gene expression profiles; serum proteomic patterns	Using genetic information in early diagnosis, classification, prognosis, and treatment; genetic services/counselling model does not apply

Although family history is considered one of the oldest diagnostic tools in medicine and is a well documented risk factor for common chronic diseases,[6] there is a need to evaluate its clinical validity as a risk assessment tool.[10] At present, there is little evidence on how well family history performs in risk assessment of patients in general clinical populations, and it is unclear how complex disease prevention guidelines build family history into their recommendations. The focus of this thesis is to examine these issues empirically.

BACKGROUND

Family history

Family history is often described as "a simple and yet powerful clinical tool"[10] which captures the interaction between the environment and heredity.[5] In clinical genetics, family history is used as a diagnostic tool and must be extensive enough to allow identification of specific disease patterns within the family. The family history is obtained through a several-step process, typically including: 1) a pre-visit telephone interview, 2) completion of a family history questionnaire, 3) a lengthy face to face interview covering information on at least three generations and 4) verification of the information elicited from the patient during the interview. This kind of approach is considered the 'gold standard' for other approaches of family history collection. However, it is time consuming and often demands resources beyond the usual in non-specialist settings.[3;12]

It has recently been suggested that this 'standard model' of family history taking may not be necessary in all clinical situations and that the characteristics of family history information needed for patient care vary depending on the purpose for which it is obtained.[13] Table 2 suggests that there are purposes beyond specialist genetics assessment for which family history information can be used, and that this should be reflected in both the specific information items of interest, and the kinds of tools that are developed to facilitate data collection and interpretation.

Table 2: Purposes of family history taking[13]

	'DATA BANKING'	'GENETIC CASE FINDING'	COMPLEX DISORDER RISK	PROMOTING BEHAVIOUR CHANGE	FAMILY GENOGRAM
Target population	Universal	Clinical suspicion/ patient concern	Large patient groups	Related to life course?	Everyone?
Type of FH info	More extensive	Depends on suspected condition(s)	Simpler?	Simple?	Variable? (Depends on family?)
Other Info	Not relevant	Generally less important	Other clinical info, important	Other health info, relevant	Family, social, emotional, etc
Timing of use	Any time. Suited to new patient intake	Responsive to concerns	PHE, patient/ physician concerns	PHE, opportunistic?	New patient intake
Resources required	Needs to be efficient	Time Confidence	Needs to be time efficient	Relates to counseling component	Time
Updating	Yes. How often?	Less important?	Yes. Linked to PHE?	Less important?	More important
Linkage with other tools	EMRs, decision support, etc	Referral/testing guidelines	Prevention guidelines	Effective behavioral interventions	--

Family history is of particular interest in primary care,[14] not least because the care of the patient as part of the family unit is recognized and emphasized in family medicine.[3;15] However, the approach to taking and using family history in this setting is necessarily different from specialist genetics.[3;16] First of all, there are no clear expectations on how to gather family history within a clinical encounter, nor any guidance on specific family history items which should be obtained.[16] In primary care, it is suggested that family history could be used to better inform individual risk of chronic diseases,[12] which indicates a focus not on single gene disorders but rather on complex disorders which, by definition, do not follow obvious Mendelian inheritance patterns.[10;12;16] The purpose of risk assessment is often less about detecting a rare genetic disorder in the family and more about identifying which healthy individuals need particular attention to reduce risk of certain diseases in the future, and/or to enhance screening strategies for asymptomatic disorders such as diabetes.[10;12] Family history is part of a broader health assessment which involves consideration of a wider range of risk factors.

The comprehensiveness of family history, which is standard in specialized settings, is not feasible and may not be necessary in the primary care setting, where physicians have been shown to devote less than 2.5 minutes to taking a family history.[3;17] Time constraints, unfavorable reimbursement practices, colleague and patient directed pressure to focus on other aspects of care, and perceived lack of skills and confidence have been identified as the main barriers to adequate family history taking in the primary care setting.[3]

Common complex diseases

The term 'common complex disease' refers to diseases which result from the interaction of genes, environment, lifestyle, and culture to promote diseases occurring frequently enough to be a public health burden.[6;7;18] Table 3 presents examples of common complex diseases and associated family history risks, revealing an increase in relative risk of the order of 1.7-11 in patients with a positive family history compared to those with no family history, with the risk increasing further with decreasing age of diagnosis in relatives and increasing number of relatives affected.[6]

In contrast, similar strength associations between genetic variants and common complex diseases have not been observed [7;8;10;18]; and no single genetic variant has been shown to affect common complex disease development on its own, rather multiple variants are involved.[8;18] To date, genome-wide association studies have yet to show that genetic variants provide significant risk prediction, apart from uncommon familial variants of common complex disorders such as familial breast, ovarian cancer or hereditary non-polyposis colorectal cancer.[7;8;18] At present genomic science is unable to offer genomic tests which provide useful personalized risk prediction for prevention of common complex diseases.[7;8;18]

Table 3: Prevalence and relative risk estimates due to family history for selected disease[6]

Disease	U.S. prevalence of the disease	Risk due to family history
Cardiovascular disease	58 million	OR=2.0 (one FDR*) OR=5.4 (two or more FDR with onset<55yr)
Breast Cancer	3 million women	RR=2.1 (one FDR) RR=3.9 (three or more FDR)
Colorectal Cancer	Yearly incidence=130,000	OR=1.7 (one FDR) OR=4.9 (two FDR)
Prostate Cancer	Yearly incidence=200,000	RR=3.2 (one FDR) RR=11.0 (three FDR)
Melanoma	200,000	OR=2.7 (one or more FDR) OR=4.3 (one FDR)
Type II Diabetes	13 million	RR=2.4 (mother) RR=4.0 (maternal and paternal relatives)
Osteoporosis	8 million women 2 million men	OR=2.0 for osteoporotic fracture (female FDR) RR=2.4 for wrist fracture (father)
Asthma	17 million	OR=3.0 (mother) RR=7.0 (mother and father)

*FDR=either parent and/or a sibling

Family History and Common Complex Disease

The potential value of family history information is illustrated in a hypothetical scenario proposed by Francis Collins (See Box below)[1] and modified by Yoon and colleagues.(6) Collins originally developed this scenario to indicate the possibilities of genomic testing.

In the year 2010, John, a 23-year-old male patient presents with elevated blood cholesterol. In addition, the patient is a smoker and the family history reveals a paternal history of myocardial infarction. John's doctor recommends a DNA screening test which gives estimated lifetime and relative risks for developing specific common complex diseases in the future. John agrees. The test is noninvasive and simply involves a cheek swab being sent for DNA analysis. One week later the test results are back. Based on the DNA test results, John learns that he is at increased risk for coronary artery disease, colon cancer and lung cancer. He also learns that his Alzheimer's disease and prostate cancer risk is lower than the general populations because he carries low risk variants of those genes. Based on these results, John is provided with customized disease prevention advice for the conditions which he is at increased risk (stop smoking, annual colonoscopy screening from the age of 45, and a prophylactic drug regimen for coronary disease). The results motivate John to kick the habit of smoking with support from a "*genetically high risk for complications from smoking"* support group.

Source: Collins et al.[1]

The DNA test described in the scenario by Collins is not available for most common complex diseases[6] – the point was to offer a vision of 'personalized' risk assessment through genomics. However, Yoon *et al*.[6] proposed that an analogous risk assessment could be conducted right now by using family history information (Figure 1). Here, John's risk could be stratified for each common complex disease of interest (he would be high risk for CVD, medium risk for diabetes and low risk for stroke). In conjunction with other risk factors (e.g. age, body mass index, smoking status) John is already in a position to be offered various long-term management and prevention strategies ranging from recommended behavior changes to DNA-based or other investigations available (e.g. colonoscopy).

This illustrates the potential for family history to serve as a risk assessment tool for population scale public health impact. The DNA-based testing envisioned by Collins has not come to fruition in 2011 and family history may be an immediately available way to assess, stratify and predict risk of common complex disease.

However, although family history is a clear risk factor for most common complex disease and is included in many prevention guidelines, there is no consensus and only fairly weak evidence on how to use it effectively and efficiently to assess an individual's risk.[10;14;19]

Recently, Scheuner *et al.*[20] suggested a model for stratifying patients into high, moderate and low risk based on family history for certain diseases. Based on their modeling results, they concluded that family history is a feasible risk assessment tool for common complex diseases. Yoon *et al*.[12] proposed how preventive activities could be implemented in response to each of these risk levels (Figure 1). This approach provides a simple idea of how

family history information could be linked to strategies for the detection, management and prevention of complex diseases in primary care.[12;20]

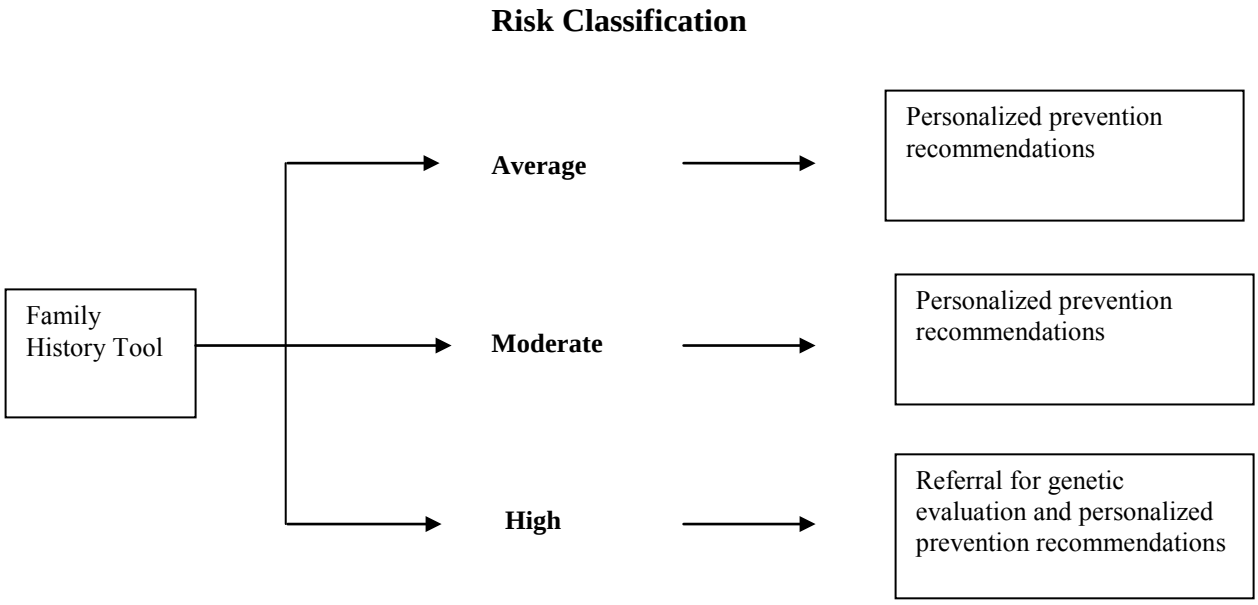

Figure 1: Proposed scheme for using family history to guide and inform prevention strategies[12]

Three studies have evaluated this approach. Hariri *et al.*[21] investigated the association between familial risk stratification and undiagnosed diabetes in a nationally representative sample of the U.S. population. They reported "a strong and proportional association between familial risk and undiagnosed diabetes", concluding that family history based risk stratification has potential as a diabetes screening tool. Scheuner *et al.*[22] applied family history risk stratification in a cross-sectional study of the U.S. population for early-onset coronary heart disease (CHD). They reported that the risk assessment model with familial stratification alone could accurately classify presence or absence of CHD in 70.9 percent of individuals (assessed by the area under the receiver-operator characteristics curve, AUC), which is considered modest discriminatory ability. In another study, Scheuner *et al.*[23]

investigated whether adding family history to a global cardiovascular risk prediction model could improve identification of individuals with advanced coronary artery calcification (CAC, a surrogate for CHD). For women, the authors reported AUC values of 75.2% without and 75.9% with family history in the model, and 71.8% and 72.5% for men, respectively. They concluded that the "incorporation of family history, especially comprehensive familial risk stratification, provides incremental prognostic value."

While the framework presented in Figure 1 has intuitive appeal, it was developed from a specialist genetics 'lens' and reflects a qualitative assessment of evidence on the association between family history and risk of disease. Direct evidence on the accuracy of this framework for detecting disease or predicting future disease in populations representative of primary care is extremely limited. Further, its clinical utility (whether its use would improve clinical and patient decision making, or lead to better health outcomes) remains unexplored.[10;24;25]

Despite this lack of evidence, there are many family history tools available for use in primary care, and the evidence suggests that using any kind of tool is associated with more extensive and accurate collection of data.[19;26] However, there is no evidence on how much, or what kind of, family history information is actually sufficient for accurate complex disease risk assessment.

These issues and others formed the focus of the 2009 NIH State-of-the-Science Consensus Panel on Family History and Improving Health[14]The Panel's questions are listed in the box below. Its conclusions published as a statement are considered the most up to date evidence at the time. [14]

1. What are the key elements of a family history in a primary care setting for the purposes of risk assessment for common diseases?

2. What is the accuracy of the family history, and under what conditions does the accuracy vary?

3. What is the direct evidence that getting a family history will improve health outcomes for the patient and/or family?

4. What is the direct evidence that getting a family history will result in adverse outcomes for the patient and/or family?

5. What are the factors that encourage or discourage obtaining and using a family history?

6. What are future research directions for assessing the value of family history for common diseases in the primary care setting?

The panels review of evidence suggested that the ability of family history alone to predict complex disease is limited, and the effect of using family history information on patient outcomes is not clear.[25;27] As a result, it concluded that currently there is only weak evidence for supporting the routine use of family history in primary care for common complex disease assessment, and further research is needed to establish an evidence base. The panel recommended that "future… efforts should evaluate family history in combination with genetic and environmental variables, for its predictive value and its potential role in improving patient outcomes." Further, the panel identified 25 specific research questions relating to FH which are listed in Appendix 1; the full summary of the panels conclusions are were published in a peer reviewed article. [14]

Given the issues with barriers in practice and the limited predictive ability of family history alone, it is necessary to evaluate the place of family history information in routine primary care practice. In particular, an assessment of what extra benefit it offers when used in combination with other standard risk factors is suggested by the NIH panel on Family History and Improving Health. This approach is more in keeping with clinical thinking and routine practice. For family history to be useful in routine practice, it must be easy to capture and able to offer 'extra value' in predicting or detecting conditions of interest.

RATIONALE

Family history taking is part of the everyday practice of primary care. Although family history has been shown to be a significant risk factor for many diseases, its predictive ability for complex diseases is poor when used on its own. There is a need to evaluate the predictive ability of family history when used in conjunction with risk factors whose measurement is considered standard of care. The evaluation of the clinical validity of family history in clinical practice has been identified as necessary to establish family history as an evidence-based public health tool.[14] The results of this study are important for generating knowledge which will be valuable in evaluating clinical validity of family history as a risk assessment tool in clinical practice.

OBJECTIVES

The overall goal of the proposed project is to determine the clinical validity and, if possible, the utility of family history in primary health care as a risk assessment tool. The specific objectives are:

1. To review how 'positive family history' is defined in disease specific prevention guidelines which are currently in use in North America
2. To identify how clinical prevention recommendations are altered for patients who have a positive family history, compared with those who do not, in these guidelines
3. Using coronary heart disease (CHD) as a case study, to assess the incremental improvement in individual risk prediction which is gained by incorporating family history information with other forms of clinical information recommended in relevant guidelines.
4. To comment on the clinical impact of any differences in patient risk classification which follow from incorporating family history information in disease risk assessment.

CHAPTER II

AN ENVIRONMENTAL SCAN OF FAMILY HISTORY ITEMS IN PREVENTION GUIDELINES

OBJECTIVES

The aim of this environmental scan is to identify the role of family history in prevention guidelines currently in use for specific conditions selected, through a review of guidelines available to North American physicians. It addresses objectives 1 and 2. The conditions of interest are: coronary heart disease, type II diabetes, asthma, colorectal cancer and breast cancer. These conditions were chosen because previous researchers[12] have proposed them as suitable for inclusion in family history tools on the basis that: 1) they are associated with a substantial public health burden; 2) there is awareness of these diseases among relatives; 3) there are well defined case definitions; 4) they are considered to be accurately reported by family members; 5) family history is an established risk factor; and 6) effective interventions for primary and secondary prevention are available.

METHODS

Search Strategy

Five electronic searches were conducted using the National Guideline Clearinghouse website (http://www.guideline.gov/). Individual search strategies were developed for each disease selected and are presented in Appendix 2. The searches were executed between March 23, 2009 to October 2, 2009 and the search results were limited to prevention, risk

assessment and screening guidelines categories. The searches were not limited by year of publication, sex, institution of publication or any other criteria.

Inclusion/Exclusion Criteria

Guidelines were included in the environmental scan if they: 1) were related to the specific diseases selected; 2) were not intended for preconditions of selected disease (e.g. hypertension for CHD); 3) included recommendations related to primary or secondary prevention; 4) were applicable to the general adult population (e.g. not confined to pregnant women); 5) were the most up to date version of the guideline; and 6) were published in the house journal of a relevant specialty society and/or authored by or on behalf of a relevant specialty society or published by a national/federal or state/provincial guideline development body. No language restrictions were placed.

Study Selection

All available guidelines identified for each condition were retrieved. Guidelines were classified as missing if they could not be located in full text despite: 1) e-mailing the corresponding author; 2) the interlibrary loan system; or 3) online searching. Duplicates of guidelines for a selected condition were removed but duplicates across conditions (i.e. multi-condition guidelines) were retained. Therefore, a guideline was counted more than once if it was eligible for two different conditions. Two reviewers (QH, BW) independently screened the full-text of all potentially eligible full-text guidelines using the inclusion/exclusion criteria, and disagreements were resolved through discussion and a third reviewer (JL)

where necessary (Appendix 3). With respect to the full-text reports that were screened, all excluded studies and reasons for exclusion were documented (Appendix 4).

Quality Assessment

A formal quality assessment of each included guideline was performed using the Appraisal of Guidelines for Research and Evaluation (AGREE)[28] instrument, applied independently by QH and BW. The AGREE instrument consists of 23 items across six domains (see below) and has been validated for evaluating clinical practice guidelines[29]. Scoring is completed for each item on a scale of 1 (strongly disagree) to 4 (strongly agree). The average percentage score of items for each domain is then calculated using a specified formula. Each domain is independent of the others and thus an overall average quality score is not obtained[28] (Appendix 5).

The domains are:

- *Scope and purpose* - whether guidelines state their goals, clinical questions addressed, the potential benefits and the intended patient population
- *Stakeholder involvement* - the involvement and contribution of groups which will be using the guideline
- *Rigor of development* - the methods used to synthesize the evidence-base, develop recommendations, and guideline updating policy.
- *Clarity of presentation* - concerns how clearly the key information is presented
- *Applicability* - concerns the organizational issues and cost of applying the guideline in practice

- *Editorial independence* - concerns the reporting of potential conflict of interest by the guideline authors to ensure that guideline recommendations are not influenced by funding bodies.

Data Extraction

One reviewer (QH) independently abstracted data from all studies meeting the inclusion/exclusion criteria using a data abstraction sheet (Appendix 6). Information was collected regarding guideline characteristics (authors, specific condition, year of publication, journal/institution), patient characteristics, definitions of 'average' and 'high' risk, specific family history items mentioned, preventive interventions or strategies indicated for different risk levels, the original evidence sources cited, and all other mentions of family history within the guideline. The reviewer was not blinded to names to the authors, journal, institution or any other information.

Data Analysis

Data were qualitatively synthesized to summarize: 1) the proportion of guidelines mentioning family history; 2) the definitions of family history used; and 3) the specific preventive recommendations made for patients with a positive FH.

The evidence cited to support family history definitions and associated preventive interventions was summarized. In addition, the definitions of 'positive FH' were compared with the NIH review quantifying the condition-specific definitions with highest predictive or screening accuracy, *noting that all of the guidelines were published before this review* [27]. Guidelines with higher and lower quality scores were compared. We assumed that for a guideline to be considered high quality it must score values of 3 or above across the 7 items on the Rigor of Development domain. Following this assumption, the AGREE instrument

formula was used to determine the corresponding percentage if all the items on the Rigor of Development domain scored a value of 3. The resulting score was 67 % and this served as our benchmark for judging the quality of guidelines as high/low. High quality guidelines were compared to low quality to determine whether they were more likely to: mention FH, use a definition that is consistent with evidence and cite evidence.

RESULTS

Study Characteristics

The electronic searching of the National Guideline Clearinghouse generated 223 guideline citations. Seven guidelines could not be retrieved, resulting in 216 available for full text screening. Of these, 191 were excluded on the basis of: high risk populations (4), ineligible patient/population group (18), not prevention (90), not disease/condition of interest (51) Health Technology Assessment (HTA)/scientific statement (4), withdrawn (4), duplicates (20). This left 25 guideline citations which met the eligibility criteria across the five conditions considered and were retained for data extraction. Of the 25 unique guidelines identified, four were multi-condition (See Table 4). A flow diagram of the search results is illustrated in Figure 2.

All 25 guidelines were published between 2003 and 2008. One guideline on breast cancer had two relevant citations.[30;31] One was produced in France,[32] one in U.K.,[33] two in Singapore,[34;35] one in Ireland,[36] one in Sweden,[37] one in Saudi Arabia, [38] and the remaining eighteen in the U.S. Of the 32 eligible guidelines included: six were for breast cancer[30;31;39-43], eleven for colorectal cancer[32;33;35;39-42;44-47], four for coronary heart disease,[36;39;48;49] ten for diabetes,[34;37;38;40;41;50-54] and one for asthma.[55] Family history was mentioned in 24 guidelines. For the purposes of this thesis, FDR (first degree relative) is defined as FH of a condition of interest in either parent and/or a sibling.

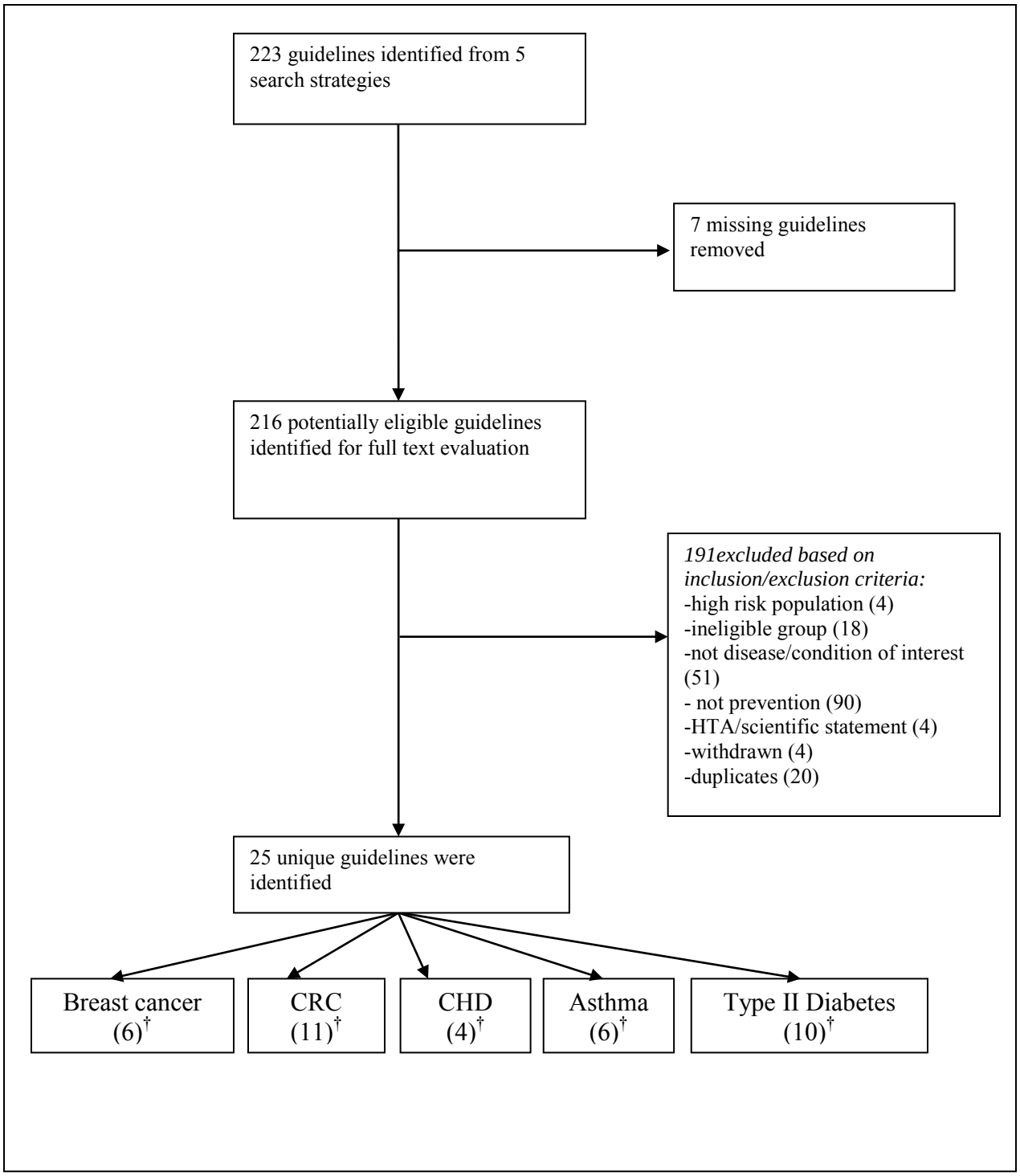

Figure 2: Flow diagram outlining the results of the guideline search and the selection of guidelines for inclusion in the environmental scan.

†There is overlap across the conditions.

Table 4: Summary of included guidelines

Authors	Country	Journal/Publication	Year	Mention FH
Breast Cancer (n=6)				
Institute for Clinical Systems Improvement (ICSI)[39]	U.S.	Institute for Clinical Systems Improvement (ICSI)	2008	Yes
Michigan Quality Improvement Consortium (18-49)[41]	U.S	Michigan Quality Improvement Consortium	2008	No
Michigan Quality Improvement Consortium (50-65+)[40]	U.S.	Michigan Quality Improvement Consortium	2008	No
Qaseem et al.[43]	U.S.	Ann Intern Med	2007	Yes
Saslow et al. & Smith et al.[30;31]	U.S.	CA Cancer J Clin	2003/2007	Yes
University of Michigan Health System[42]	U.S	University of Michigan Health System	2004	Yes
Colorectal Cancer (n=11)				
Davila et al.[44]	U.S.	Gatrointest Encosc	2006	Yes
Calonge et al.[45]	U.S.	Ann Intern Med	2007	Yes
Singapore Ministry of Health[35]	Singapore	Singapore Ministry of Health	2004	Yes
Scottish Intercollegiate Guidelines Network (SIGN)[33]	U.K.	Scottish Intercollegiate Guidelines Network (SIGN)	2003	Yes
University of Michigan Health System[42]	U.S.	University of Michigan Health System	2004	Yes
Ko et al.[46]	U.S.	Dis Colon Rectum	2006	Yes
Institute for Clinical Systems Improvement (ICSI)[39]	U.S.	Institute for Clinical Systems Improvement (ICSI)	2008	Yes
Michigan Quality Improvement Consortium (18-49)[41]	U.S.	Michigan Quality Improvement Consortium	2008	Yes
Michigan Quality Improvement Consortium (50-65+)[40]	U.S	Michigan Quality Improvement Consortium	2008	No
World Gastroenterology Organization (WGO)[32]	France	World Gastroenterology Organization (WGO)	2007	Yes
U.S. Preventive Services Task Force [47]	U.S.	U.S. Preventive Services Task Force	2008	Yes
Coronary Heart Disease (n=4)				
Mosca et al.[49]	U.S.	Circulation	2007	Yes
Graham et al.[36]	Ireland*	Eur J Cardiovasc Prev Rehabil	2007	Yes
Institute for Clinical Symptoms Improvement (ICSI)[39]	U.S.	Institute for Clinical Symptoms Improvement (ICSI)	2008	No
U.S. Preventive Services Task Force[48]	U.S.	U.S. Preventive Services Task Force	2004	No
Type II Diabetes (n=10)				
Rodbard et al.[50]	U.S.	Endor Pract	2007	Yes
Singapore Ministry of Health[34]	Singapore	Singapore Ministry of Health	2006	Yes
Ryden et al.[37;56]	Sweeden*	European Society of Cardiology (ESC)	2007	Yes
Wisconsin Diabetes Advisory Group[51]	U.S.	Wisconsin Diabetes Prevention and Control Program	2008	Yes
Calonge et al.[52]	U.S.	Ann Intern Med	2008	No
University of Michigan Health System[53]	U.S.	University of Michigan Health System	2008	No
Quality Improvement Team in Chronic Care (CCQI)[38]	Saudi Arabia	Qatif Primary Health Care	2008	Yes
American Diabetes Association (ADA)[54]	U.S.	Diabetes Care	2008	Yes
Michigan Quality Improvement Consortium (18-49)[41]	U.S.	Michigan Quality Improvement Consortium	2008	Yes
Michigan Quality Improvement Consortium (50-65+)[40]	U.S.	Michigan Quality Improvement Consortium	2008	Yes
Asthma (n=1)				
Global Initiative for Asthma (GINA)[55]	U.S.	Global Initiative for Asthma (GINA)	2008	No

*corresponding author

Breast Cancer

Of the six guidelines identified, four mentioned family history and are summarized in Table 5. Two definitions of 'average' risk for breast cancer were used, none of which included family history. Four definitions of 'high risk' for breast cancer were used and all included family history in risk assessment. For the four guidelines which included a family history component for high risk assessment, three definitions were used, two of which were consistent with the NIH consensus review. Family history was not mentioned elsewhere as a 'stand alone' risk factor, therefore all rrecommendations for patients who 'fulfilled' the FH criterion for breast cancer were the same as for those who fulfilled other high risk criteria, and centred around earlier, more frequent, or additional modalities of screening. Citations of the evidence used for the family history recommendations were provided in three out of the four included guidelines.

Table 5: Summary of Breast Cancer guidelines FH definitions and recommendations

Study (Year)	Average risk definition	High risk Def.	Recommendation for high risk	Family History		Studies Cited
		≥ 1 of the following		**Definition of Positive FH**	**Recommendation in response of Positive FH**	
Institute for Clinical Systems Improvement (ICSI)[39] * (2008)	• asymptomatic pt's over 50 with no FH of breast cancer,	• FH of breast cancer in patients mother, sister or daughter • Past personal history of breast cancer • Previous breast biopsy demonstrating atypical hyperplasia	• earlier screening, shorter screening interval	• ≥ 1 FDR affected (mother, daughter, sister)	• same as for high risk	• none
Qaseem et al. [43](2007)	•no history of breast cancer	• 2 FDR with breast cancer, • 2 previous breast biopsies • 1 FDR with breast cancer and 1 previous breast biopsy • Previous diagnosis of breast cancer • ductal carcinoma in situ, or previous hyperplasia • previous chest irridation • BRCA1 or BRCA2 mutation	• periodic risk assessment to determine risk and initiate screening	• 2 FDR with breast cancer • 1 previous breast biopsy and 1 FDR with breast cancer	• same as for high risk	• [57] (in accompanying systematic review) otherwise none
Saslow et al. & Smith et al. [30;31] (2007)	• defined as over 40 with no FH of breast cancer (annual mammography at 40 onward)	• women with any history of breast or/and ovarian cancer • women with BRCA1/2 genes • increasing age	• insufficient evidence to recommend earlier screening, shorter screening intervals, or the addition of additional screening modalities (e.g. MRI, ultrasound imaging)	• any family history of breast or/and ovarian cancer	• same as for other high risk	• [58;59]
University of Michigan	• defined as	• women with a	• earlier screening	• ≥ 1 FDR affected	• Same as for high risk	• [60]

Study (Year)	Average risk definition	High risk Def.	Recommendation for high risk	Family History		Studies Cited
		≥ 1 of the following		Definition of Positive FH	Recommendation in response of Positive FH	
Health System[42] (2004)*	women who are 40 or older and have no FH of breast cancer	personal history of breast cancer • FH of breast cancer in mother or sister • Proliferative benign breast disease, particularly atypical hyperplasia, • radiologically dense breasts • early age at menarche or late menopause • Nulliparity • First child after 30 • Women who received chest irradiation • BRCA1, BRCA2 • Hormone Replacement Therapy		(mother or sister)		

***consistent with NIH definition**

Colorectal Cancer (CRC)

Of the eleven guidelines identified, ten mentioned family history and are summarized in Table 7. Seven definitions of 'average' risk for CRC were used, whereas each included guideline had a slightly different definition of 'high risk' for CRC. Among the guidelines that mentioned family history, all used it in the definition of 'high risk' and none were 'stand alone', also none were consistent with the NIH consensus review. Recommendations for patients who fulfilled high risk criteria for colorectal cancer centred on earlier, more frequent screening and initiation of screening. Citations supporting the use of family history were provided in five out of the ten guidelines.

Table 6: Summary of CRC guidelines FH definitions and recommendations

Author (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation**	
Davila et al.[44] (2006)	**avg. risk** • no personal or FH of CRC and over 50	• personal history of CRC or adenomatous polyps • personal history of inflammatory bowels disease • familial polyposis syndromes e.g. Familial adenomatous polyposis, FAP • hereditary nonpolyposos colon cancer (HNPCC) • 1) individuals with ≥ 1 FDR with sporadic CRC at age <60, or • 2) individuals with ≥ 1 FDR with sporadic CRC at ≥60, or 3) individuals with a FH of adenomatous polyps in FDR < 60 yrs	• genetic testing and counseling • colectomy • earlier screening • colonoscopic surveillance • more frequent screening	1) individuals with ≥ 1 FDR with sporadic CRC at age <60, or2) individuals with ≥ 1 FDR with sporadic CRC at ≥60, or 3) individuals with a FH of adenomatous polyps in FDR < 60 yrs	1) Earlier colonoscopy screening, followed with 3-5 yr screening interval (if normal) 2) earlier colonoscopy screening, followed with 10 yr screening interval (if normal) 3) earlier colonoscopy screening, followed with 5 yr screening) (if normal)	• [61-63]
Calonge et al. [45] (2007)	• asymptomatic adults with avg. risk of CRC, including those with FH of CRC	• FAP, Hereditary non-polyposis, colon cancer syndromes or a history of colorectal cancer or adenomas	• none	• any FH of CRC	• none	
Singapore Ministry of Health[35] (2004)	• asymptomatic over 50 yrs with a FH limited to non-FDR (annual Feccal occult	• age 50 or older • a personal history of CRC or adenoma • a FH of CRC or adenoma • history of ulcerative	• Earlier screening • Genetic counseling • Surgery • Surveillance colonoscopy	• 1 FDR diagnosed with CRC before 45 yrs or two 2DR diagnosed with CRC at any age from the same side of the family	• earlier screening	• [64-66]

Author (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation**	
	blood testing)	colitis • FAP • HNPC				
Scottish Intercollegiate Guidelines Network (SIGN) [33] **(2003)**	• not meeting moderate or high risk criteria and recommend lifestyle changes, no screening required	• **moderate risk based on FH→**1 FDR affected by CRC when < 45 yrs • or 2 affected FDR (one CRC less than 55 years) • or 2 (one CRC less than 55 years) or 3 affected individuals with CRC or endometrial cancer who are FDR of each other and one a FDR of consultand • **high risk based on FH→**at least 3 family members affected by CRC • or at least 2 with CRC and one with endometrial cancer in at least two generations, one affected relative must be age ≤ to 50 yrs at diagnosis: one of the relatives must be a FDR of the other two, • Gene carriers (HNPCC), • untested primary relatives of gene carriers other symptoms • Rectal bleeding and changed bowel	• Mod risk→earlier screening • High risk.→earlier screening, shorter screening interval, referral to genetic • Counseling Other symptoms • Referral to a specialist • Examination	• **moderate risk→**1 FDR affected by CRC when < 45 yrs **or** • or 2 affected FDR (one CRC less than 55 years) or • or 2 (one CRC less than 55 years) or 3 affected individuals with CRC or endometrial cancer who are FDR of each other and one a FDR of consultand • **high risk→**at least 3 family members affected by CRC • or at least 2 with CRC and one with endometrial cancer in at least two generations, one affected relative must be age ≤ to 50 yrs at diagnosis: one of the relatives must be a FDR of the other two, • Gene carriers (HNPCC), • untested primary relatives of gene carriers	• **Mod risk→**one time earlier screening at age 30-35 and then again at 55 • **High risk**.→earlier screening, shorter screening interval, referral to genetic counseling	• [64;67]

Author (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation**	
		movements • Rectal without anal symptoms • Palpable abdominal mass • Palpable rectal mass • Intestinal obstruction • anemia				
University of Michigan Health System[42] (2004)	• no FH of CRC, asymptomatic, over 50	• 1) FDR affected with CRC or adenomatous polyps at age ≥60, or 2 second degree relatives affected with CRC • 2) ≥2 FDR with CRC, or a single FDR with CRC or adenomatous polyps diagnosed at < 60 yrs • Gene carrier for HNPCC • Gene carrier for FAP • Personal history of CRC • Inflammatory bowel disease • History of adenomatous polyps	• Earlier screening, shorter screening interval, surveillance colonoscopy, systemic biopsies, sigmoidoscopy	• 1) FDR affected with CRC or adenomatous polyps at age ≥60, or 2 second degree relatives affected with CRC • 2) ≥2 FDR with CRC, or a single FDR with CRC or adenomatous polyps diagnosed at < 60 yrs	• 1) earlier screening, • 2) earlier screening and shorter screening interval	
Ko et al.[46] (2006)	• no FH of CRC and <50 (no screening) • no FH of CRC and > 50, offer screening	• greater than 50 • 2 or more FDR affected or 1 FDR affected < 60 years	• Earlier screening •	• 1) people with 1 FDR with CRC or adenomatous polyps diagnosed at <60 yrs or 2 FDR diagnosed with CRC at any age OR, • 2) FDR with CRC or adeomatous polyp diagnosed at ≥60 yrs or two second degree relatives with CRC	• 1) earlier screening, shorter screening interval • 2) earlier screening but same interval as average risk	• none

Author (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation**	
Institute for Clinical Systems Improvement (ICSI)[39] (2008)	**avg. risk** • no FH of CRC or adentomatous polyps in FDR before age 60, or 2 FDR at any age • no FH of adenomatous polyps • over 50 yrs for whites, over 45 for blacs • no personal history of polyps/ and or CRC • no history of inflammatory bowel disease	• Having any of risk factors listed in average risk.	• Earlier screening	• 1 FDR diagnosed after 60 yrs with CRC or adenomatous polyps	• Earlier screening	• [61;68]
Michigan Quality Improvement Consortium (18-49)[41] (2008)	**avg. risk** ➢ no FH of CRC	in adults 18-39 • any FH of CRC or • history of colorectal polyps or • chronic inflammatory bowel disease	• initiate screening	• any FH of CRC	• initiate screening	• none[61]
World Gastroenterology Organization (WGO)[32] (2007)	**avg. risk** • no FH of CRC, screen for CRC starting at age 50	• FH of CRC or adenomatous polyp • ≥ FDR with colon cancer or adneomatous polyp diagnosed before the age of 60, or with 2 FDR diagnosed with CRC at any age • Familial adenomatous polyposis (FAP) • Hereditary nonpolyposis colorectal	• Earlier screening, shorter screening interval, surveillance, genetic testing	• 1) ≥ 1 FDR diagnosed with CRC or adnomatous polyp < 60 yrs, or 2 FDR diagnosed with CRC at any age, • ≥ 1FDR diagnosed over the age of 60, or 2 second degree relatives with CRC start screening at age 40, but with the same	• 1) earlier screening, shorter screening interval • 2) earlier screening	• none

Author (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation**	
		cancer (HNPCC)		frequency as average risk		
U.S. Preventive Services Task Force[47] (2008)	**avg. risk** ➢ individuals > 50 yrs, including those with FH of CRC in first and second degree relatives	• lynch syndrome • familial adenomatous polyposis	• recommendations not made for the high risk category, mentioned and excluded from guideline	• ≥ FDR of colorectal adenomas or CRC at young age or in multiple affected FDR's	• Earlier screening	• none

Coronary Heart Disease (CHD)

Of the four guidelines identified, two mentioned family history and are summarized in Table 9. Only one definition of 'average' risk was given which did not include family history. Two definitions of 'high risk' for coronary heart disease were used and both included family history. Again, no 'stand alone' family history criteria were presented. The two guidelines used different definitions, neither consistent with the NIH consensus review. Recommendations for patients who fulfilled the high risk criteria for CHD centred on lifestyle modifications, and therapeutic management of risk factors. Citations of the evidence used for the family history recommendations were provided in one guideline.

Table 7: Summary of CHD guidelines FH definitions and recommendations

Study (Year)	Average Risk	High Risk	Recommendation for High Risk	Family History		Studies Cited
				Definition of Positive FH	**Recommendation in response of Positive FH**	
Mosca et al [49] (2007)	• Framingham risk score < 10% and no risk factors	**Two levels:** **At risk** • ≥1 risk factor for CVD including: smoking, poor diet, physical inactivity, obesity, esp. central adiposity, family history of premature CVD (<55 yrs in male relative, and <65 yrs in female relatives) • Evidence of subclinical vascular disease (e.g. coronary calcification) • Poor exercise capacity on treadmill test and/or abnormal heart rate after stopping exercise **High risk** • Established CHD • Cerebrovascular disease • Peripheral arterial disease • Abdominal aortic aneurysm • End-stage or chronic renal failure • Diabetes mellitus • 10 year Framingham score of >20%	• Interventions recommended for lowering/ managing high lipids, diabetes, lifestyle modifications etc, if one or more risk factor present	• FH of premature CVD (< 55 yrs in males, <65 yrs in females)	• None specific to FH alone	• none
Graham et al.[36] (2007)	• not specified	• high blood pressure • family history of CVD • dyslipidemia • obesity • age • smoking • diabetes	• lifestyle modification, therapeutic management of risk factors	• family history of premature CHD before 55 yrs in males and 65 yrs in females	• Lifestyle Modifications, Therapeutic management of risk factors	• [69;70]

Type II Diabetes

Of the ten guidelines identified, eight mentioned family history and are summarized in Table 11. Three definitions of 'average' risk were given, and none included family history. All eight guidelines included definitions for 'high risk' for diabetes which were broadly similar, and all incorporated family history. Family history did not appear as a separate criterion. None of the family history definitions were consistent with the NIH consensus review. Recommendations for patients who fulfilled the high risk criteria centred on earlier and more frequent screening. Citations of the evidence used for the family history recommendations were not provided for any of the guidelines.

Table 8: Summary of Type II Diabetes guidelines FH definitions and recommendations

Study (Year)	Average risk definition	High Risk	Recommendation for High Risk	Family History		Studies cited
				Definition of Positive FH	Recommendation	
Rodbard et al.[50](2007)		• screening is recommended with one or more risk factors: FH, CVD, sedentary lifestyle, overweight, hypertension, etc.	• earlier screening	• any FH	• earlier screening	• none
Singapore Ministry of Health[34] (2006)	• asymptomatic ≥40 yrs with no risk factors	• Individuals are those with one or more risk factors such as: FH, hypertension, BMI > 25 kg/m2, previous gestational diabetes mellitus, CHD, PCOS, Dyslipidemia etc.	• earlier screening	• FH in ≥ 1 FDR	• earlier screening	• none
Ryden et al.[37](2007)	• asymptomatic individuals, risk score given based on presence and absence of risk factors including FH	• those who receive risk score of 12-14, based on risk factors: age, BMI, Waist circumference, physical activity, diet, anti-hypertensive medication, blood glucose, FH	• Lifestyle changes, and drug therapy if necessary	• FH in FDR or 2nd degree relatives	• Lifestyle changes	• none
Quality Improvement Team in Chronic Care (CCQI)[38]	• asymptomatic , ≥45 yrs with no risk factors	• if overweight and have one or more additional risk factors such as: FH, physical inactivity,	• earlier and more frequent screening	• FH in ≥ 1 FDR	• earlier screening, more frequent screening	• none

Study (Year)	Average risk definition	High Risk	Recommendation for High Risk	Family History		Studies cited
				Definition of Positive FH	Recommendation	
(2008)		hypertensive, PCOS, history of vascular disease etc.				
American Diabetes Association (ADA) (2008)[54]	• asymptomatic ≥ 45 yrs with no risk factors	• all adults with BMI > 25kg/m^2 and one or more risk factors : FH, physical inactivity, history of CVD, hypertensive, PCOS etc.	• earlier screening (<45 yrs)/more frequent screening depending on risk status	• FH in ≥ 1 FDR	• earlier screening (<45 yrs)	• none
Michigan Quality Improvement Consortium[40] (2008) (50-65+)	• no risk factors	• having one or more risk factors such as: BMI ≥ 25kg/m^2, family history, high risk ethnic groups	• screen earlier	• any FH	• earlier screening	• none
Michigan Quality Improvement Consortium[41] (2008) (18-49)	• no risk factors	• >18-39 with risk factors such as: obesity, family history, high risk ethnic groups, history of gestational diabetes, hypertension, polycystic ovarian syndrome etc.	• Screen earlier	• any FH	• earlier screening	• none
Wisconsin Diabetes Prevention and Control Program[51] (2008)	• ≥45 with no risk factors	• if one or more risk factors present at any age : BMI >25 kg/m^2, physical inactivity, history of hypertension or	• earlier and more frequent screening	• FH in ≥ 1 FDR	• earlier and more frequent screening	• none

Study (Year)	Average risk definition	High Risk	Recommendation for High Risk	Family History		Studies cited
				Definition of Positive FH	Recommendation	
		on therapy for hypertension, women with PCOS, history of gestational diabetes mellitus, FH				

Asthma

The single guideline[55] which met the inclusion criteria did not mention family history.

Methodological Quality Evaluation

The purpose of the quality scoring was to assess whether higher quality guidelines were more likely than lower quality guidelines to incorporate family history, use similar definitions, use definitions consistent with the NIH review, indicate similar interventions to address high risk, and cite evidence to support the way they used family history (See Table 10). The AGREE instrument scores for the 25 included guidelines are detailed in Table 9.

The scores for the *scope and purpose* domain ranged from 22–100%, with a median score of 61%. The s*takeholder involvement* domain scores ranged from 22–100%, with a median score of 33%. For r*igor of development*, the scores were 0%–88% with a median of 50%. The *clarity of presentation* scores were 33–94%, with a median score of 71%. For *applicability,* the scores ranged from 0–55%. The median score was 11%. For the domain of *editorial independence,* scores from 0–100% and the median score was 50%.

Table 9: Summary of AGREE scores of guidelines included

Authors	Scope and Purpose (%)	Stakeholder Involvement (%)	Rigor of Development (%)	Clarity of Presentation (%)	Applicability (%)	Editorial Independence (%)
Institute for Clinical Systems Improvement (ICSI)[39]	78	46	62	94	39	83
Michigan Quality Improvement Consortium (18-49)[41] (18-49)	28	0	2	46	0	0
Michigan Quality Improvement Consortium (50-65+)[40]	22	0	2	46	0	0
Qaseem et al.[43]	100	50	57	75	5	83
Saslow et al. & Smith et al.[30;31]	67	50	59	75	0	92
University of Michigan Health System (2004)[42]	61	21	40	71	11	50
Davila et al.[44]	50	29	40	67	0	25
Calonge et al.[45]	94	33	88	71	11	100
Singapore Ministry of Health (2006)[34]	50	42	19	67	28	17
Scottish Intercollegiate Guidelines Network (SIGN)[33]	72	75	95	87	33	100
Ko et al.[46]	34	37	23	58	0	17
World Gastroenterology Organization (WGO)[32]	61	50	40	62	55	0
U.S. Preventive Services Task Force (2008)CRC[47]	94	46	86	75	17	100
Mosca et al [49]	77	42	71	75	22	100
Graham et al.[36]	83	37	50	67	39	50
U.S. Preventive Services Task Force (2004)CHD[48]	44	25	83	54	22	100
Rodbard et al.[50]	55	29	55	58	0	83
Singapore Ministry of Health (2004)[35]	50	37	28	71	11	17
Ryden et al. [37;56]	61	21	50	83	0	83
Wisconsin Diabetes Advisory Group[51]	33	33	0	46	5	8
Calonge et al.[52]	72	33	62	71	5	100
Quality Improvement Team in Chronic Care (CCQI)[38]	61	37	52	75	55	8
American Diabetes Association (ADA)[54]	44	0	12	33	0	0
University of Michigan Health System (2008)[53]	66	25	28	71	0	50
Global Initiative for Asthma (GINA)[55]	38	21	43	33	55	42

Table 10 presents the condition-specific guidelines ranked by the rigor of development score. Although the sample size is small for each condition, there appears to be no clear correlation between the quality of the guidelines, as determined by our criteria (only 5 guidelines scored greater than 67%), and whether or not family history was included, the consistency of the definition, or the specific details of the recommended interventions (other than that they all related to earlier or more screening). There was also no overlap between the guidelines regarding the evidence cited to support the use of family history. Sixteen of the 24 guidelines which included family history cited no evidence.

Table 10: Summary of guidelines by family definition, associated preventive interventions and evidence cited.

Guideline	Rigor of Development score (%)	Includes FH?	FH definition consistent with NIH review?	Interventions indicated for those with FH	Evidence cited to support FH
Breast Cancer (n=6)					
Institute for Clinical Systems Improvement (ICSI)[39]	62	Yes	No	• Earlier screening • Shorter screening interval	none
Saslow et al. & Smith et al.[30;31]	59	Yes	No	• None (insufficient evidence cited)	[58;59]
Qaseem et al.[43]	57	Yes	No	• Periodic risk assessment • Initiate screening	[57]
University of Michigan Health System[42]	40	Yes	Yes	• Earlier screening	[60]
Michigan Quality Improvement Consortium (18-49)[41]	2	No	N/A	N/A	N/A
Michigan Quality Improvement Consortium (50-65+)[40]	2	No	N/A	N/A	N/A
Colorectal Cancer (n=11)					
Scottish Intercollegiate Guidelines Network (SIGN)[33]	95	Yes	No	Moderate risk • One time earlier screening at age 30-35 and then again at 55 High risk • Earlier screening, shorter screening interval, referral to genetic counseling	[64;67]
Calonge et al.[45]	88	Yes	No	None	none

Guideline	Rigor of Development score (%)	Includes FH?	FH definition consistent with NIH review?	Interventions indicated for those with FH	Evidence cited to support FH
U.S. Preventive Services Task Force [47]	86	Yes	No	• Earlier screening	none
Institute for Clinical Systems Improvement (ICSI)[39]	62	Yes	No	• Earlier screening	61;68
Davila et al.[44]	40	Yes	No	Three dentitions of positive FH • 1) earlier colonoscopy screening, followed with 2-5 yr screening interval (if normal) • 2) earlier colonoscopy screening, followed with 10yr screening interval (if normal) • 3) earlier colonoscopy screening, followed with 5yr screening interval (if normal)	61-63
World Gastroenterology Organization (WGO)[32]	40	Yes	No	Two definitions of positive FH • 1) earlier screening, shorter screening interval • 2) earlier screening	none
University of Michigan Health System[42]	40	Yes	No	Two definitions of positive FH • 1) earlier screening • 2) earlier screening and shorter screening interval	none
Ko et al.[46]	34	Yes	No	• Earlier screening, shorter screening interval • Earlier screening but same interval as average risk	none
Singapore Ministry of Health[35]	19	Yes	No	• Earlier screening	64-66
Michigan Quality Improvement Consortium (18-49)[41]	2	Yes	No	• Earlier screening	none
Michigan Quality Improvement Consortium (50-65+)[40]	2	No	N/A	N/A	N/A
Coronary Heart Disease (n=4)					

Guideline	Rigor of Development score (%)	Includes FH?	FH definition consistent with NIH review?	Interventions indicated for those with FH	Evidence cited to support FH
U.S. Preventive Services Task Force[48]	83	No	N/A	N/A	N/A
Mosca et al [49]	71	Yes	No	none	none
Institute for Clinical Symptoms Improvement (ICSI)[39]	62	No	N/A	N/A	N/A
Graham et al.[36]	50	Yes	No	• Lifestyle modification, therapeutic management of risk factors	[69;70]
Type II Diabetes (n=10)					
Calonge et al. [52]	62	No	N/A	N/A	N/A
Rodbard et al. [50]	55	Yes	No	• Earlier screening	none
Quality Improvement Team in Chronic Care (CCQI)[38]	52	Yes	No	• Earlier and more frequent screening	none
Ryden et al. [37;56]	50	Yes	No	• Lifestyle changes	none
Singapore Ministry of Health[34]	28	Yes	No	• Earlier screening	none
University of Michigan Health System[53]	28	No	N/A	N/A	none
American Diabetes Association (ADA)[54]	12	Yes	No	• Earlier screening (< 45 yrs)	none
Michigan Quality Improvement Consortium (18-49)[41]	2	Yes	No	• Earlier screening	none
Michigan Quality Improvement Consortium (50-65+)[40]	2	Yes	No	• Earlier screening	N/A
Wisconsin Diabetes Advisory Group[51]	0	Yes	No	• Earlier and more frequent screening	none
Asthma (n=1)					
Global Initiative for Asthma (GINA)[55]	43	No	N/A	N/A	N/A

Summary

The environmental scan showed that more than two thirds of eligible disease prevention guidelines included family history as a specific item in disease risk assessment. Overall, there was wide variation in how guidelines for the same condition defined average risk, and there was no consistency in how a 'positive FH' was defined, whether across or within the conditions considered. Few guidelines used the definitions consistent with the most recent evidence report.(20) There was also no consistency in how the family history information was used to inform specific preventive recommendations. Most guidelines that included family history did not cite specific evidence to support its use, and those that did cited evidence drew on different sources.

CHAPTER III

ANALYSIS OF PREDICTIVE ACCURACY OF FAMILY HISTORY FOR CORONARY HEART DISEASE (CHD) RISK

OBJECTIVE

The main aim of this chapter is to assess the incremental improvement in individual risk prediction which is gained by incorporating family history information with other forms of clinical information recommended in CHD guidelines, and the impact this would make, if any, on the interventions recommended, and its overall clinical significance. It addresses objectives 3 and 4.

METHODS

This study used data from the Aberdeen Study of Cardiovascular Health in Women (ASCHW)[71]. ASCHW is a retrospective cohort study originally designed to examine the association between gestational complications (hypertension and pre-eclampsia/eclampsia) and the development of CVD in women later in life. Gestational hypertension is sustained elevation of blood pressure in a pregnant woman without known pre-existing hypertension (when non-pregnant). Pre-eclampsia is characterized by gestational hypertension accompanied by significant proteinuria and other clinical features. If untreated (through delivery of the infant), pre-eclampsia can progress to eclampsia, which is characterized by convulsions and is a medical emergency(72) (See box in following page for specific case definitions). Ethics board approval for the original study was obtained from the Grampian Health Board and University of Aberdeen Joint Ethical Committee (Appendix 7). Ethics

board approval for the current analysis was obtained from the Ottawa Hospital Research Ethics Board (Appendix 8). It should be noted that the current analysis is cross-sectional, because most of the risk factor variables were captured at the time of follow-up, not at the original cohort baseline.

Study design

The Aberdeen Maternity and Neonatal Databank (AMND) was used to identify all Aberdeen residents who were diagnosed with pre-eclampsia or eclampsia and delivered their first live singleton infant during the 1951–1970 period. Two comparison groups, consisting of a gestational hypertension group and control group with neither gestational hypertension nor eclampsia/pre-eclampsia, were individually matched to the nearest year of delivery and gestational age with the pre-clampsia/ eclampsia group. Women with chronic hypertension were excluded and no other exclusions criteria were used.[71]

Box 2: Case Definitions[71]

Pre-eclampsia: "*gestational hyptertension plus proteinuria of ≥ 0.3 g/24 hours*"

Eclampsia: "*convulsions occurring in the presence of pre-eclampsia*"

Gestational hypertension: "*diastolic pressure ≥90 mm Hg on two occasions at least four hours apart or a single reading of ≥110 mm Hg from 20 weeks gestation onwards in a previously normotensive woman*"

After the identification of eligible participants through the databank, tracing exercises at the local (1996) and national level (1999) were conducted to identify their vital status, name, address, current primary care practitioner and hospital admission records. Their current primary care practitioners were asked for permission to contact these patients.[71]

If consent was given, the women were asked to: 1) complete the ASCHW questionnaire: a postal survey on general health, lifestyle, wellbeing and obstetric history (Appendix 9) and 2) undergo a detailed clinical examination where an electrocardiogram (ECG) reading, blood pressure, and anthropometric measurements were taken and blood samples drawn for biological analyses (Appendix 10) for the clinical examination protocol [71].

The invitation to attend the clinical examination was sent with the postal questionnaire. Additionally, two reminder questionnaires were sent to non responders. The study participants and research nurses were blind to the study group status.[71]

Participants

The databank identified 3593 eligible participants from the cohort. The primary care practitioners gave permission to contact 1876 of those eligible participants and 1312 (71%) correctly completed the ASCHW questionnaire. Of the 1312 women who completed this, 992 (75.6%) attended the clinical examination.[71] (Figure 3)

For the purposes of this thesis, the analysis was limited to the participants who attended the clinical examination and consented to having blood samples drawn. The analysis required data on participants' ECG readings, and total cholesterol, high density

lipoprotein cholesterol (HDL) and systolic blood pressure (SBP) measurements. The ECG readings formed part of the outcome definition, and the others are considered standard of care when assessing patients for heart disease and are included in prevention guidelines relevant to this population so were needed for our analysis.[72;73]

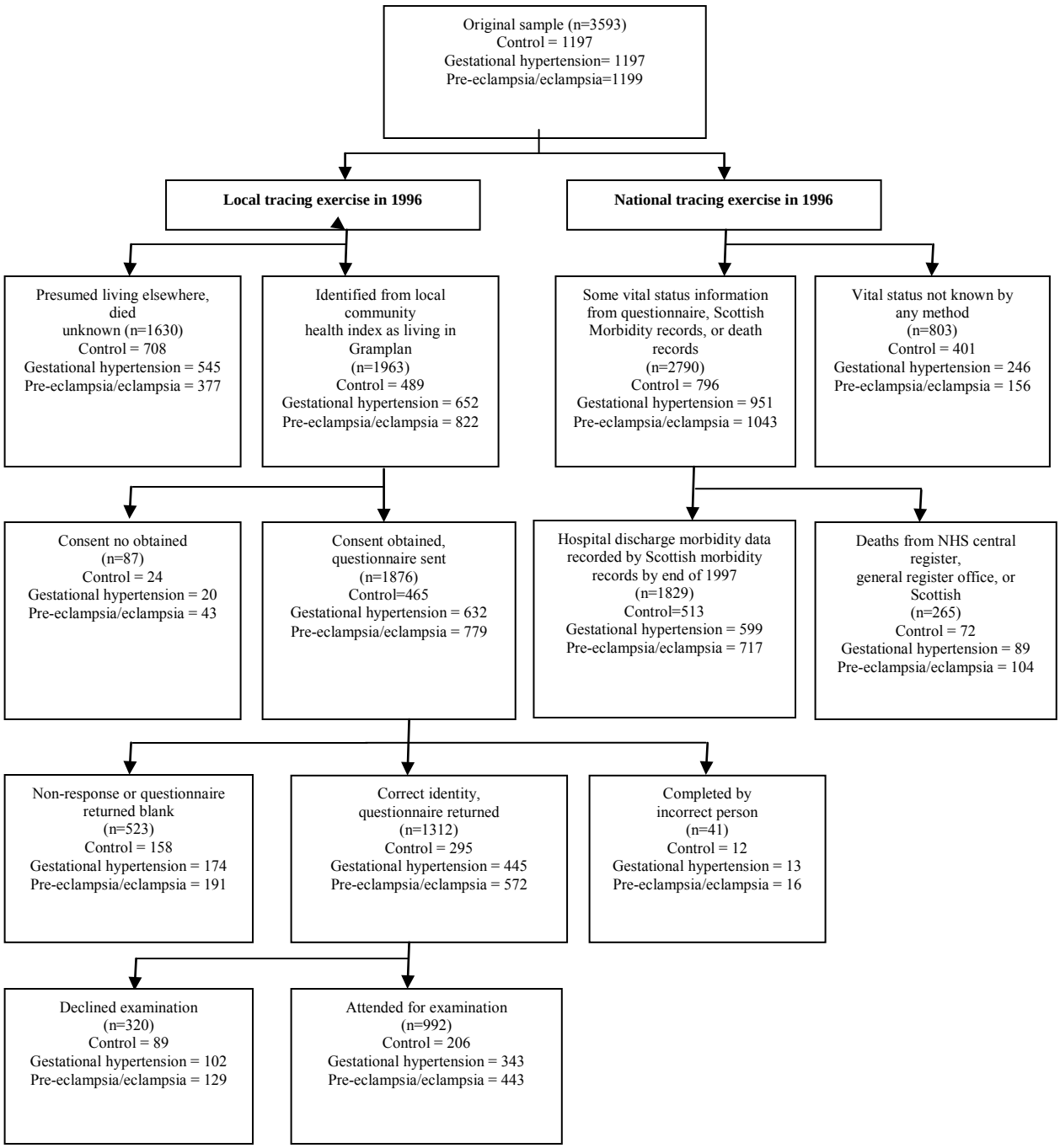

Figure 3: Cohort tracing details up to 1997[71]

Variables

Main Outcome

The main outcome was coronary heart disease (CHD). For this, we developed a dichotomous variable, derived from self-report responses to the Rose Angina questionnaire[74] embedded in the ASCHW questionnaire, and ECG readings recorded at the clinical examination. CHD was considered present if participants had

1. Angina or possible myocardial infarction as defined by the Rose criteria (see below) and/or
2. One or more ECG abnormalities consistent with ischaemic heart disease (see below)

Rose criteria questionnaire

The Rose Angina Questionnaire is a validated tool for measuring angina and myocardial infarction in epidemiologic studies.[74;75] It is a self-report instrument which captures data on symptoms and signs consistent with ischemic heart disease (Appendix 8 q48-49).

ECG

Each participant's ECG was coded according to the Minnesota coding system.[76] Participants were classified as having CHD if their ECG showed either Q/QS pattern changes and/or other coded 'ischemic' changes.

Independent variables

We used an evidence based guideline, *JBS 2: Joint British Societies' Guidelines on Prevention of Cardiovascular Disease in Clinical Practice*[72], to identify variables for the analysis. The 'JBS 2'[1] is a U.K. based cardiovascular disease prevention guideline, and was used because the prevalence of risk factors such as cholesterol and blood pressure differs among populations/regions and affects the calibration of risk prediction models. We considered a U.K. guideline as most appropriate for a U.K. sample.

We selected the variables included in the JBS 2 risk prediction models, as well as those we considered to be important for the description of the sample, and those we regarded as potential confounders or effect modifiers. Table 11 summarizes the variables considered.

[1] JBS2 was not included in Part I because it was not identified during search of National Guideline Clearinghouse database

Table 11: List of Independent Variables

Variable	Type of Variable	Levels	Variable Source
CHD	Categorical	Yes No (ref)	ASCHW and clinical exam
Age Group	Categorical	0-49 50-59 60+	ASCHW
Attained Higher Education	Categorical	Yes No (ref)	ASCHW
Social Class	Categorical	I-III non manual (ref) III-V manual	ASCHW
Exercise 3x20	Categorical	Yes No (ref)	ASCHW
Alcohol	Categorical	0 (ref) 1-14 15+	ASCHW
Current Smoking	Categorical	Yes No	ASCHW
ASCHW groups	Categorical	Control Gestational Hypertension Pre-eclampsia, Eclampsia	AMND
Family History	Categorical	Yes No (ref)	ASCHW
BMI	Categorical	Underweight (ref) Normal range Overweight Obese	Clinical exam
Type II Diabetes	Categorical	Yes No (ref)	ASCHW
Total cholesterol	Continuous		Clinical exam
HDL cholesterol	Continuous		Clinical exam
Systolic blood pressure	Continuous		Clinical exam
Diastolic blood pressure	Continuous		Clinical exam

Ref=reference category

Age was originally recorded as a continuous variable, derived from date of birth recorded within the AMND, and calculated at the date of the clinical examination. Based on the age categorization of JBS 2's recommendations,[72] age was reclassified as a categorical variable: under 50, 50-59, 60 and older. The youngest age category served as a reference category during analysis.

Attained Higher Education was categorized on whether the respondents reported having higher education (post-secondary) or not, as reported in the ASHCW questionnaire.

Social Class was assigned based on respondents' self-reported occupation and employment status in the ASCHW questionnaire, using the U.K. Registrar General's social class guidelines (http://www.ons.gov.uk/about-statistics/classifications/current/ns-sec/glossary-of-terms/index.html). This occupational classification scheme was used extensively in the U.K. According to convention, if a female's social class could not be determined or fell outside classes I-V then the partner's reported social class was used. Social class was then dichotomized into class I-III non manual vs. III-V manual.

Exercise was defined as being physically active 3 times/week for at least 20 minutes, based on ASCHW questionnaire responses. Physical activity was defined as any type of activity which resulted in shortness of breath, perspiration or having a faster heart beat than normal.

Alcohol: for alcohol consumption, respondents were asked in the ASCHW questionnaire how many times/week they drink alcohol, what kind of alcohol and in what amounts. Alcohol was categorized in (units/week) 0, 1-14, 15+.

Smoking: was based on questionnaire responses, and categorized according to whether the respondents reported being a current smoker or not.

Eclampsia/ pre-eclampsia or gestational hypertension was originally obtained from the clinical charts which formed the basis for diagnostic data entered into the AMND.

Family History: was based on the respondent's self-report of FH of heart disease in the ASCHW questionnaire. A positive FH was defined as heart disease before the age of 60 in either parent or any siblings. Family history was dichotomized as having a ≥1 FDR with CHD vs. no FH of CHD.

Body Mass Index (BMI): was calculated as a continuous variable from the height and weight of each participant according to the formula weight (kg)/height $(m)^2$, measured at the clinical examination. BMI was reclassified as a categorical variable according to World Health Oraganization (WHO) criteria.[77] (See Table 12)

Table 12: WHO criteria for BMI classification[77]

Classification	BMI (kg/m^2)	Frequency
Underweight	< 18.5	4
Normal Range	18.5-24.99	334
Overweight	≥25	338
Obese	≥30	219
	Total	945

Frequency counts of the BMI categorized according to the WHO criteria showed that the underweight category had only four observations, so it was collapsed with the normal range category (Table 13).

Table 13: BMI reclassification

Classification	BMI (kg/m^2)	Frequency
Normal Range	< 24.99	338
Overweight	≥25 and ≤30	388
Obese	≥40	219
	Total	945

Type II Diabetes: was categorized based on the respondent's report of having been diagnosed with diabetes by a doctor or not, in the ASCHW questionnaire.

Total cholesterol: was measured as a continuous variable, in accordance with the clinical examination protocol (Appendix 10)

High Density Lipoprotein cholesterol (HDL): was measured as a continuous variable, in accordance with the clinical examination protocol (Appendix 10)

Systolic blood pressure (SBP): was measured as a continuous variable, in accordance with the clinical examination protocol (Appendix 10)

Diastolic blood pressure (DBP): was measured as a continuous variable, in accordance with the clinical examination protocol (Appendix 10)

Outliers

Extreme values for continuous variables were identified through univariate statistics and were examined individually to determine whether they should be excluded. If the extreme values were plausible they were retained. For certain variables such as blood pressure and BMI, two sources of data were available (self-reported BMI and BMI measurement at clinical exam, random zero sphygmomanometer and automatic blood pressure reading). For these variables, the outliers were investigated for consistency between the two measurement methods and any discrepancy was identified and dealt with.

STATISTICAL ANALYSIS

SAS software (version 9.2) was used for all analyses.

Univariate Analysis:

Descriptive statistics of the dependent and all independent variables considered in the analysis were conducted according to: 1) original ASCHW grouping (eclampsia/pre-eclampsia group, gestational hypertension group, control group) and 2) the outcome of interest (CHD). χ^2, t tests, Fisher's exact test and analysis of variance tests (ANOVA) were used to assess the differences between the groups of interest.

Applied Logistic Regression:

We developed three models: Model 1 (core model) included only the covariates in JBS 2; Model 2 added FH to Model 1; and Model 3 was developed using a fuller range of risk factors available in the dataset. Linearity of continuous variables of interest was assessed using the LOESS smoothing on the logit scale. We assessed the performance of model 1 vs. model 2 and model 3 using: 1) Hosmer and Lemeshow tests 2) likelihood ratios and 3) Receiver Operating Curves (ROC).

Reclassification Tables:

In addition to the above methods, an assessment was planned of each model's performance using risk reclassification tables. To determine the improvements in risk reclassification, we intended to use the net reclassification index (NRI), a measure of the correct movement of individuals to higher/lower risk strata.[78].

RESULTS

Overall sample

Of the 992 participants who correctly completed the ASCHW questionnaire, 973 (98.0%) consented to having blood samples drawn, of which 28 (2.8%) were excluded due to missing data, resulting in 945 respondents who were included in the final analysis. (Figure 4)

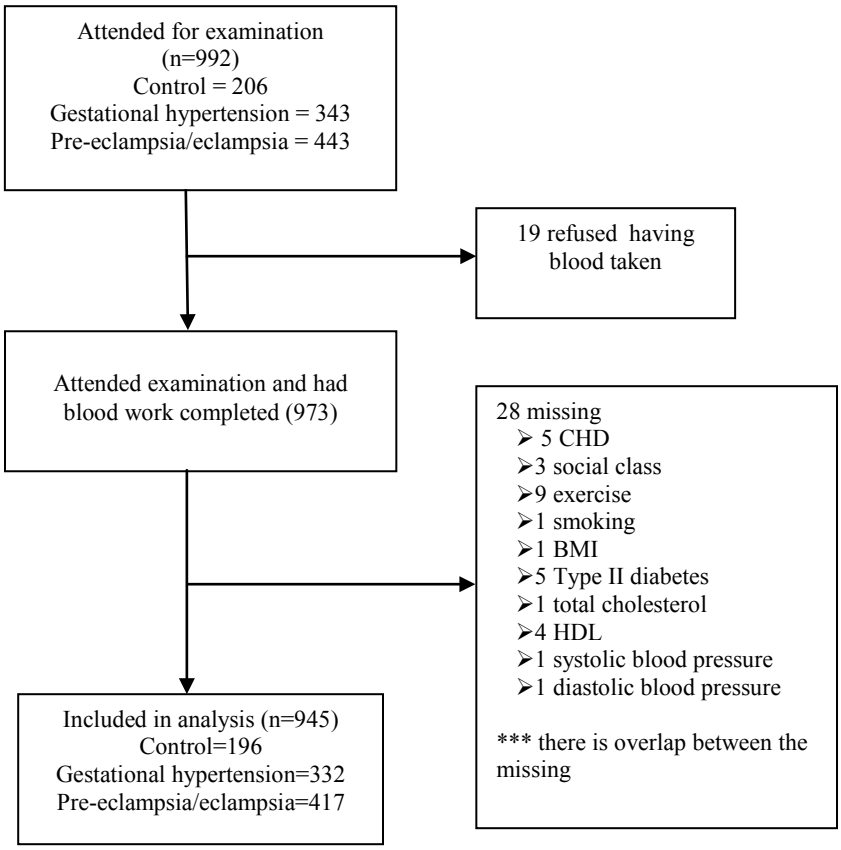

Figure 4: Sample details

Outliers

One extreme BMI value was identified which could not be verified/ did not match through comparison to self-reported data (participant ID 2352). For this value, it was assumed that the recorded **weight at exam** of 34.8 kg was a data entry error, and that the **self-reported weight** in the questionnaire of 54.43 was more accurate. We therefore used the questionnaire-based BMI of 20.59 kg/m^2 for the analyses rather than that based on the clinical examination data (13.49 kg/m^2).

Sub-group comparison

ASCHW grouping

The results of the univariate analysis for the variables of interest according to original ASCHW grouping (control, gestational hypertension, pre-eclampsia/eclampsia) are presented in Table 14.

The mean age at time of clinical examination was similar for all three groups, perhaps reflecting matching of groups during the original study design. The majority of the women were in the 60 and older category.

Respondents in the control group were more likely to be current smokers (21.9%) compared to those in gestational hypertension (15.3%) and pre-eclampsia/eclampsia (10.0%) groups. They were also less likely to be obese (15.3%) than those in the gestational hypertension (26.8%) and pre-eclampsia/eclampsia (24.0%) groups. The prevalence of type II diabetes was 3.6 percent in the gestational hypertension group and 4.5 percent in the pre-eclamspsia/eclampsia group. There were no respondents with type II diabetes in the control group. Mean HDL, systolic and diastolic blood pressure increased, with the lowest values for the control group, intermediate for the gestational hypertension group, and highest for the pre-eclampsia/eclampsia group.

There were no statistically significant differences in age, attainment of higher education, social class, exercise, alcohol intake, family history and mean total cholesterol across the groups.

Table 14: Comparison of final analytical sample by ASCHW group

Characteristics	Control (n=196)	Gestational hypertension (n=332)	Pre-eclampsia/ eclampsia (n=417)	Chi-square/ ANOVA
Age group (years), *n (%)*				
0-49	18 (9.1)	23 (6.9)	31(7.4)	
50-59	68 (34.6)	115 (34.6)	155(37.1)	0.81
60 and older	110 (56.1)	194 (58.4)	231(55.3)	
Attained Higher Education, *n (%)*	83(42.3)	109 (32.8)	139 (33.3)	0.05
Social Class categories I-III Non Manual, *n (%)*	132 (67.3)	218 (65.6)	269 (64.5)	0.78
Exercise, *n (%)*	55(28.0)	89 (26.8)	127 (30.4)	0.53
Alcohol, *n (%)*				
0	84 (42.8)	157 (47.2)	208 (49.8)	0.25
1-14	103 (52.5)	164 (49.3)	201 (48.2)	
14+	9 (4.5)	11 (3.3)	8 (1.9)	
Smoking, *n (%)*	43 (21.9)	51 (15.3)	42 (10.0)	0.0004
BMI, *n (%)*				
normal range	87 (44.3)	112 (33.7)	139 (33.3)	0.01
overweight	79 (40.3)	131 (39.4)	178 (42.7)	
obese	30 (15.3)	89 (26.8)	100 (24.0)	
Family history, *n (%)*	77 (39.2)	127 (38.2)	172 (41.2)	0.69
Type II diabetes, *n (%)*	0	12 (3.6)	19 (4.5)	0.0022¥
Total cholesterol (mmol/l), *mean (SD)*	6.18 (1.19)	6.31(1.24)	6.23 (1.14)	0.43
HDL cholesterol (mmol/l), *mean (SD)*	1.39 (0.39)	1.44 (0.38)	1.50 (0.37)	0.002
Systolic BP, (mmHg) *mean (SD)*	136.1 (27.3)	144.5 (25.5)	146.3 (26.1)	0.0001
Diastolic BP, (mmHg) *mean (SD)*	77.2 (11.5)	80.5 (10.0)	81.2 (11.1)	0.0001

¥ *Fisher Exact Test*

CHD grouping

The results of the univariate analysis for the variables of interest according to the outcome variable are presented in Table 15.

Of the 945 eligible subjects, 212 fulfilled the definition for CHD. Comparing the groups, those with CHD were slightly older (64.6% in the oldest age category) compared to those without CHD (54.2%). Age, exercise, BMI, family history, HDL and systolic blood pressure were also statistically significantly different between the two groups. Participants in the CHD group were less likely to be participate in physical activity 3 times/week (56.1% vs. 75.7%) and more likely to report a family history (50.0% vs. 36.8%) of CHD. Respondents in the CVD group were more likely to be obese (30.1%) than those in the non-CHD group (21.1%). Mean systolic blood pressure was significantly higher in the CHD group and the mean HDL was lower.

There were no statistically significant differences in attainment of higher education, social class, alcohol intake, diastolic blood pressure, total cholesterol, diabetes, ASCHW grouping, and current smoking status across the two levels of the main outcome.

Table 15: Comparison of final analytical sample by CHD

Characteristics	CHD (n=212)	No CHD (n=733)	Chi-square/T-test
Age group (years), *n (%)*			
0-49	6 (2.8)	66 (9.0)	0.002
50-59	69 (32.5)	269 (36.6)	
60 and older	137(64.6)	398 (54.2)	
Attained Higher Education, *n (%)*	74 (34.9)	257 (35.0)	0.96
Social Class categories I-III Non Manual, *n (%)*	135 (63.6)	484 (66.0)	0.52
Exercise, *n (%)*	119(56.1)	555 (75.7)	0.0001
Alcohol, *n (%)*			
0	97 (45.7)	352 (48.0)	0.65
1-14	107 (50.4)	361(49.2)	
14+	8 (3.7)	20 (2.7)	
Smoking, *n (%)*	28 (13.2)	108 (14.7)	0.57
BMI, *n (%)*			
normal range	60 (28.3)	278 (37.9)	0.006
overweight	88 (41.5)	300 (40.9)	
obese	64 (30.1)	155 (21.1)	
Family history, *n (%)*	106 (50.0)	270 (36.8)	0.0006
Diabetes, *n (%)*	10 (4.7)	21 (2.8)	0.18
Total cholesterol (mmol/l), *mean (SD)*	6.31 (1.24)	6.23 (1.17)	0.39
HDL cholesterol (mmol/l), *mean (SD)*	1.40 (0.36)	1.47 (0.39)	0.01
Systolic BP, (mmHg) *mean (SD)*	147.7 (28.9)	142.4 (25.5)	0.01
Diastolic BP, (mmHg) *mean (SD)*	80.2 (12.2)	80.1 (10.4)	0.92
ASCHW group, n (%)			
Control	43 (20.2)	153 (20.8)	0.21
Hypertension	65 (30.6)	267 (36.4)	
Eclampsia & Pre-eclampsia	104 (49.0)	313 (42.7)	

¥ Fisher exact test

Candidate Models

Table 16: JBS 2 Variables-Core model

VARIABLE	P-value
AGE	0.002
DIABETES	0.18
HDL	0.01
TOTAL CHOLESTEROL	0.39
SMOKING	0.57
SYSTOLIC BP	0.01

Additional variables identified as important through univariate analysis and meeting the Hosmer and Lemeshow criteria of P<0.25.[79]

Table 17: Additional variables

VARIABLE	P-value
Exercise	0.0001
BMI	0.006
Family History	0.0006
ASCHW groups	0.21

Based on the univariate analysis three preliminary multivariate models were formed:

MODEL 1: JBS 2 + ASCHWgrouping
MODEL 2: JBS 2+ ASCHWgrouping+ FH
MODEL 3: JBS 2+ ASCHWgrouping + FH + BMI + EXCERCISE

ASCHW grouping was included in all three models because it is a design variable.

JBS 2 guideline covariates were included in all multivariate models regardless of univariate analysis results as the goal of our analysis was to assess the performance of JBS 2 on its own and when combined with FH and other important risk factors identified through the dataset. Furthermore, the JBS 2 covariates represent clinical features, the measurement of which is considered standard of care in clinical practice.

Linearity Testing for Continuous Variables

Logistic regression models are based on the assumption that continuous variables are linearly related with the logit of the outcome variable.[79] Before regression models were carried the assumption of the linearity of the logit was tested for *HDL*, *total cholesterol*, and *systolic blood pressure* using the graphical method LOESS smoothing of the logit.

Figure 5 shows that there was no violation of linearity for *total cholesterol, w*hereas Figures 6 and 7 show deviations from linearity for *HDL* and *SBP*, respectively. Various transformations were used to improve the linearity of these two variables. Taking *log HDL* somewhat improved its linearity **(**Figure 8**)** but it did not improve the model, rather it rendered HDL non-significant. As such, HDL was included in the final model as a continuous variable without any transformation. The same analysis was completed for

systolic blood pressure; no transformation (not shown) improved the linearity of systolic blood pressure therefore this variable was left as is.

Figure 5: Total cholesterol and CHD (LOESS smoothing on logit scale)

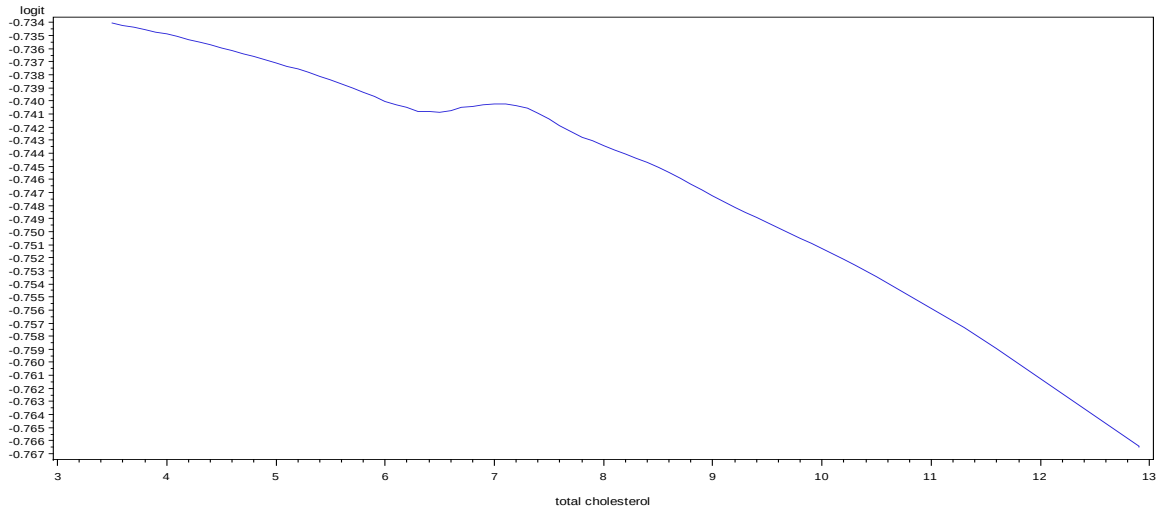

Figure 6: HDL and CHD (LOESS smoothing on logit scale)

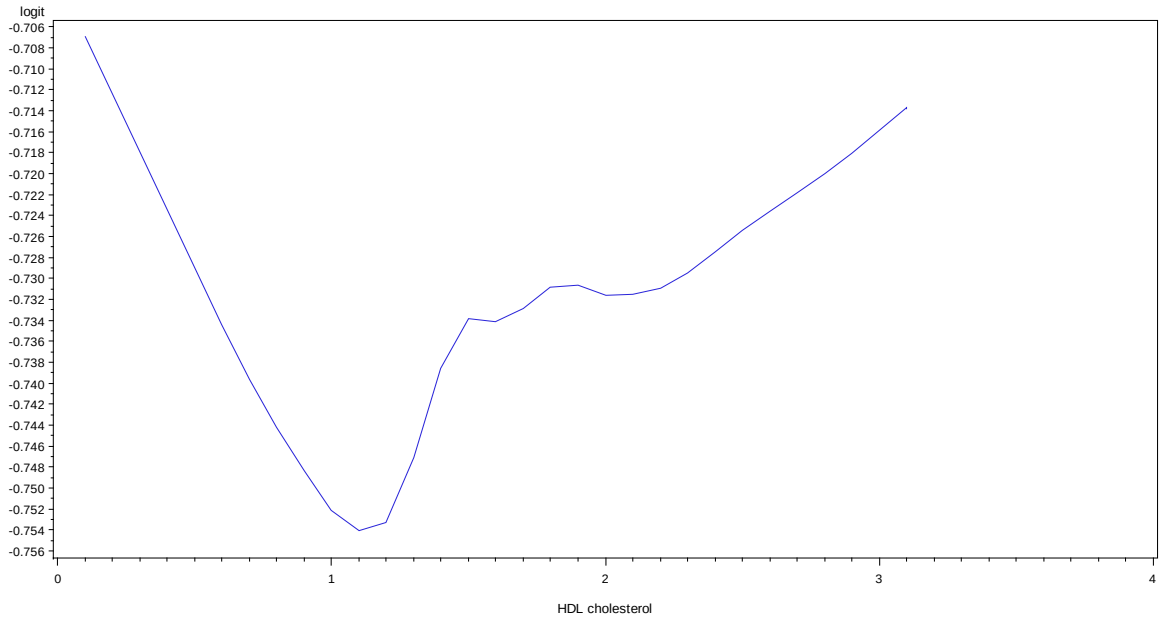

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Figure 7: Log HDL and CHD (LOESS smoothing on logit scale)

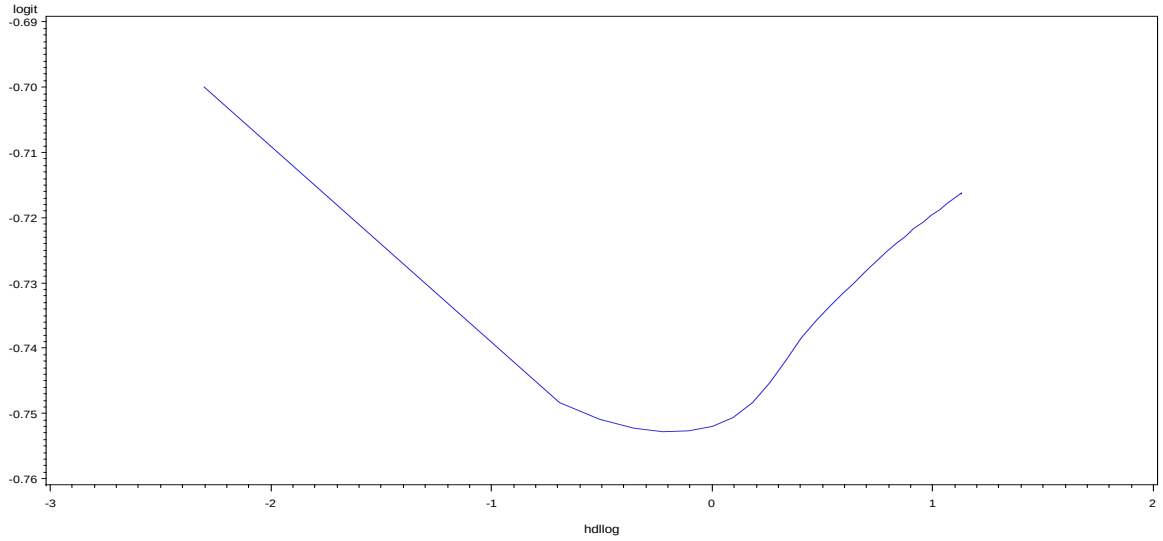
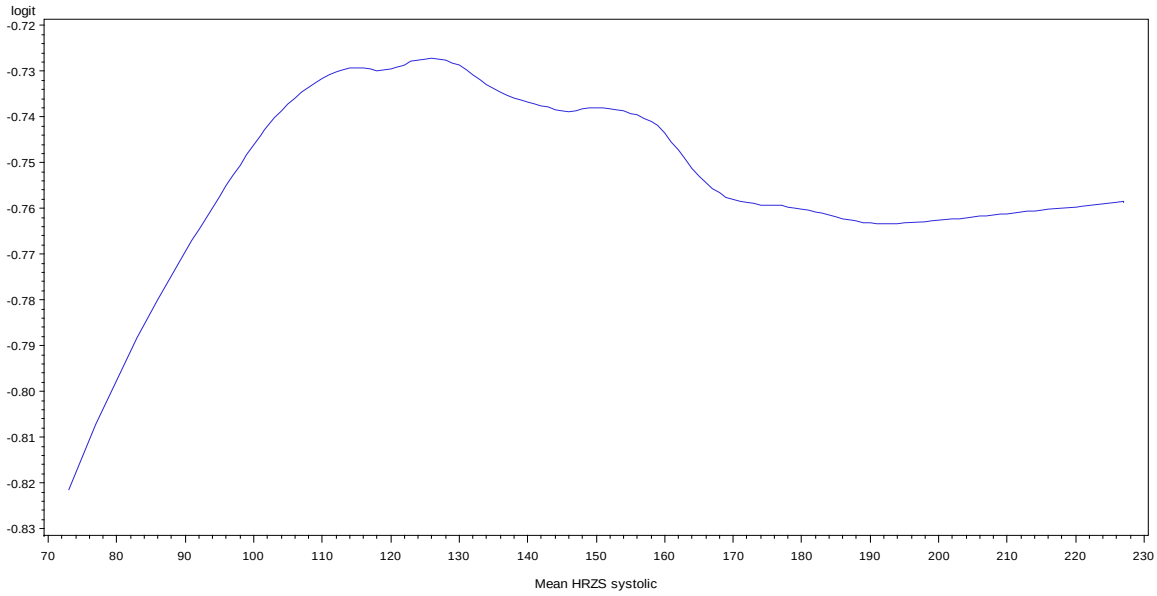


Figure 8: SBP and CHD (LOESS smoothing on logit scale)



Regression Results

MODEL 1: JBS 2 +ASCHWgrouping

a) Preliminary main effects model

The results of the preliminary multivariate MODEL 1 presented in Table 18 showed that out of the seven covariates considered only *age* and *HDL* were significantly associated with CHD at the p = 0.05 level.

Table 18: JBS 2 preliminary multivariate model

Variable	Estimated Coefficient	Estimated Standard Error	p-value
Intercept	-2.3516	0.7470	0.0016
Age 50-59 vs. 0-49	1.0187	0.4519	0.0242
Age ≥ 60 vs. 0-49	1.2273	0.4491	0.0063
Diabetes	0.3792	0.4063	0.3506
Total Cholesterol	0.0187	0.0662	0.7771
HDL	-0.5197	0.2139	0.0151
Smoking	-0.0501	0.2356	0.8315
Systolic BP	0.00445	0.00311	0.1523
ASCHW 1 vs. 0*	-0.1990	0.7698	0.3803
ASCHW 2 vs. 0*	0.1477	0.2155	0.4931

0*=control group 1=gestational hypertension 2=pre-eclampsia/eclampsia

b) Interactions considered

In order to assess effect modification for MODEL 1, all biologically meaningful interaction terms were entered in the preliminary multivariate model in a stepwise fashion. The likelihood ratio test was used to examine the significance of each interaction term considered. The results presented in Table 19 showed that none of the interaction terms considered were significant at the p= 0.05 level. As a result, no interaction terms were entered in the final model resulting in a main effects only model.

Table 19: JBS 2 interaction terms considered

Interaction Term	Log-Likelihood	G	Df	p-value
Main Effects Only Model	978.779			
Age x Diabetes	977.921	0.858	2	0.65116
Age x Total cholesterol	976.676	2.103	2	0.34941
Age x HDL	974.961	4.088	2	0.12951
Age x Smoking	978.221	0.558	2	0.75654
Age x Systolic BP	978.106	0.673	2	0.71427
Age x ASCHW	977.759	1.02	4	0.90675
Smoking x Systolic BP	977.369	1.41	1	0.23506
Smoking x diabetes	978.720	0.059	1	0.80808
Smoking x Total cholesterol	978.673	0.106	1	0.74474
Smoking x HDL	975.605	3.174	1	0.074819

c) Final Model

The results of the multivariate model for MODEL 1 are presented in Table 20. Increased *age* and *HDL* were significantly associated with CHD. Women in the 50-59, and ≥60 *age groups* had 2.76 (95% CI 1.14, 6.71) and 3.41 (95% CI 1.41, 8.22) times higher odds of having CHD than those in the 0-49 group, respectively. For each one unit increase in *HDL* there was a 0.41 decrease in the odds of CHD (OR 0.59 95% CI 0.39, 0.90). The other variables considered (type II *diabetes, total cholesterol, smoking, systolic blood pressure, ASCHW group*) were not significant in the final model.

Table 20: JBS 2 final multivariate model

Variable	OR	95% CI
Age (years)		
0-49 (ref)		
50-59	2.76	(1.14, 6.71)
≥ 60	3.41	(1.41, 8.22)
Type II Diabetes		
No (ref)		
Yes	1.46	(0.65, 3.24)
Total Cholesterol (mmol/l)	1.01	(0.89, 1.16)
HDL cholesterol (mmol/l)	0.59	(0.39, 0.90)
Smoking		
No (ref)		
Yes	0.95	(0.59, 1.50)
Systolic BP (mmHg)	1.004	(0.99, 1.01)
ASCHW group		
Control (ref)		
Gestational hypertension	0.82	(0.52, 1.27)
Pre-elcampsia/eclampsia	1.15	(0.76, 1.76)

MODEL 2: JBS 2 + ASCHWgrouping + FH

a) Main effects model

The results of the preliminary multivariate MODEL 2 presented in Table 21 showed that out of the eight covariates considered only three (*age*, *HDL* and *family history*) were significantly associated with CHD at the p = 0.05 level.

Table 21: JBS 2 and FH preliminary multivariate model

Variable	Estimated Coefficient	Estimated Standard Error	p-value
Intercept	-2.7305	0.7590	0.0003
Age 50-59 vs. 0-49	1.0607	0.4535	0.0193
Age ≥ 60 vs. 0-49	1.2711	0.4505	0.0048
Diabetes	0.2275	0.4114	0.5803
Total Cholesterol	0.0302	0.0665	0.6503
HDL	-0.5154	0.2150	0.0165
Smoking	-0.0542	0.2367	0.8190
Systolic BP	0.00461	0.00311	0.1373
ASCHW 1 vs. 0*	-0.1844	0.2282	0.4190
ASCHW 2 vs. 0*	0.1469	0.2168	0.4979
Family History	0.5503	0.1610	0.0006

0*=control group 1=gestational hypertension 2=pre-eclampsia/eclampsia

b) Interactions considered

In order to assess effect modification for MODEL 2, all biologically meaningful interaction terms were entered in the preliminary multivariate model in a stepwise fashion. The likelihood ratio test was used to examine the significance of each interaction term considered. The results presented in Table 22 showed that none of the interaction terms considered were significant at the p = 0.05 level. As a result, no interaction terms were entered in the final model resulting in a main effects only model.

Table 22: JBS 2 and FH interaction terms considered

Interaction	Log-Likelihood	Δ	df	p-value
Main Effects Only Model	967.125			
FH x Age	966.345	0.78	2	0.67706
FH x Total cholesterol	966.969	0.156	1	0.69287
FH x HDL	966.544	0.581	1	0.44592
FH x smoker	965.059	2.066	1	0.15062
FH x systolic BP	966.784	0.341	1	0.55925
FH x code	963.095	4.03	2	0.13332
FH x diabetes	966.975	0.15	1	0.69854

c) Final Model

The results of the multivariate model for MODEL 2 are presented in Table 23. Increased *age, HDL* and *family history* were significantly associated with CHD. Women in the 50-59, and ≥ 60 *age group* had 2.88 (95% CI 1.18, 7.02) and 3.56 (95% CI 1.47, 8.62) times greater odds of CHD than those in the 0-49 group, respectively. For each one unit increase in *HDL* there was a 0.40% reduction in odds of CHD (OR 0.60 95% CI 0.39, 0.91). Women with *family history* of CHD were 1.73 times (95% CI 1.26, 2.47) more likely to have CHD than women without *family history*. The other variables considered (*type II diabetes, total cholesterol, smoking, systolic blood pressure,* and *ASCHW group*) were not significant in the final model.

Table 23: JBS 2 and FH final multivariate model

Variable	OR	95% CI
Age (years)		
0-49 (ref)		
50-59	2.88	(1.18, 7.02)
≥ 60	3.56	(1.47, 8.62)
Type II Diabetes		
No (ref)		
Yes	1.25	(0.56, 2.81)
Total cholesterol (mmol/l)	1.03	(0.90, 1.17)
HDL (mmol/l)	0.60	(0.39, 0.91)
Smoking		(0.59, 1.50)
No (ref)		
Yes	0.94	
Systolic BP (mmHg)	1.005	(0.99, 1.01)
ASCHW group		
Control (ref)		
Gestational hypertension	0.83	(0.53, 1.30)
Pre-elcampsia/eclampsia	1.15	(0.75, 1.77)
Family History		
No (ref)	1.73	(1.26, 2.47)
Yes		

MODEL 3: JBS 2 + ASCHW grouping + FH + BMI + EXCER3X20

a) Main effects model

The results of the preliminary multivariate MODEL 3 presented in Table 24 showed that out of the ten covariates considered five (*age, HDL, family history,* and *exercise*) were significantly associated with CHD at the p = 0.05 level.

Table 24: Expanded JBS 2 preliminary multivariate model

Variable	Estimated Coefficient	Estimated Standard Error	p-value
Intercept	-2.4256	0.7784	0.0018
Age 50-59 vs. 0-49	1.1315	0.4603	0.0140
Age ≥ 60 vs. 0-49	1.4203	0.4580	0.0019
Diabetes	0.2486	0.4297	0.5629
Total Cholesterol	0.0317	0.0686	0.6434
HDL	-0.3834	0.2267	0.0908
SMOKER	0.0226	0.2437	0.9262
Systolic BP	0.00379	0.00323	0.2404
ASCHW 1 vs. 0*	-0.2314	0.2336	0.3219
ASCHW 2 vs. 0*	0.0918	0.2212	0.6782
Family History	0.5065	0.1643	0.0021
Overweight vs. normal	0.1745	0.1991	0.3809
Obese vs. normal	0.2896	0.2342	0.2162
Exercise	-0.8985	0.1703	0.0001

0*=control group 1=gestational hypertension 2=pre-eclampsia/eclampsia

b) Interactions considered

In order to assess effect modification for MODEL 3, all biologically meaningful interaction terms were entered in the preliminary multivariate model in a stepwise fashion. The likelihood ratio test was used to examine the significance of each interaction term considered. The results presented in Table 25 showed that none of the interaction terms considered were significant at the p = 0.05 level. As a result, no interaction terms were entered in the final model resulting in a main effects only model.

Table 25: Expanded JBS 2 interaction terms considered

Interaction	Log-Likelihood	Δ	df	p-value
Main Effects Only Model	936.154			
Exercise x Age	934.186	1.968	2	0.37046
Exercise x BMI	935.416	0.738	2	0.69143
Exercise x Systolic BP	936.110	0.044	1	0.83385
Exercise x HDL	935.973	0.181	1	0.67052
Exercise x Total Cholesterol	935.158	0.996	1	0.31828
Exercise x Diabetes	935.481	0.673	1	0.41201
BMI x Age	931.035	5.119	4	0.27530
BMI x Systolic BP	935.499	0.655	2	0.72072
BMI x Diabetes	932.559	3.595	2	0.16571
BMI x Total Cholesterol	935.461	0.693	2	0.70716
BMI x HDL	935.216	0.938	2	0.62563
BMI x FH	934.516	1.638	2	0.44087

c) Final Model

The results of the multivariate model for MODEL 3 are presented in Table 26. Increased *age*, *HDL*, *family history,* and *exercise* were significantly associated with CHD. Women in the 50-59, and ≥60 *age groups* had 3.15 (95% CI 1.28, 7.76) and 4.13 (95% CI 1.68, 10.15) greater odds of having CHD than those in the 0-49 group, respectively. Women reporting a *family history* of CHD had 1.67 (95% CI 1.21, 2.31) greater odds of having CHD than women without family history. Women reported participating in regular *exercise* (20 min3 times/week) had a 60.0 percent (OR, 0.40 95% CI 0.28, 0.55) lower odds of CHD than those who did not. The other variables considered (*type II diabetes, total cholesterol, HDL, smoking, systolic blood pressure,* and *ASCHW group,*) were not significant in the final model. *BMI* was removed from the final model as it was not significant in the model on its own, and also none of interactions considered with BMI were significant.

Table 26: Expanded JBS 2 final multivariate model

Variable	OR	95% CI
Age		
0-49 (ref)		
50-59	3.15	(1.28, 7.76)
≥ 60	4.13	(1.68, 10.15)
Type II Diabetes		
No (ref)		
Yes	1.34	(0.58, 3.08)
Total cholesterol (mmol/l)	1.04	(0.91, 1.90)
HDL (mmol/l)	0.63	(0.41, 0.96)
Smoking		
No (ref)		
Yes	0.98	(0.61, 1.57)
Systolic BP, (mmHg)	1.005	(0.99, 1.01)
ASCHW group		
Control (ref)		
Gestational hypertension	0.81	(0.51, 1.28)
Pre-elcampsia/eclampsia	1.11	(0.72, 1.72)
Family History		
No (ref)	1.67	(1.21, 2.31)
Yes		
Exercise		
No (ref)	0.40	(0.28, 0.55)
Yes		

Assessment of model performance

The goodness of fit of each multivariate model was assessed using the Hosmer-Lemeshow, likelihood ratio tests and ROC curves.

1) Hosmer-Lemeshow

Hosmer-Lemeshow test was carried out to assess the adequacy of the data for each of the three models. The results of the tests in Table 27 show that for all three models, we failed to reject the H_0, where rejection indicates lack of fit, thus indicating that there is evidence of good fit for the models.

Table 27: Hosmer-Lemeshow results for the final multivariate models

Model	Chi-Square	df	Pr>ChiSq
1	8.0869	8	0.4250
2	6.6925	8	0.571
3	9.5298	8	0.2996

2) Likelihood ratio test

The results of the likelihood ratio tests are shown in Table 28. MODEL 2 performance was assessed versus MODEL1, and MODEL 3 performance was assessed against MODEL 2. The results indicate that the addition of FH to JBS2 made a statistically significant independent contribution to the MODEL 1 and improved it. Similarly, the addition of exercise and BMI to the model with FH (MODEL 2) made a statistically significant independent contribution to MODEL 2 and improved it.

Table 28: Likelihood ratio tests results for the final multivariate models

Model	Likelihood ratio	Δ	df	Δdf	p-value
MODEL 1	978.779		9		
MODEL 2 (testing model 2 vs. 1)	967.125	11.654	10	1	0.0006
MODEL 3 (testing model 3 vs.2)	937.745	41.034	11	2	1.2291E-09

3) C-statistic and ROC curves

The overall discriminatory ability of the model was assessed using c-statistic and receiver operator curves (ROC) where c=0.5 indicates no discrimination (chance). The results represented in Table 29 and Figures 9-11, show that c statistic for the models 1-3 were 0.603, 0.631 and 0.681 respectively.

Table 29: C-statistic tests results for the final multivariate models.

Model	C
MODEL 1	0.603
MODEL 2	0.631
MODEL 3	0.681
FH alone	0.566

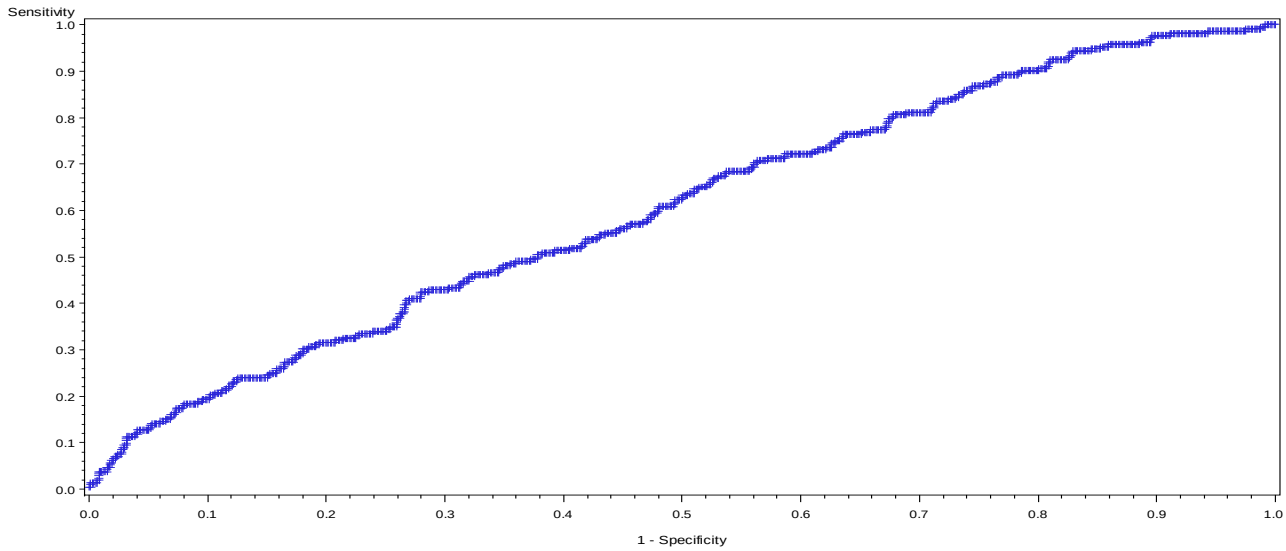


Figure 9: MODEL 1 - ROC curve (AUC 0.603)

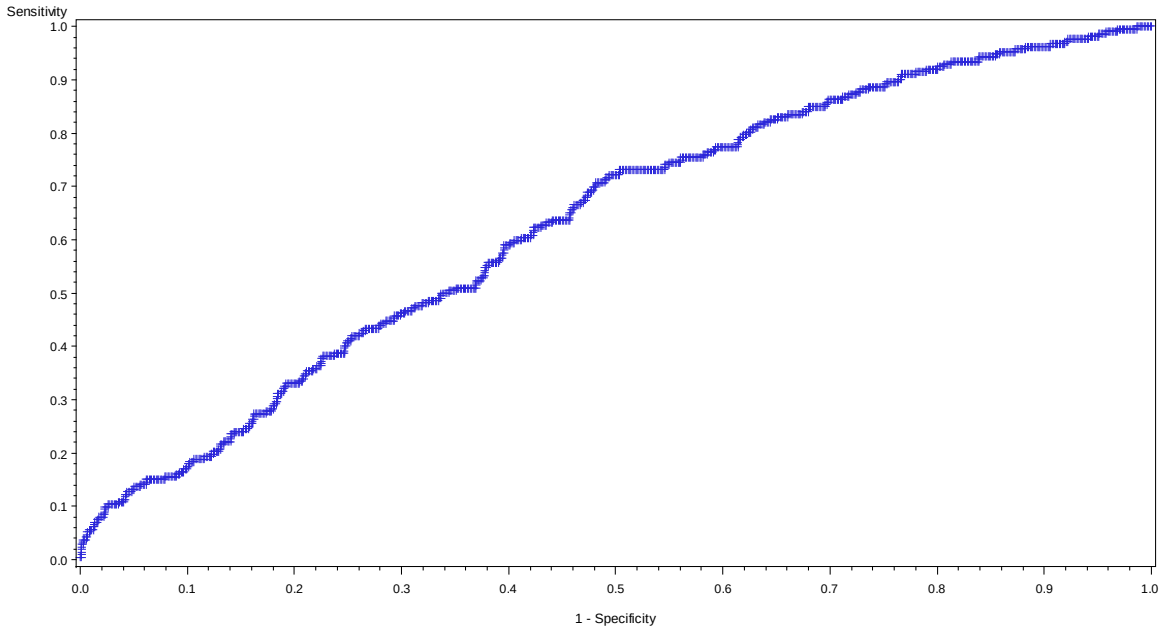


Figure 10: MODEL 3 - ROC curve (AUC 0.631)

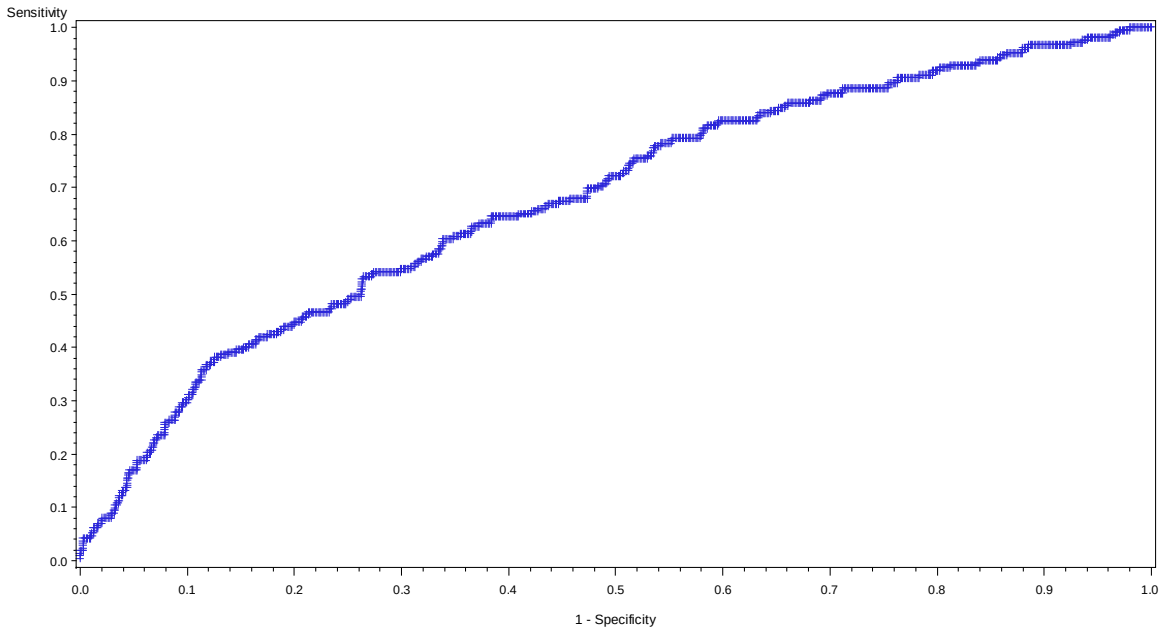


Figure 11: MODEL 3 - ROC curve (AUC 0.681)

4) Classification Tables

Review of the AUC data indicated that adding the family history variable to the other clinical variables improved the overall discriminatory ability of the models by no more than 0.03 (3 percent in absolute terms). Consultation with the thesis committee confirmed a consensus view that this very small incremental improvement, over a baseline model which itself had only modest predictive accuracy, was unlikely to be of clinical significance. In this situation, assessment of risk re-classification is not recommended.[80-82]

SUMMARY

This analysis showed that family history is an independent risk factor for CHD and improved the discriminatory ability of JBS 2. FH's discriminatory ability on its own approximated that of JBS 2.

CHAPTER IV

DISCUSSION

The lack of an adequate evidence base to inform clinical utility of family history for common complex disease risk assessment identified by NIH indicated a major research need. This thesis aimed to address this and improve the evidence base through an environmental scan of prevention guidelines and examining the incremental improvements in prediction gained by the inclusion of family history information with other clinical risk factors for coronary heart disease.

Part I: Environmental Scan

The environmental scan examined how family history is currently represented in prevention guidelines for the major common complex disease of public importance including breast cancer, colorectal cancer, type II disease, coronary heart disease and asthma. The relevant guidelines were identified through the National Guideline Clearinghouse, a U.S. website dedicated to the dissemination of prevention guidelines to North American health professionals. The Clearinghouse accepts only guidelines that have been based on systematic reviews of scientific evidence published in peer reviewed journals, and that have been produced under the auspices of professional organizations, medical specialty associations, government agencies, or health care or other organizations. This means that the guidelines we reviewed would be viewed as the most likely to be evidence-based, and to represent the guidance of the most relevant professional bodies or health care organizations.

The result showed that more than two thirds of eligible disease prevention guidelines included family history as a specific item to be included in disease risk assessment. Overall, there was wide variation on what guidelines for the same condition considered 'average' risk, and there was little consistency in the way 'positive family history' was defined, whether across or within the conditions considered. Few guidelines used definitions consistent with the most recent systematic review,[27] which may reflect the lack of any clarity of evidence until this point. Also, few cited evidence to support their incorporation of family history, and there was little overlap in the evidence cited by those that did offer this. There was also a wide range in how the risk from a positive family history was addressed by preventive recommendations, with no consistency in specific prevention recommendations between guidelines for the same condition.

Strengths and Limitations

Strengths of this environmental scan are the use of a replicable search strategy, independent screening and quality assessment using a validated appraisal instrument[29] by two reviewers. A limitation is that the data abstraction was performed by only one reviewer, which may have introduced error/bias; however, the time and budget constraints did not allow for a second data abstracter. While the scan was limited to guidelines available through the National Guideline Clearinghouse[83] thus limiting its generalizability; this meant we could focus on those most likely to be used by North American health providers. It did, in fact, include guidelines developed outside North America. However, we have no evidence on whether non-included guidelines differed in terms of quality or the way they dealt with family history (although the latter seems unlikely).

Part II: Predictive Assessment of FH

This cross-sectional analysis of a retrospective cohort study of Scottish women examined the incremental predictive ability gained by incorporating family history into a general risk model for cardiovascular disease. The JBS 2 guideline was chosen as appropriate for our sample, and informed our risk factor selection for multivariate modeling to evaluate its performance on its own and with the addition of family history information. Additionally, other risk factors identified as important were used to develop an expanded model to examine its performance compared to JBS 2, and to JBS 2 combined with family history information.

The analysis showed that women in our sample affected by CHD were on average older, had higher cholesterol and lower HDL levels, were more likely to be obese, and less likely to report regular physical activity. They were also more likely to report a family history of heart disease. These observations are all consistent with the extensive literature on CHD risk factors.

Our analysis also suggested that family history is an important risk factor for CHD independent of the JBS 2 risk factors, and it adds to the predictive models based on other well-known risk factors.

However, the baseline discriminatory ability of both the guideline-based and expanded models was modest; while the improvement seen by including family history was statistically significant, it was of questionable clinical relevance.

Janssens and Khoury argue that AUC analysis is an appropriate first step in examining incremental improvements in risk prediction conferred by a risk factor, and that a clinically meaningful change in AUC must be present to warrant further investigation to

determine its impact on risk reclassification and management. If clinically significant improvements in AUC are not present, the authors illustrate that reclassification analysis can lead to as many individuals classified incorrectly as correctly.[80] In our results, the three percent improvement conferred by the addition of FH to the JBS 2, a model with modest predictive ability to begin with, indicated that risk reclassification assessment was not necessary and could possibly misleadingly imply that the gain was clinically meaningful.

We note that that the results suggest that family history alone offered almost as much predictive accuracy as the core JBS 2 model (AUC 0.57 vs. 0.60, respectively). If this was confirmed, it might argue that it would be cheaper and less invasive to ask about family history than to check cholesterol, blood pressure, etc. However, it is unlikely that providers or their patients would be persuaded to forgo what has become standard of care. In addition, most experts would argue that single risk factors, such as hypertension and hypercholesterolaemia, cannot legitimately be ignored, and that they would merit intervention even in the absence of elevated cardiovascular risk according to a risk calculator.

Our results are consistent with those of the two other similar published studies on improvements to discrimination and reclassification of patients by the addition of family history information to risk prediction models. Scheuner *et al.*[23] investigated the improvements in identification of individuals with advanced coronary artery calcification (CAC) by the addition of family history to a multivariate model which predicts global cardiovascular disease risk. CAC is a proxy for cardiovascular disease. The general cardiovascular risk profile was improved by the addition of family history information. Although the improvement results were statistically highly significant ($p<0.0001$), they were

of marginal clinical relevance and there was no net improvement in risk classification. Another study by Scheuner *et al*.[22] assessed the performance of family history risk stratification in a cross-sectional study of the U.S. population for early-onset coronary heart disease. The family history- based model produced an AUC of 0.71, which improved to 0.87 with the addition of other risk factors. The large difference in the predictive accuracy in this paper compared with the analysis in this thesis may reflect the definition of family history used. In our study, it was defined simply as presence/absence of heart disease in a first degree relative before the age of 60, whereas Scheuner *et al*. used a three level classification (17) (low, moderate, high, see Chapter 1) in their analyses (22, 23).

Our results are consistent with a theoretical paper by Wald *et al*.[81;82] which argues that a known risk factor does not necessarily translate into a strong predictor of disease and consequently is often a poor screening test. The authors argue that the combination of moderate risk factors does not necessarily result in additive improvements in predictive ability, rather the improvement can be small. This seemed to be the situation in our study.

Strengths and limitations

This study had both strengths and limitations. The original study used data from three sources, and the original investigators documented the steps taken to promote their validity. The first data source, the Aberdeen Maternity and Neonatal Databank, is a high quality database in which coding and case definition are given a high level of attention and data audits are carried out.[84-86] This extends to non-clinical variables such as coding social class according to the British Registrar General's classification. The second source of data was the self-report survey. The questionnaire was developed from several validated instruments, including the WHO (Rose) Angina Questionnaire,[74] and the main instrument

for the European Prospective Investigation into Cancer (http://epic.iarc.fr/index.php). The final source was the clinical examination, and the research team documented the steps they took to promote high intra- and inter-observer reliability, including research nurse training and the use of a standardized procedures manual.

In the early stages of the analysis, the availability of two sets of measurements for height and weight from the ASCHW questionnaire and clinical examination allowed us to examine the consistency of findings between the two methods of measurement and verify outliers. Similarly, the availability of two sets of measurements for blood pressure from the random zero and automated sphygmomanometers allowed us to investigate outliers for this variable and examine the consistency of findings also.

Despite this attention to validity, the analyses were inevitably constrained by the design of the original study. A major issue is that we were only able to perform a cross-sectional analysis. Although the data were derived from a cohort study, the variables of interest were obtained from the follow-up component. Thus, the analyses here evaluated the discriminatory accuracy of family history and other risk factors to detect current disease, not predict future disease. It is difficult to assess quantitatively the relationship between tests to detect and to predict disease, i.e. whether the findings from a cross-sectional analysis are more likely to under- or over-estimate the predictive scenario. In order to properly examine disease prediction, it is necessary to have a genuine longitudinal approach, which demands access to datasets where the full range of variables is available at the 'exposure' time point as well as a sufficient number of events to offer sufficient statistical power for meaningful analysis. Although the current study is limited, it at least sets out a framework for, and

highlights a number of issues in, assessing the role of family history in these kinds of enquiries.

Setting aside this major issue, there were some other aspects of study design which are relevant to its interpretation. Of considerable importance was that there were still variables of interest which were not captured adequately in the original study; this had important consequences for our analysis. For example, the ability to classify diabetes status using a more robust measure such as fasting plasma glucose was not available from the original study. Rather, we had to rely on self-report data for this important variable.

Another important issue was the case definition for the primary outcome, i.e. evidence of coronary heart disease. While this outcome is more directly clinically relevant than the only similar study,[23] where coronary artery calcium was used as a proxy, the ascertainment of cases was based on ECG findings and symptom self-report is likely to have led to misclassification errors.

The ECG data were evaluated using Minnesota coding, which is a well-developed and accepted method for the detection of cardiac electrical abnormalities.[76] It uses predetermined criteria to detect deviations from normal heart rhythm and allows for these deviations to be identified and classified accordingly. The coding was performed by professional coders. This allowed us to identify participants with clear abnormalities but who were asymptomatic. However, some individuals with significant atherosclerosis have normal ECGs at rest; therefore this approach produces some false negatives.[87]

The other approach to ascertaining cases was the WHO Questionnaire which is a well validated tool designed for the detection of angina and myocardial infarction in epidemiologic studies.[74;75] However, this relies on report of symptoms, and therefore fails to

identify individuals with silent ischaemic disease. The combination of ECG coding and symptom questionnaire is likely to reduce, but not eliminate, the false negative rate, but the rate of misclassification is unknown. We used a standard UK guideline, the JBS 2,(54) to select the variables of interest for our analyses. It should be noted that this guideline defines CVD as including stroke, whereas our outcome excluded it. However, the variables are common across many coronary heart disease risk assessment algorithms therefore this difference is probably not relevant to the current study. It is plausible (but still hypothetical) that the baseline AUC would have been higher for CHD plus stroke than for CHD alone, but if so this does not indicate that the family history information would have offered a greater incremental increase than for the CHD only analysis.

We also had to accept the self-reported nature of some of the variables, and the possibility for imprecision and bias that might have occurred as a consequence. While it is possible that all of the self-report data was subject to some reporting and recall errors, it is difficult to judge whether this would have had a biasing effect on the main analyses, and, if so, the direction of this effect. Perhaps of more concern is the likelihood of misclassification bias. For example, participants' diabetes status was ascertained from a single question on the questionnaire, and will have classified some undiagnosed diabetics as unaffected, whereas their true underlying CHD risk was probably higher than the genuinely unaffected. It is less likely that non-diabetics erroneously reported being affected. The net effect would be a reduction in the power of the analysis to detect an effect. Although the clinical examination data contained participants' random plasma glucose levels, guidelines published by the American Diabetes Society[88] and WHO[89] indicate that these are not sufficient for diagnosing diabetes in the absence of information on symptoms. Furthermore,

a previous study(62) suggested that random plasma glucose did not improve the predictive value of a Framingham-based risk model for CVD.

Smoking habit was also self-reported. Even with unbiased reporting, the inclusion of ex-smokers along with never smokers in the non-smoking reference group may have attenuated the risk difference between the two groups: studies have shown that there may be a time lag of 3-20 years before ex-smokers' risk equals the risk of never-smokers for coronary heart disease.[90-92]

Registrars General's social class is a variable which has been demonstrated to have a clear negative association with CVD[93;94] (i.e., higher occupational classes have lower rates of CVD); however, we did not observe this in our univariate analysis.. This may possibly be related to the differential tracing rates across the original cohort groups (noting that our analysis was based on those who could be traced and responded to the follow up invitations). In the original study, women in the control group (no gestational hypertension, pre-eclampsia or eclampsia) were most likely to have moved out of the area by the time of the follow up. They were also more likely to be in a higher social class at baseline. Whether this introduced bias, and the direction in which it might operate, is difficult to work out, but it may have altered the power of the analysis to identify an independent effect of social class on CHD.

Because of the original purpose of the ASCHW study, our sample was limited to females. However, most CHD research has been conducted on males, so this is not necessarily a weakness. Also, we used a sex-specific guideline in selecting variables for the models.

The original purpose of the ASCHW study was to examine the association between hypertensive conditions in pregnancy and the development of cardiovascular disease later in life. Therefore, there was the oversampling of women with a history of these conditions. The ASCHW study in fact suggested a positive association, which has been confirmed in several later studies.[95] However, the results of our univariate analysis did not support this hypothesis, which may reflect the limitations of the cross-sectional analysis and possibly the more limited definition of the outcome variable than the parent study.

Finally, we could have extended the analyses with a fuller consideration of some of the variables available in the dataset. For example, we examined body mass index (BMI) as a potential variable in the third model. It is a well developed and accepted standard for assessing risk of disease as a result of excess weight, and is also commonly used in clinical settings. However, BMI does not distinguish between muscle and fat as it is not sensitive to body composition. In a fuller analysis, we could have selected waist circumference as a better proxy for central obesity[96;97] and examined whether it made an independent contribution to the risk assessment.

Family history vs. genomic variants

To return to the original rationale for examining family history, we might consider whether it offers some insights relating to assessing the value of putative 'genomic tests'. Table 30 presents some similar published analyses of adding information on genetic polymorphisms to traditional risk factors for common complex disease. These suggest that the genetic variants might also have only limited discriminative accuracy for common complex diseases beyond traditional risk factors. In fact, if the findings of the study reported here were confirmed in further investigations, they might suggest that family history information offers at least as much incremental gain in risk prediction accuracy than adding information on several genetic variants. However, this is conjecture because of the limitations of the current study.

Table 30: Discriminatory accuracy of various genetic variants vs. clinical characteristics for common complex disease

Study	Disease	Clinical risk factors	Genetic Variants (n)	AUC clinical characteristics 95% CI	AUC genetic variants 95% CI	AUC combined 95% CI
Van Hoek et al.[98]	Type 2 Diabetes	Age, sex, BMI	18	0.66 (0.63-0.68)	0.60 (0.57-0.63)	0.68 (0.66-0.71)
Morrison et al.[99]	CHD	AGE, SBP, Total cholesterol, HDL, diabetes, anti-hypertensive medication, smoking	116	Whites: 0.764 Blacks: 0.758	-	Whites: 0.766 Blacks: 0.769
Lango et al.[100]	Type 2 Diabetes	BMI, age, gender	18	0.78	0.60	0.80
Lyssenko et al.[101]	Type 2 Diabetes	BMI, fasting plasma glucose	2	0.68	-	0.68
Vaxillare et al.[102]	Type 2 Diabetes	Age, sex, BMI	3	0.82	0.56	0.84
Zheng et al.[103]	Prostate Cancer	Age, region, FH	5	0.608 (59.1-62.4)	-	0.633 (61.7-65.0)
Paynter et al.[104]	CVD	AGE, Systolic BP, hypertensive medication, smoking, diabetes, total cholesterol, HDL	101	0.79	-	0.79
Payner et al.[105]	CVD	BP, smoking, diabetes, blood level of cholesterol, high-sensitivity C-reactive protein,	3	0.807	-	0.809

Study	Disease	Clinical risk factors	Genetic Variants (n)	AUC clinical characteristics 95% CI	AUC genetic variants 95% CI	AUC combined 95% CI
Van Hoek et al.[98]	Type 2 Diabetes	Age, sex, BMI	18	0.66 (0.63-0.68)	0.60 (0.57-0.63)	0.68 (0.66-0.71)
		FH of premature myocardial infraction				
Kathiresan et al.[106]	CVD	Age, sex, FH, LDL, HDL, BP, Triglycerides, BMI, Diabetes, smoking, drug therapy (antihypertensive, lipid-lowering), c-reactive protein	9	0.80	-	0.80

Conclusion and Implications

The 2009 NIH State-of-the-Science panel on Family History and Improving Health[14] concluded that currently there is weak evidence for supporting the use of family history in primary care and further research is needed to establish it as an evidence-based tool. The panel recommended that "future systematic reviews and search efforts should evaluate family history in combination with genetic and environmental variables, for its predictive value and its potential role in improving patient outcomes."

This thesis contributes to the evidence base on this issue and suggests that, not only are major chronic disease prevention guidelines highly inconsistent in how they incorporate the family history aspect, but also there may be limitations to the ability of family history to improve prediction of CHD beyond traditional risk factors. These observations need to be examined in further analyses in other datasets.

For family history to be useful in primary care it must at least be able to predict or detect disease at some clinically relevant level. Currently, the evidence base is weak on whether the family history provides information actually useful for clinical prevention, in comparison with information on 'standard' risk factors. If it is to be useful in assessing chronic disease risk across all patient populations, it is necessary to consider whether and how it should be incorporated into practice in a valid and efficient way. Therefore, before recommending either the inclusion or exclusion of family history as a risk marker, 'evidence-based' guidelines should take account of this lack of evidence base.

Our results indicate that family history, when used on its own, might plausibly have similar discriminatory ability to the standard array of clinical risk factors, suggesting potential as a means of fast and cheap risk classification of patients. However, this is

unlikely to occur in clinical practice where a range of risk factors are embedded in clinical guidelines and are accepted as standard of care. In addition, taken at face value, the results presented here cast doubt on the clinical utility of family history information in addition to these risk factors. The impact of family history within risk prediction algorithms depends not only on the 'ΔAUC' but on how the reclassification of risk plays out (e.g. whether it reflects a net gain in correct classification of true negatives or true positives) and on the absolute gains in morbidity and mortality, and the risks and costs of, the recommended alterations in preventive interventions which are applied.

Further research which replicates this general analysis strategy in longitudinal datasets is required. Such research needs to attend to the definition and ascertainment of CHD, the definitions of 'positive' family history, and be sufficiently powered to detect meaningful changes in predictive accuracy. This means also that the 'minimum clinically important difference' of improvements in risk classification need to be clearly defined, informed by quantitative evidence on the relative benefits, harms and costs of preventive interventions in appropriate target populations.

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Appendix 1-NIH Family History Future Research Recommendations

Structure or Characteristics of a Family History

1. What is a parsimonious series of questions (key elements) for use as a family history screening tool in primary care practice?
2. What are the environmental and lifestyle elements of a family history that are most useful in helping patients make positive changes in health-related behaviors?
3. What are the best methods and key elements to collect family history across multiple common disease entities (e.g., multiple diseases versus one)?
4. How do the accuracy and completeness of family history information vary according to the setting in which it is collected (e.g., specialty care, primary care, community outreach, the Internet)?
5. What is the optimal frequency for ascertaining and updating family history?
6. What are the best tools and methods for family history collection and interpretation?
7. What personnel and information technology resources and settings facilitate the collection of family histories that meet individual, community, and clinical goals?
8. What are the best statistical approaches to ascertain the benefit of one key element of family history relative to another element?
9. How does the definition of family in diverse racial, ethnic, religious, social, cultural, and economic population groups influence the collection and use of family history?
10. Do key elements of family history vary by race, ethnicity, religious belief, life stage, socioeconomic status, and culture?
11. How do family dynamics and health disorders affect an individual's awareness and ability to report on family health history?

Process of Acquiring a Family History

12. Who is the best family informant to convey a family history (i.e., the "family history expert")?
13. To what extent do demographic factors modify an informant's ability to provide an accurate family history?
14. How might individuals, their families, and communities be best engaged in the collection of family history over time?
15. What are methods to minimize the time for collecting family history? Are there approaches to the assessment of family history across several office visits, self-administered questionnaires, ancillary personnel, or record linkage that are effective?

16. How do the clinician's knowledge, attitudes, beliefs, training, and skills influence the ability to collect, interpret, and use family history?
17. How might family history, including environmental and behavioral risk factors, be improved by a systematic, technology-supported approach (e.g., electronic health records, record linkage, enhancing communication between family members)?
18. What are optimal ways to use family history in a primary care setting to identify individuals who can benefit from enhanced surveillance or referral to genetics services?
19. What are the key facilitators, incentives, and barriers for clinicians, individuals, families, and organizations for the collection of family history in primary care practice?

Expected Outcomes of Family History Interpretation

20. Besides disease risk assessment, what are the additional potential benefits to the individual, family, and clinician in taking a thorough family history; e.g., building trust and partnering through a personal interview in a primary care setting?
21. How and why does family history information change the behavior of the clinician?
22. How are family history interpretations and findings best communicated to the individual and family to change health and disease prevention and detection behaviors over time? What strategies will minimize potential harms?
23. What are the short- and long-term effects on individuals, families, and clinicians of inaccurate, misinterpreted, or unavailable family history information?
24. Can family history information be linked to genomic information or to important intermediate markers of common chronic diseases (e.g., body mass index, drug adherence, tobacco cessation) to predict change in outcome?
25. What are the short- and long-term effects on family dynamics of systematic family-history taking in diverse populations and cultural settings?

Appendix 2-Environemental Scan Search Strategy

Condition	Breast Cancer	Diabetes	CRC	Coronary Heart Disease	Asthma
Date searched:	*March 23, 2009*	*March 31, 2009*	*June 15, 2009*	*September 1, 2009*	*October 2, 2009*
Guideline Category:	*1.Prevention 2.Risk Assessment 3.Screening*	*1.Prevention 2.Risk Assessment 3.Screening*	*1.Prevention 2.Risk Assessment 3.Screening*	*1.Prevention 2.Risk 3.Assessment Screening*	*1.Prevention 2.Risk Assessment 3.Screening*
Year of publication limit:	*None*	*None*	*None*	*None*	*None*

Appendix 3-Environmental Scan Study Selection Form

Screening: Level 1

Reviewer:_____
RM: _____

1. Does this paper mention disease of interest (coronary heart disease, type II diabetes, asthma, colorectal and breast cancer)?

   1. No (exclude)
   2. Yes (include) – please answer question 2, if relevant
   3. Unsure (pass to level 2)

2. If there are any other reasons to exclude this article, please describe them here:
   _____
   _____

Screening: Level 2

Reviewer:_____
RM: _____

Does this paper meet the eligibility criteria?

1. No (exclude-note reason)
2. Yes (go to Abstraction Forms)
3. Don't know (need to resolve)

If question above was answered NO, please record reason:

1. not primary or secondary prevention
2. Other (Specify) _____
3. Don't know (need to resolve)

Appendix 4- Environmental Scan Excluded Studies

Author (Year)	Reason for Exclusion
Asthma	
British Occupational Health Research Foundation (BOHRF) (2004)(107)	high risk population
American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology (2003)(108)	not prevention
Kaiser Permanente Care Management Institute (2007)(109)	not prevention
National Heart, Lung and Blood Institute (2007)(110)	not prevention
National Heart, Lung and Blood Institute (2007)(110)	not prevention
Institute for Clinical Systems Improvement (ICSI) (2008)(111)	not prevention
Michigan Quality Improvement Consortium (2008)(112)	not prevention
Michigan Quality Improvement Consortium (2008)(113)	not prevention
Michigan Quality Improvement Consortium (2008)(114)	not prevention
American Academy of Pediatrics-Medical Specialty Society. (2008)(115)	not prevention
Scottish Intercollegiate Guidelines Network (SIGN), British Thoracic Society (2008)(116)	not prevention
Registered Nurses' Association of Ontario (RNAO) (2008)(117)	not prevention
Michigan Quality Improvement Consortium (2008)(118)	not prevention
Allergic Rhinitis and its impact on Asthma Workshop Group-Independent Expert Panel(119)	not prevention
Health Care for the Homeless (HCH) Clinician's Network-Medical Specialty Society, National Health Care for the Homeless Council Inc.(120)	not prevention
National Heart, Lung and Blood Institute (2007)(121)	not prevention
National Heart, Lung and Blood Institute (2007)(122)	not prevention
National Heart, Lung and Blood Institute (2007)(123)	not prevention
National Heart, Lung and Blood Institute (2007) (124)	not prevention

National Heart, Lung and Blood Institute (2007)(125)	not prevention
Kaiser Permanente Care Management Institute (2006)(126)	not prevention
American Academy of Pediatrics-Medical Specialty Society (2005)(127)	not prevention
American Academy of Pediatrics-Medical Specialty Society (2006)(128)	not prevention
Finish Medical Society Duodecim-Professional Association (2008)(129)	not prevention
Finish Medical Society Duodecim (2002)(130)	not prevention
Finish Medical Society Duodecim (2001)(131)	not prevention
American Society of Breast Disease (2004)(132)	high risk population
Royal College of Obstetricians and Gynecologists (RCOG) (2004) (133)	ineligible group (pregnant women) not population base
Singapore Ministry of Health, National Committee on Cancer Care (2004)(134)	not prevention
New York State Department of Health (2004)(135)	not disease/condition of interest
Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit (2004)(136)	not disease/condition of interest
The North American Menopause Society(137)	not disease/condition of interest
Berliner JL,et al. (2007)(138)	high risk population
Royal College of Obstetricians and Gynecologists (RCOG) (2004)(139)	not disease/condition of interest
Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit (2004)(140)	not disease/condition of interest
Gartner LM, et al. ((127)	not disease/condition of interest
Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit (2005)(141)	not disease/condition of interest
U.S. Preventive Services Task Force (2005)(142)	not disease/condition of interest
Khatcheressian JL, et al. (2006)(143)	not prevention
Green S, et al. (2006)(144)	not prevention
Breast Cancer Disease Site Group (2004)(145)	not prevention
Winer EP, et al. (2005)(146)	not prevention
Harvey JA, et al.(2006) ((147)	not prevention
Lyman GH et al. (2005)(148)	not prevention
U.S. Preventive Services Task Force (2005)(149)	high risk group (not prevention)
Harris L, et al. (2007) (150)	not prevention
University of Michigan Health System (2007) (151)	not prevention
Smith RA, et al. (2006)(152)	not prevention (early detection and resource availability recommendations)
Massachusetts Department of Mental Retardation, Univ of Massachusetts Medical School's Center for Developmental Disabilities Evaluation and Research (2003)(153)	ineligible group
American College of Obstetricians and Gynecologists (ACOG) (2003)(154)	missing
Desch CE, et al. (2005)(155)	not prevention
Cohen JL, et al (2005)(156)	not disease/ condition or

	interest
Massachusetts Department of Mental Retardation and University of Massachusetts Medical School's Center for Developmental Disabilities Evaluation and Research (2003)(153)	duplicate
Harris L, et al. (2007) (150)	duplicate
Figueredo A, et al. (2003)(157)	not prevention
New Zealand Guidelines Group (NZGG) (2004)(158)	not prevention
Locker GY, et al.(2006)(159)	not prevention
Wineawer SJ, et al. (2006)(160)	not prevention
Faculty of Family Planning and Reproductive Health Care(141)	duplicate
U.S. Preventive Services Task Force (2005)(142)	duplicate
Association of Coloproctology of Great Britain and Ireland(161)	not prevention
Heiken JP, et al. (2006)(162)	HTA assessment
Rex DK, et al. (2006)(163)	not prevention
Foran Melanson S et al (2006)(164).	not disease/ condition or interest
Institute for Clinical Systems Improvement (ICSI) (2008)(39)	duplicate
Kaiser Permanente Care Management Institute (2006(165))	missing
Finnish Medical Duodecim (2008)(166)	missing
University of Michigan Health System 92004)(42)	duplicate
Institute for Clinical Systems Improvement (ICSI) (2008)(39)	duplicate
Michigan Quality Improvement Consortium (18-49) (2008)(41)	duplicate
Michigan Quality Improvement Consortium (50-65+) (2008)(40)	duplicate
Scottish Intercollegiate Guidelines Network (SIGN) (2004)(167)	not prevention/not disease of interest
not stated (2005)(168)	not prevention
Van de Werf F, et al. (2003)(169)	not prevention
Mieres JH et al. (2005)(170)	not prevention
Lauer M et al. (2005)(171)	HTA (Assessment of procedure)
Dickstein K et al. (2008)(172)	not prevention
Betsy Lehman Center for Patient Safety and Medical Error Reduction (2007)(173)	not disease/condition of interest
Greenland P, et al. (2007)(174)	not prevention
AACE Diabetes Mellitus Clinical Practice Guidelines Task Force (2007)(175)	not disease/condition of interest
Scottish Intercollegiate Guidelines Network (SIGN) (2007)(176)	not prevention
Grines CL, et al. (2007)(177)	not prevention
American Diabetes Association (ADA) (2008)(178)	not disease/condition of interest
Anderson JL et al.(2007)(179)	NOT PREVENTION
Eagle KA, et al. (2004)(180)	NOT PREVENTION
New York State Department of Health (2007)(181)	ineligible group (HIV positive)

Snow V et al (2004)(182)	not prevention
National Kidney Foundation (2005)(183)	ineligible group (dialysis pt's)
Institute for Clinical Systems Improvement (ICSI).(2007)(184)	not prevention
Klein S, et al. (2004)(185)	not prevention
Patrono C et al.(2004)(186)	not prevention
University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program (2004)(187)	not prevention
Jitramontree N (2007)(188)	ineligible group
University of Michigan Health System (2009)(189)	not condition of interest
U.S. Preventive Services Task Force (2008)(190)	scientific statement/evidence review not a guideline
U.S. Preventive Services Task Force Recommendation(191)	not prevention
Mancia G, et al. (2007) (192)	not condition of interest
Veterans Administration Department of Defense (2004)(193)	not condition of interest
Singapore Ministry of Health (2006)(194)	not condition of interest
National Institute for Health and Clinical Excellence (NICE) (2006)(195)	not condition of interest
Grundy SM, et al.(2004)(196)	not condition of interest
Michigan Quality Improvement Consortium (2007) (197)	not condition of interest
Institute for Clinical Symptoms Improvement (ICSI) (2008)(39)	duplicate
Finish Medical Society Duodecim (2008)(198)	missing
Finish Medical Society Duodecim (2007)(199)	missing
none stated(200)	not disease/condition of interest
Leuder GT et al. (2005)(201)	not disease/condition of interest
American Medical Directors Association (AMDA) (2008)(202)	not prevention
Polycystic Ovary Syndrome Writing Committee (2005)(201)	not disease/condition of interest
National Collaborating Centre for Primary Care (2004)(203)	not prevention
KDOQI (2007)(204)	not prevention
AACE Diabetes Mellitus Clinical Practice Guidelines Task Force (2007) (205)	not prevention
National Collaborating Centre for Women's and Children's Health (2004)(206)	not disease/condition of interest
Joselin Diabetes Centre (2007) (207)	not prevention
AACE Diabetes Mellitus Clinical Practice Guidelines Task Force (2007)(205)	not disease/condition of interest
Silverstein J, et al. (2005)(208)	not disease/condition of interest
Kitabchi AE, et al.(2004)(209)	not prevention
Diabetes Coalition of California, California Diabetes Program (2005)(210)	not prevention
American College of Obstetricians and Gynecologists (ACOG) (2008)(211)	not disease/condition of interest

Canadian Stroke Network, Heart & Stroke Foundation of Canada (2006)(212)	not disease/condition of interest
Eyre H, et al.(2004)(213)	not a guideline/scientific statement
Kaiser Permanente Care Management Institute (2005)(214)	missing
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force (2007).(50)	ineligible population (pregnant women)
Institute for Clinical Systems Improvement (ICSI) (2008) (215)	ineligible population (pregnant women)
Michigan Quality Improvement Consortium (2008)(216)	not prevention
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force (2008)(205)	not prevention
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force (2008)(205)	not prevention
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force (2008).(205)	not prevention
American Diabetes Association (ADA) (2008) (178)	not prevention
American Diabetes Association (ADA) (2008) (178)	not prevention
U.S. Preventive Services Task Force (2008) (217)	not disease/condition of interest
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force.(2008)(205)	not prevention
American Diabetes Association (ADA) (2008) (178)	not disease/condition of interest
AACE Diabetes Mellitus Clinical Practical Guidelines Task Force(205)	not prevention
American Diabetes Association (ADA)(2008) (178)	not prevention
American Diabetes Association (ADA) (2008)(218)	not prevention
Vermont Program for Quality Health Care, Vermont Department of Health (2004)(219)	withdrawn
Veterans Health Administration, Department of Defense (2003)(220)	withdrawn
American Diabetes Association (2008)(221)	not prevention (medical nutrition therapy)
Finish Medical Duodecim (2007)(222)	not disease/condition of interest
International Diabetes Center (2003) (223)	not disease/condition of interest
International Diabetes Center (2004)(224)	not disease/condition of interest
U.S. Department of Veteran Affairs, Veterans Health Administration, Veterans Health Administration (2002)(222)	withdrawn
National Collaborating Center for Chronic Conditions (2004)(225)	not disease/condition of interest
Institute for Clinical Systems Improvement (ICSI) (2008)(226)	not disease/condition of interest
U.S. Department of Health and Human Resources, U.S. Department of Agriculture (2005)(227)	not disease/condition of interest
Qaseem A, et al. (2007)(228)	not prevention
American Diabets Association (ADA) (2008)(178)	not prevention
Gahagan S et al. (2003)(229)	ineligible group
Registered Nurses' Association of Ontario (RNAO)(230)	not prevention
Feig DS, et al. (2005)(231)	not prevention
Royal College of Obstetricians and Gynecologists (RCOG) (2003)(232)	not disease/condition of interest
Gartner LM et al. (233)	not disease/condition of interest

New York State Department of Health (2007)(234)	ineligible group (HIV pt's)
Michigan Quality Improvement Consortium (18-49) (2008)(41)	duplicate
Michigan Quality Improvement Consortium (50-65+) (2008)(40)	duplicate
University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program (2004)(235)	not prevention
Grundy SM, et al. (2004)(196)	duplicate
Krebs NF, Jacobson MS, American Academy of Pediatrics Committee on Nutrition. (2003)(236)	ineligible population
Van de Werf F, et al.(169)	duplicate
Lyons SS (2004)(237)	not disease/condition of interest
Qaseem A, et al. (2005)(238)	not disease/condition of interest
Hunt SA, et al. (2005) (239)	not disease/condition of interest
Wound, Ostomy and Continence Nurse Society (WOCN) (2004)(240)	not disease/condition of interest
U.S. Preventive Services Talks Force (2006)(241)	not disease/condition of interest
Institute for Clinical Systems Improvement (ICSI) (2008)(242)	not prevention
Betsy Lehman Center for Patient Safety and Medical Error Reduction (2007)(173)	duplicate
Finish Medical Society Duodecim (2008)(243)	not prevention
Basssand JP, et al.(2007) (244)	not disease/condition of interest
Jitramontree N (2007)(188)	duplicate
Texas Tech University Managed Health Care Network Pharmacy & Therapeutics Committee (2003)(245)	withdrawn
Philippine Academy of Ophthalmology (2001)(246)	not disease/condition of interest
Gidding SS, et al. (2005)(247)	ineligible population
Mieres JH, et al. (2005)(170)	duplicate
American Optometric Association (AOA) (2005)(248)	not disease/condition of interest
University of Texas at Austin, School of Nursing, Family Nurse Practitioner Program (2004)(249)	not disease/condition of interest
U.S. Preventive Services Task Force(250)	not disease/condition of interest
New York State Department of Health (2008)(251)	ineligible group (HIV)
Newborn Nursery QI Committee (2004)(252)	ineligible group (infants)
Bonham PA, Flmister BG (2008)(253)	not disease/condition of interest
Grabe M, et al. (2008)(254)	not prevention
Briggs C, et al. (2008) (255)	not prevention
Mosca L, et al. (2007)(49)	duplicate
Health Partners Dental Group and Clinics (2006)(256)	not disease/condition of interest
Massachusetts Department of Mental Retardation, Univ of Massachusetts Medical School's Center for Developmental Disabilities Evaluation and Research (2003)(257)	ineligible group
Baker S, et al.(2005)(258)	ineligible group
National Kidney Foundation (2005)(183)	ineligible group
The North American Menopause Society (2003)(137)	duplicate
Veterans Administration, Department of Defense (2004)(193)	duplicate
Joselin Diabetes Center (2006)(259)	not prevention
Sheard NF, et al. (2004)(260)	not prevention
Snow V, et al. (2004)(182)	not prevention
Institute for Clinical Systems Improvement (ICSI) (2008)(261)	not prevention

Joselin Diabetes Center & Joselin Clinic (2005)(262)	not disease/condition of interest
Graham I, et al. (2007)(36)	not disease/condition of interest
Klein S, et al. (2004)(263)	not prevention
International Diabetes Center (2003)(264)	missing

APPRAISAL OF GUIDELINES FOR RESEARCH & EVALUATION

AGREE

INSTRUMENT

The AGREE Collaboration

September 2001

ISBN 1 8981 8321 X

SUGGESTED CITATION:

The AGREE Collaboration.
Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument.
www.agreecollaboration.org

FUNDING:

The development of the AGREE Instrument was funded by a grant from the EU BIOMED2 Programme (BMH4-98-3669)

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Typeset by CA Group, London

INTRODUCTION

Purpose of the AGREE Instrument.

The purpose of the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument is to provide a framework for assessing the quality of clinical practice guidelines.

Clinical practice guidelines are 'systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances'[1]. Their purpose is 'to make explicit recommendations with a definite intent to influence what clinicians do'[2].

By quality of clinical practice guidelines we mean the confidence that the potential biases of guideline development have been addressed adequately and that the recommendations are both internally and externally valid, and are feasible for practice. This process involves taking into account the benefits, harms and costs of the recommendations, as well as the practical issues attached to them. Therefore, the assessment includes judgements about the methods used for developing the guidelines, the content of the final recommendations, and the factors linked to their uptake.

The AGREE Instrument assesses both the quality of the reporting, and the quality of some aspects of recommendations. It provides an assessment of the predicted validity of a guideline, that is the likelihood that it will achieve its intended outcome. It does not assess the impact of a guideline on patients' outcomes.

Most of the criteria contained in the AGREE Instrument are based on theoretical assumptions rather than on empirical evidence. They have been developed through discussions between researchers from several countries who have extensive experience and knowledge of clinical guidelines. Thus, the AGREE Instrument should be perceived as reflecting the current state of knowledge in the field.

Which guidelines can be appraised with the AGREE Instrument.

The AGREE Instrument is designed to assess guidelines developed by local, regional, national or international groups or affiliated governmental organisations. These include:

1. New guidelines
2. Existing guidelines
3. Updates of existing guidelines

The AGREE Instrument is generic and can be applied to guidelines in any disease area including those for diagnosis, health promotion, treatment or interventions. It is suitable for guidelines presented in paper or electronic format.

[1] Lohr KN, Field MJ. A provisional instrument for assessing clinical practice guidelines. In: Field MJ, Lohr KN (eds). Guidelines for clinical practice. From development to use. Washington D.C. National Academy Press, 1992.

[2] Hayward RSA, Wilson MC, Tunis SR, Bass EB, Guyatt G, for the Evidence-Based Medicine Working Group. Users' guides to the Medical Literature. VIII. How to Use Clinical Practice Guidelines. A. Are the Recommendations Valid? JAMA, 1995;274, 570-574.

INTRODUCTION

Who can use the AGREE Instrument?

The AGREE Instrument is intended to be used by the following groups:

i) By policy makers to help them decide which guidelines could be recommended for use in practice. In such instances, the instrument should be part of a formal assessment process.
ii) By guideline developers to follow a structured and rigorous development methodology and as a self-assessment tool to ensure that their guidelines are sound.
iii) By health care providers who wish to undertake their own assessment before adopting the recommendations
iv) By educators or teachers to help enhance critical appraisal skills amongst health professionals.

Key references

The following sources have been used for developing the AGREE Instrument criteria.

Lohr KN, Field MJ. A provisional instrument for assessing clinical practice guidelines. In: Field MJ, Lohr KN (eds). Guidelines for clinical practice. From development to use. Washington D.C. National Academy Press, 1992.

Cluzeau F, Littlejohns P, Grimshaw J, Feder G, Moran S. Development and application of a generic methodology to assess the quality of clinical guidelines. International Journal for Quality in Health Care 1999;11:21-28.

Grol R, Dalhuijzen J, Mokkink H, Thomas S, Veld C, Rutten G. Attributes of clinical guidelines that influence use of guidelines in general practice: observational study. BMJ 1998;317:858-861.

Lohr KN. The quality of practice guidelines and the quality of health care. In: Guidelines in health care. Report of a WHO Conference. January 1997, Baden-Baden: Nomos Verlagsgesellschaft, 1998.

INSTRUCTIONS FOR USE

Please read the following instructions carefully before using the AGREE Instrument.

1. Structure and content of the AGREE Instrument

AGREE consists of 23 key items organised in six domains. Each domain is intended to capture a separate dimension of guideline quality.

Scope and purpose (items 1-3) is concerned with the overall aim of the guideline, the specific clinical questions and the target patient population.

Stakeholder involvement (items 4-7) focuses on the extent to which the guideline represents the views of its intended users.

Rigour of development (items 8-14) relates to the process used to gather and synthesise the evidence, the methods to formulate the recommendations and to update them.

Clarity and presentation (items 15-18) deals with the language and format of the guideline.

Applicability (items 19-21) pertains to the likely organisational, behavioural and cost implications of applying the guideline.

Editorial independence (items 22-23) is concerned with the independence of the recommendations and acknowledgement of possible conflict of interest from the guideline development group.

2. Documentation

Appraisers should attempt to identify all information about the guideline development process prior to appraisal. This information may be contained in the same document as the recommendations or it may be summarised in a separate technical report, in published papers or in policy reports (e.g. guideline programmes). We recommend that you read the guideline and its accompanying documentation fully before you start the appraisal.

3. Number of appraisers

We recommend that each guideline is assessed by at least two appraisers and preferably four as this will increase the reliability of the assessment.

4. Response scale

Each item is rated on a 4-point scale ranging from 4 ‘Strongly Agree’ to 1 ‘Strongly Disagree’, with two mid points: 3 ‘Agree’ and 2 ‘Disagree’. The scale measures the extent to which a criterion (item) has been fulfilled.

- If you are confident that the criterion has been fully met then you should answer ‘Strongly Agree’.
- If you are confident that the criterion has not been fulfilled at all or if there is no information available then you should answer ‘Strongly Disagree’.
- If you are unsure that a criterion has been fulfilled, for example because the information is unclear or because only some of the recommendations fulfil the criterion, then you should answer ‘Agree’ or ‘Disagree’, depending on the extent to which you think the issue has been addressed.

5. User Guide

We have provided additional information in the User Guide adjacent to each item. This information is intended to help you understand the issues and concepts addressed by the item. Please read this guidance carefully before giving your response.

INSTRUCTIONS FOR USE

Please read the following instructions carefully before using the AGREE Instrument.

6. Comments

There is a box for comments next to each item. You should use this box to explain the reasons for your responses. For example, you may 'Strongly Disagree' because the information is not available, the item is not applicable, or the methodology described in the information provided is unsatisfactory. Space for further comments is provided at the end of the instrument.

7. Calculating domain scores

Domain scores can be calculated by summing up all the scores of the individual items in a domain and by standardising the total as a percentage of the maximum possible score for that domain.

Example:

If four appraisers give the following scores for Domain 1 (Scope & purpose):

	Item 1	Item 2	Item 3	Total
Appraiser 1	2	3	3	8
Appraiser 2	3	3	4	10
Appraiser 3	2	4	3	9
Appraiser 4	2	3	4	9
Total	**9**	**13**	**14**	**36**

Maximum possible score = 4 (strongly agree) x 3 (items) x 4 (appraisers) = 48
Minimum possible score = 1 (strongly disagree) x 3 (items) x 4 (appraisers) = 12

The standardised domain score will be:

$$\frac{\text{obtained score} - \text{minimum possible score}}{\text{Maximum possible score} - \text{minimum possible score}} =$$

$$\frac{36-12}{48-12} = \frac{24}{36} = 0.67 \times 100 = 67\%$$

Note:

The six domain scores are independent and should not be aggregated into a single quality score. Although the domain scores may be useful for comparing guidelines and will inform the decision as to whether or not to use or to recommend a guideline, it is not possible to set thresholds for the domain scores to mark a 'good' or 'bad' guideline.

8. Overall assessment

A section for overall assessment is included at the end of the instrument. This contains a series of options 'Strongly recommend', 'Recommend (with provisos or alterations)', 'Would not recommend' and 'Unsure'. The overall assessment requires the appraiser to make a judgement as to the quality of the guideline, taking each of the appraisal criteria into account.

SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

2. The clinical question(s) covered by the guideline is(are) specifically described.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

3. The patients to whom the guideline is meant to apply are specifically described.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

SCOPE AND PURPOSE

1.

This deals with the potential health impact of a guideline on society and populations of patients. The overall objective(s) of the guideline should be described in detail and the expected health benefits from the guideline should be specific to the clinical problem. For example specific statements would be:

- Preventing (long term) complications of patients with diabetes mellitus;
- Lowering the risk of subsequent vascular events in patients with previous myocardial infarction;
- Rational prescribing of antidepressants in a cost-effective way.

2.

A detailed description of the clinical questions covered by the guideline should be provided, particularly for the key recommendations (see item 17). Following the examples provided in question 1:

- How many times a year should the HbA1c be measured in patients with diabetes mellitus?
- What should the daily aspirin dosage for patients with proven acute myocardial infarction be?
- Are selective serotonin reuptake inhibitors (SSRIs) more cost-effective than tricyclic antidepressants (TCAs) in treatment of patients with depression?

3.

There should be a clear description of the target population to be covered by a guideline. The age range, sex, clinical description, comorbidity may be provided. For example:

- A guideline on the management of diabetes mellitus only includes patients with non-insulin dependent diabetes mellitus and excludes patients with cardiovascular comorbidity.
- A guideline on the management of depression only includes patients with major depression, according to the DSM-IV criteria, and excludes patients with psychotic symptoms and children.
- A guideline on screening of breast cancer only includes women, aged between 50 and 70 years, with no history of cancer and with no family history of breast cancer.

STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all the relevant professional groups.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

5. The patients' views and preferences have been sought.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

6. The target users of the guideline are clearly defined.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

7. The guideline has been piloted among target users.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

STAKEHOLDER INVOLVEMENT

4.

This item refers to the professionals who were involved at some stage of the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations. This item excludes individuals who have externally reviewed the guideline (see Item 13). Information about the composition, discipline and relevant expertise of the guideline development group should be provided.

5.

Information about patients' experiences and expectations of health care should inform the development of clinical guidelines. There are various methods for ensuring that patients' perspectives inform guideline development. For example, the development group could involve patients' representatives, information could be obtained from patient interviews, literature reviews of patients' experiences could be considered by the group. There should be evidence that this process has taken place.

6.

The target users should be clearly defined in the guideline, so they can immediately determine if the guideline is relevant to them. For example, the target users for a guideline on low back pain may include general practitioners, neurologists, orthopaedic surgeons, rheumatologists and physiotherapists.

7.

A guideline should have been pre-tested for further validation amongst its intended end users prior to publication. For example, a guideline may have been piloted in one or several primary care practices or hospitals. This process should be documented.

RIGOUR OF DEVELOPMENT

8. Systematic methods were used to search for evidence.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

9. The criteria for selecting the evidence are clearly described.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

10. The methods used for formulating the recommendations are clearly described.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

11. The health benefits, side effects and risks have been considered in formulating the recommendations.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

8.

Details of the strategy used to search for evidence should be provided including search terms used, sources consulted and dates of the literature covered. Sources may include electronic databases (e.g. MEDLINE, EMBASE, CINAHL), databases of systematic reviews (e.g. the Cochrane Library, DARE), handsearching journals, reviewing conference proceedings and other guidelines (e.g. the US National Guideline Clearinghouse, the German Guidelines Clearinghouse).

9.

Criteria for including/excluding evidence identified by the search should be provided. These criteria should be explicitly described and reasons for including and excluding evidence should be clearly stated. For example, guideline authors may decide to only include evidence from randomised clinical trials and to exclude articles not written in English.

10.

There should be a description of the methods used to formulate the recommendations and how final decisions were arrived at. Methods include for example, a voting system, formal consensus techniques (e.g. Delphi, Glaser techniques). Areas of disagreement and methods of resolving them should be specified.

11.

The guideline should consider health benefits, side effects, and risks of the recommendations.
For example, a guideline on the management of breast cancer may include a discussion on the overall effects on various final outcomes. These may include: survival, quality of life, adverse effects, and symptom management or a discussion comparing one treatment option to another. There should be evidence that these issues have been addressed.

RIGOUR OF DEVELOPMENT

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

14. A procedure for updating the guideline is provided.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

12.

There should be an explicit link between the recommendations and the evidence on which they are based. Each recommendation should be linked with a list of references on which it is based.

13.

A guideline should be reviewed externally before it is published. Reviewers should not have been involved in the development group and should include some experts in the clinical area and some methodological experts. Patients' representatives may also be included. A description of the methodology used to conduct the external review should be presented, which may include a list of the reviewers and their affiliation.

14.

Guidelines need to reflect current research. There should be a clear statement about the procedure for updating the guideline. For example, a timescale has been given, or a standing panel receives regularly updated literature searches and makes changes as required.

CLARITY AND PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

16. The different options for management of the condition are clearly presented.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

17. Key recommendations are easily identifiable.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

18. The guideline is supported with tools for application.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

CLARITY AND PRESENTATION

15.

A recommendation should provide a concrete and precise description of which management is appropriate in which situation and in what patient group, as permitted by the body of evidence.

- An example of a specific recommendation is: Antibiotics have to be prescribed in children of two years or older with acute otitis media if the complaint last longer than three days or if the complaint increase after the consultation despite adequate treatment with painkillers; in these cases amoxycillin should be given for 7 days (supplied with a dosage scheme).
- An example of a vague recommendation is: Antibiotics are indicated for cases with an abnormal or complicated course.

However, evidence is not always clear cut and there may be uncertainty about the best management. In this case the uncertainty should be stated in the guideline.

16.

A guideline should consider the different possible options for screening, prevention, diagnosis or treatment of the condition it covers. These possible options should be clearly presented in the guideline. For example, a recommendation on the management of depression may contain the following alternatives:

a. Treatment with TCA
b. Treatment with SSRI
c. Psychotherapy
d. Combination of pharmacological and psychological therapy

17.

Users should be able to find the most relevant recommendations easily. These recommendations answer the main clinical questions that have been covered by the guideline. They can be identified in different ways. For example, they can be summarised in a box, typed in bold, underlined or presented as flow charts or algorithms.

18.

For a guideline to be effective it needs to be disseminated and implemented with additional materials. These may include for example, a summary document, or a quick reference guide, educational tools, patients' leaflets, computer support, and should be provided with the guideline.

APPLICABILITY

19. The potential organisational barriers in applying the recommendations have been discussed.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

20. The potential cost implications of applying the recommendations have been considered.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

21. The guideline presents key review criteria for monitoring and/or audit purposes.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

APPLICABILITY

19.

Applying the recommendations may require changes in the current organisation of care within a service or a clinic which may be a barrier to using them in daily practice. Organisational changes that may be needed in order to apply the recommendations should be discussed. For example:

i. A guideline on stroke may recommend that care should be co-ordinated through stroke units and stroke services.

ii. A guideline on diabetes in primary care may require that patients are seen and followed up in diabetic clinics.

20.

The recommendations may require additional resources in order to be applied. For example, there may be a need for more specialised staff, new equipment, expensive drug treatment. These may have cost implications for health care budgets. There should be a discussion of the potential impact on resources in the guideline.

21.

Measuring the adherence to a guideline can enhance its use. This requires clearly defined review criteria that are derived from the key recommendations in the guideline. These should be presented. Examples of review criteria are:

- The HbA1c should be < 8.0%.
- The level of diastolic blood pressure should be < 95 mmHg.
- If complaints of acute otitis media lasts longer than three days amoxicillin should be prescribed.

EDITORIAL INDEPENDENCE

22. The guideline is editorially independent from the funding body.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

23. Conflicts of interest of guideline development members have been recorded.

Strongly Agree	4	3	2	1	Strongly Disagree

Comments

FURTHER COMMENTS

EDITORIAL INDEPENDENCE

22.

Some guidelines are developed with external funding (e.g. Government funding, charity organisations, pharmaceutical companies). Support may be in the form of financial contribution for the whole development, or for parts of it, e.g. printing of the guidelines. There should be an explicit statement that the views or interests of the funding body have not influenced the final recommendations.
Please note: If it is stated that a guideline was developed without external funding, then you should answer 'Strongly Agree'.

23.

There are circumstances when members of the development group may have conflicts of interest. For example, this would apply to a member of the development group whose research on the topic covered by the guideline is also funded by a pharmaceutical company. There should be an explicit statement that all group members have declared whether they have any conflict of interest.

FURTHER COMMENTS

OVERALL ASSESSMENT

Would you recommend these guidelines for use in practice?

Strongly recommend

Recommend
(with provisos or alterations)

Would not recommend

Unsure

Comments

NOTES

The AGREE Collaboration.
Appraisal of Guidelines for Research & Evaluation (AGREE) Instrument.
www.agreecollaboration.org

Appendix 6-Environmental Scan Data Abstraction Form

Form 1. Study Characteristics:

RM: _____ Journal/Association: _____

Reviewer: _____ Year of Publication: _____

Author: _____ Country: _____

Condition:_____

Patient Characteristics & Family History Items Mentioned:_____

Preventive Recommendation/s:_____

Evidence Cited:

GHB

GRAMPIAN HEALTH BOARD
AND
UNIVERSITY OF ABERDEEN

JOINT ETHICAL COMMITTEE

Chairman

Reverend Professor Alan Main
Faculty of Arts & Divinity
King's College
University of Aberdeen
Old Aberdeen

[redacted]

Clerk to the Committee

Ms Lynn Conway
Dept of Public Health Medicine

[redacted]

Project No: 2364

Dr W Cairns S Smith
Dept of Public Health
Medical School
Polwarth Building
Foresterhill
Aberdeen

Dear Dr Smith

Cardiovascular Sequelae of Pre-eclampsia and Gestational Hypertension

I am pleased to confirm that, following further discussion and amendments to the above project, ethical approval has now been given.

With regards to medical indemnity, I enclose a form which should be completed and returned to either: (i) Dr J Hern, Clinical Director, Aberdeen Royal Hospitals NHS Trust, Foresterhill House, Ashgrove Road West, Aberdeen, (ii) Dr R Scorgie, Medical Director, Grampian Healthcare NHS Trust, Westholme, Woodend Hospital, Aberdeen, or (iii) Clinical Director, Moray Health Services NHS Trust, 317 High Street, Elgin, as appropriate, if you wish one of the above Trusts to accept liability for medical indemnity for this project. Where drugs are received from a drug company for use in a trial, these must be stored in the Pharmacy Department for reasons of good practice.

I also enclose a standard Joint Ethical Committee proforma for future use. We would be very glad to receive, in due course, copies of any publications arising from this research.

Thank you for bringing this study to the Committee's attention.

Yours sincerely,

[redacted]

Lynn Conway,
Clerk to the Committee

GRAMPIAN HEALTH BOARD
AND
UNIVERSITY OF ABERDEEN

JOINT ETHICAL COMMITTEE

Chairman:

Reverend Professor Alan Main
Faculty of Arts & Divinity
King's College
University of Aberdeen
Old Aberdeen

Clerk to the Committee:

[redacted]

Our Ref: LC\IAA

30 January 1996

Dr W C S Smith
Reader in Public Health
Dept of Public Health
Medical School
Foresterhill
Aberdeen

Dear Dr Smith

The Aberdeen 1921 birth cohort - 75 year follow-up study

The above project was considered at the Joint Ethical Committee meeting of 25th January 1996, and I am pleased to confirm that ethical approval for this project has now been granted.

With regards to medical indemnity, I enclose a form which should be completed and returned to either: (i) Dr J Hern, Clinical Director, Aberdeen Royal Hospitals NHS Trust, Foresterhill House, Ashgrove Road West, Aberdeen, (ii) Dr R Scorgie, Medical Director, Grampian Healthcare NHS Trust, Westholme, Woodend Hospital, Aberdeen, or (iii) Clinical Director, Moray Health Services NHS Trust, 317 High Street, Elgin, as appropriate, if you wish one of the above Trusts to accept liability for medical indemnity for this project. Where drugs are received from a drug company for use in a trial, these must be stored in the Pharmacy Department for reasons of good practice.

We would be very glad to receive, in due course, copies of any publications arising from this research. Thank you for bringing this study to the Committee's attention.

Yours sincerely,

Lynn Conway,
Clerk to the Committee

Ottawa Hospital Research Ethics Boards / Conseils d'éthique en recherches

June 10, 2011

Dr. Brenda Wilson
University of Ottawa
Epidemiology & Community Medicine

Dear Dr. Wilson:

Re: Protocol # 2011409-01H Family History in the Risk Assessment of Common Complex Diseases

Protocol approval valid until - June 9, 2012

Thank you for the e-mail dated June 8, 2011 from Ms. J. Wells. I am pleased to inform you that this protocol underwent expedited review by the Ottawa Hospital Research Ethics Board (OHREB) and is approved. No changes, amendments or addenda may be made to the protocol or the consent form without the OHREB's review and approval.

If the study is to continue beyond the expiry date noted above, a Renewal Form should be submitted to the OHREB approximately six weeks prior to the current expiry date. If the study has been completed by this date, a Termination Report should be submitted.

The Ottawa Hospital Research Ethics Board is constituted in accordance with, and operates in compliance with the requirements of the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans; Health Canada Good Clinical Practice: Consolidated Guideline; Part C Division 5 of the Food and Drug Regulations of Health Canada; and the provisions of the Ontario Health Information Protection Act 2004 and its applicable Regulations.

Raphael Saginur, M.D.
Chairman
Ottawa Hospital Research Ethics Board

/cb

ABERDEEN STUDY OF CARDIOVASCULAR HEALTH IN WOMEN

This questionnaire asks for some background information about you and your health.

Please answer every question. If you are uncertain about how to answer a question then do the best you can, but please do not leave a question blank.

Your answers will be treated as strictly confidential and will be used only for medical research.

Thank you for taking the time to fill in this questionnaire.

British Heart Foundation
The heart research charity

PERSONAL HISTORY

1. **(a)** What is your date of birth?

Day	Month	Year

(b) What is your place of birth?

2. How tall are you in bare feet? **(write in ONE measurement)**

either ft inches **or** m cm

3. What weight are you without clothes? **(write in ONE measurement)**

either st lbs **or** kg

4. Please tick (✓) the box showing your present marital status

- Single (never married) ☐
- Married (first marriage) ☐
- Re-married ☐
- Divorced ☐
- Separated ☐
- Cohabiting (living with a partner) ☐
- Widowed ☐

5. Please list all previous surnames.

Maiden Name

Surnames

EMPLOYMENT

6. Whether working, retired, or looking after the home etc, which of the following things were you **and** your partner doing LAST WEEK?

(tick (✓) ONE box for you AND one for your partner)

	You	Your Partner
• Working for an employer full-time (more than 30 hours/week)	☐	☐
• Working for an employer part-time (less than 30 hours/week)	☐	☐
• Self-employed, employing other people	☐	☐
• Self-employed, not employing other people	☐	☐
• On government employment or training scheme	☐	☐
• Waiting to start a job which was already accepted	☐	☐
• Unemployed and looking for a job	☐	☐
• At school or in full-time education	☐	☐
• Unable to work because of long term illness	☐	☐
• Retired from paid work	☐	☐
• Looking after home and family	☐	☐
• Working for more than one employer	☐	☐

• Other, please specify

7. **(a)** Do **you** have a paid job at present? Yes ☐

No ☐ → **(Go to Q. 7d)**

If you are working please give the following details about your present **main** job.

(b) Full job title

	Please give the **full** title by which the job is known. Give rank or grade if you have one.

Main things done in job

	Write down the main things you actually do in the job. If manager or supervisor state how many persons you supervise.

Name of employer
(We will **not** contact employer. For our coding only)

	Please give trading name if one is used. If self-employed give name of business. Do not use abbreviations.

Description of employer's business

	Please describe clearly what your employer (or you if self-employed) make or do.

(c) Are you a:

- Manager ☐
- Supervisor ☐
- Neither ☐

(d) If you are **not** currently working, what did you do in your **last** job?

Please describe

8. (a) If married or living as married, does your **partner** have a job? Yes ☐

No ☐ → **(Go to Q. 9)**

(b) If **yes**, please describe your partner's job.

Full job title

	Please give the **full** title by which the job is known. Give rank or grade if you have one.

Main things done in job

	Write down the main things you actually do in the job. If manager or supervisor state how many persons you supervise.

Name of employer
(We will **not** contact employer. For our coding only)

	Please give trading name if one is used. If self-employed give name of business. Do not use abbreviations.

Description of employer's business

	Please describe clearly what your employer (or you if self-employed) make or do.

(c) Is your partner a:

- Manager ☐
- Supervisor ☐
- Neither ☐

9. If your partner is **not** currently working, what did he do in his **last** job?

Please describe

EDUCATION

10. For how many years, altogether, did you go to school or study **full-time** from the age of 5 years?

☐ Years

11. **(a)** What was the **highest** level of school education you completed **(tick (✓) ONE box)**

- Primary ☐
- Junior Secondary ☐
- Senior Secondary ☐

(b) Have you obtained any of the following qualifications? **(tick (✓) ALL appropriate boxes)**

- University Degrees ☐
- Diplomas, HNC, HND ☐
- Teaching qualifications ☐
- Nursing qualifications ☐
- Other professional, educational or vocational qualifications ☐
- Graduate or corporate membership of professional institutions ☐

HOUSING

12. Please tick (✓) the box which **BEST** describes how you and your household occupy your accommodation.

- As an owner/occupier (including purchase by mortgage) ☐
- By renting, rent free, or by lease -
  - **a)** from local authority ☐
  - **b)** from special housing authority ☐
  - **c)** from private landlord ☐
- Other, please specify ☐

SMOKING

For our study a regular smoker is someone who has smoked at least one cigarette, pipe, or cigar a day for at least one year.

13. **(a)** Have you **ever** been a regular smoker?

Yes ☐

No ☐ → **(Go to Q. 20)**

(b) If **yes**, are you **currently** a regular smoker?

Yes ☐

No ☐

14. What age were you when you **first** started smoking regularly? ☐ years

15. Which of the following statements best describes you at present? **(tick (✓) ONE box only)**

- I have only tried smoking once or twice ☐ → **(Go to Q. 18)**
- I have given up smoking ☐ → **(Go to Q. 18)**
- I smoke some days ☐
- I smoke every day ☐
- I gave up smoking, but restarted in the last year ☐ → **(Go to Q. 18)**

16. If you **CURRENTLY** smoke cigarettes

(a) How many a day do you **currently** smoke? **(tick (✓) ONE box)**

	number of cigarettes a day							
	less than 1	1-4	5-9	10-14	15-19	20-29	30-39	40 or more
I currently smoke...								

(b) How many did you smoke **this time last year**? **(tick (✓) ONE box)**

This time last year I smoked...								

17. (a) Have you ever smoked cigars?

- No, never ☐
- Used to, but not now ☐
- Now smoke occasionally (less than 1/day) ☐
- Now smoke regularly ☐

About how many cigars do you smoke per week? ☐ a week

(b) Have you ever smoked a pipe?

- No, never ☐
- Used to, but not now ☐
- Now smoke a pipe occasionally (less than 1/day) ☐
- Now smoke regularly ☐

About how much pipe tobacco do you smoke per week? ☐ ounces

NOW PLEASE GO TO Q. 20

18. If you **USED** to smoke cigarettes but no longer do, how many a day did you smoke previously? **(tick (✓) ONE box)**

	number of cigarettes a day							
	less than 1	1-4	5-9	10-14	15-19	20-29	30-39	40 or more
I currently smoke...								

19. (a) How old were you when you gave up smoking? ☐ years old

(b) Before you gave up smoking, for how many years **did** you smoke regularly?

- Less than 5 years ☐
- 5 - 10 years ☐
- 11 - 20 years ☐
- More than 20 years ☐

19. (c) Why did you give up smoking?

- Personal choice ☐
- Doctor's advice ☐
- Pregnancy ☐
- Definite illness ☐
- Other, please specify ☐

ALCOHOL

20. Which of the following statements best describes you? **(tick (✓) ONE box only)**

- I never drink alcohol ☐ → **(Go to Q. 22)**
- I have given up drinking ☐ → **(Go to Q. 22)**
- I drink alcohol very occasionally (eg one glass of sherry at Christmas or on special occasions) ☐
- I drink alcohol less often than once a month ☐
- I drink alcohol more often than once a month, but not weekly ☐
- I drink alcohol 1-2 days per week ☐
- I drink alcohol 3-5 days per week ☐
- I drink alcohol 6-7 days per week ☐

21. (a) Have you had an alcoholic drink **in the last 7 days**?

Yes ☐

No ☐ → **(Go to Q. 21c)**

21. (b) Think back carefully over the **last seven days**. Please write in the boxes below the amount of each type of drink that you have consumed on each day during the past week (eg bottles of beer, glasses of wine, etc).

	Mon	Tues	Wed	Thurs	Fri	Sat	Sun
Beers – cans or bottles							
Spirits – eg whisky, gin, vodka							
Table Wines							
Fortified Wines – eg sherry, port							
Low Alcohol Drinks							

(c) Have you reduced your alcohol intake in the last 5 years? Yes ☐

No ☐ → **(Go to Q. 23)**

(d) If yes, did you reduce because of:

	Yes	No
• Personal choice	☐	☐
• Doctor's advice	☐	☐
• Pregnancy	☐	☐
• Definite illness	☐	☐
• Religious belief	☐	☐
• Other, please specify		

NOW GO TO Q. 23 PLEASE

22. **(a)** If you **NEVER** drink alcohol, or if you have **GIVEN UP** drinking, is this because of:

	Yes	No
• Personal choice	☐	☐
• Religious beliefs	☐	☐
• Doctor's advice	☐	☐
• Pregnancy	☐	☐
• Definite illness	☐	☐

• Other, please specify ☐

(b) Did you drink in the past? Yes ☐ No ☐

(c) If yes, when did you last drink alcohol? Month ☐ Year ☐

PHYSICAL ACTIVITY

Think back over the **last seven days**

23. **(a)** How many **hours** a **day** do you do paid or voluntary work? ☐ hours a day

How many **hours** a **day** do you do housework? ☐ hours a day

(b) How many **days** a **week** do you do paid or voluntary work? ☐ days a week

How many **days** a **week** do you do housework? ☐ days a week

24. **(a)** When **working** (including housework), for how long are you physically very active, moderately active, or inactive on average **in a week?**

Very Active
(For example, heavy lifting or carrying, hurried walking, going up stairs and ladders, digging, strenuous exercise, heavy housework). ☐ hours a week

Moderately Active
(For example, light lifting or carrying, moderate walking, light housework, shopping, painting, decorating) ☐ hours a week

Inactive
(For example sitting, standing, light arm movements, unhurried walking, driving.) ☐ hours a week

24. (b) When **working** (including housework), how often are you physically active for **at least 20 minutes** during which time you become short of breath, perspire, and/or have a faster heart beat?

- More than 3 times a week ☐
- 2-3 times a week ☐
- Once a week ☐
- Less than once a week ☐
- Never ☐

25. (a) During your **non-working time** (including going to and from work), for how long are you physically very active, moderately active, or inactive on average in a week?

Very Active
(For example, competitive sports, football, hockey, squash, badminton, hill-walking, bicycling, swimming, running, aerobics, heavy gardening) ☐ hours a week

Moderately Active
(For example, moderate walking, golf, light gardening, cricket, dancing, bowls, playing pool, shopping, sailing, taking a shower or bath, getting dressed) ☐ hours a week

Inactive
(For example, sitting, standing, watching TV, listening to music, cooking, visiting the pub, drinking, eating, piano-playing, card-playing, driving. DO NOT COUNT TIME IN BED) ☐ hours a week

(b) During your **non-working time**, how often are you physically active for at least 20 minutes during which time you become short of breath, perspire, and/or have a faster heart beat?

- More than 3 times a week ☐
- 2-3 times a week ☐
- Once a week ☐
- Less than once a week ☐
- Never ☐

26. Would you say that over the past year your level of physical activity has

Increased ☐ Stayed the same ☐ Decreased ☐

If it has changed, for how many months has it been at its current level? ☐ months

27. How many hours a day do you usually spend in bed?

- On work days ☐ hours
- On non-work days ☐ hours

GENERAL HEALTH

28. How would you describe your usual state of health? **(tick (✓) ONE box only)**

- I am very healthy ☐
- I am reasonably healthy ☐
- I am sometimes well, sometimes not ☐
- I am not very healthy ☐
- I am in poor health ☐

29. Have you ever been told by a doctor that you have, or have had:

	Yes	No
• Angina	☐	☐
• Heart Attack	☐	☐
• Stroke	☐	☐
• High Blood Pressure	☐	☐
• Diabetes	☐	☐
• Deep Vein Thrombosis (DVT, clots in your leg)	☐	☐
• Asthma	☐	☐
• Kidney disease	☐	☐

30. Do you have any other medical problems for which you see a doctor regularly?

Yes ☐ → **(please specify below)**

No ☐

If **yes**, please specify ☐

31. Are you currently taking any medication for high blood pressure? Yes ☐ → **(please specify below)**
No ☐

If **yes**, please write the names of the medicine(s) you are taking for high blood pressure

32. Are you currently taking any medication for high cholesterol? Yes ☐ → **(please specify below)**
No ☐

If **yes**, please write the name of the medicine(s) you are taking for high cholesterol

33. Are you currently taking aspirin regularly? Yes ☐
No ☐

If **yes**, why are you taking aspirin?

- For your heart ☐
- For pain ☐
- Other reason, please describe

34. Are you regularly taking any other medication or vitamins, etc, at present?

Yes ☐
No ☐

If **yes**, please write the name of the medicine(s) and what you are taking them for (if you know). Please include all pills, bottles, tablets, inhalers (puffers), injections, etc.

35. Are you currently taking the contraceptive pill?

Yes ☐

No ☐

36. (a) Have you ever taken the contraceptive pill?

Yes ☐

No ☐ → **(Go to Q. 37)**

(b) If **yes**, for how many years in total have you taken the pill?

- Less than 1 year ☐
- 1 - 5 years ☐
- 6 - 10 years ☐
- Longer than 10 years ☐

37. (a) Have you ever used Hormone Replacement Therapy? (HRT)

Yes ☐

No ☐ → **(Go to Q. 38)**

(b) If **yes**, were you still having periods when you started HRT?

Yes ☐

No ☐

(c) Are you still using HRT?

Yes ☐

No ☐

38. (a) Are you still having periods?

- No ☐
- Yes, usual periods ☐
- Yes, but irregularly ☐
- Yes, but only because I am taking hormones (HRT) ☐

(b) If NO, when did they stop?

19 ☐

(c) Was this because of a hysterectomy? (operation to remove the womb)

Yes ☐

No ☐

39. (a) Have you ever been pregnant? Yes ☐

No ☐ → **(Go to Q. 43)**

(b) How many pregnancies have you had (including any who died at birth or in childhood)?

Please write in the number of pregnancies for each of the following:

- Still births ☐
- Miscarriages ☐
- Terminations ☐
- Live births ☐

40. List the dates of birth of all your children: (If you have any adopted children, please include them but write 'adopted' next to their date of birth)

1st Born	Day ☐	Month ☐	Year 19 ☐
2nd Born	Day ☐	Month ☐	Year 19 ☐
3rd Born	Day ☐	Month ☐	Year 19 ☐
4th Born	Day ☐	Month ☐	Year 19 ☐
5th Born	Day ☐	Month ☐	Year 19 ☐
6th Born	Day ☐	Month ☐	Year 19 ☐
7th Born	Day ☐	Month ☐	Year 19 ☐

41. Did you have high blood pressure during your **first** pregnancy? Yes ☐

No ☐

42. (a) Did you have high blood pressure during any of your other pregnancies?

Yes ☐

No ☐

(b) If **yes**, which pregnancies ☐

43. Did your mother have high blood pressure during any of her pregnancies?

- Yes ☐
- No ☐
- Don't know ☐

If **yes** which ones ☐

44. If you have any sisters, have any of them had high blood pressure during any of their pregnancies?

- Yes ☐
- No ☐
- Don't know ☐

45. Did your mother or father have heart disease before they were 60 years old?

- Yes ☐
- No ☐
- Don't know ☐
- Not yet 60 years old ☐

46. How many natural brothers and sisters do **you** have?

Brothers ☐ Sisters ☐

47. Did any of your brothers or sisters have heart disease before they were 60 years old?

- Yes ☐
- No ☐
- Don't know ☐
- They are not yet 60 years old ☐

CHEST PAIN

48. (a) Have you ever had any pain or discomfort in your chest?

Yes ☐

No ☐ → **(Go to Q. 50)**

(b) Do you get this pain or discomfort when you walk uphill or hurry?

Yes ☐

No ☐ → **(Go to Q. 49)**

(c) Do you get this pain or discomfort when you walk at an ordinary pace on level ground?

Yes ☐

No ☐

(d) When you get any pain or discomfort in your chest, what do you do? **(tick (✓) ONE box only please)**

- Stop ☐
- Slow Down ☐
- Continue at the same pace ☐

(e) Does it go away if you stand still?

Yes ☐

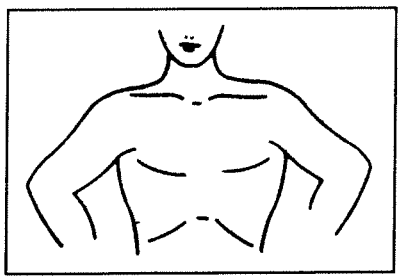
No ☐

(f) How long does it take to go away?

- 10 minutes or less ☐
- more than 10 minutes ☐

(g) Where do you get this pain or discomfort **(mark the place or places with an X on the diagram)**.

YOUR right **YOUR left**



49. Have you ever had a severe pain across the front of your chest lasting for **half an hour or more**?

Yes ☐

No ☐

LEG PROBLEMS

50. **(a)** Do you get a pain or discomfort in either leg on walking?

Yes ☐

No ☐ → **(Go to Q. 51)**

(b) Does this pain ever begin when you are standing still or sitting? Yes ☐

No ☐

(c) Do you get this pain in your calf (or calves)? Yes ☐

No ☐

(d) Do you get it when you walk uphill or hurry? Yes ☐

No ☐

(e) Do you get it when you walk at an ordinary pace on the level ground? Yes ☐

No ☐

(f) Does this pain ever disappear while you are still walking? Yes ☐

No ☐

(g) What do you do if you get it when you are walking?
(tick (✓) ONE box only please)

- Stop ☐
- Slow down ☐
- Continue at the same pace ☐

(h) What happens if you stand still? **(tick (✓) ONE box only please)**

- Pain usually continues for more than 10 minutes ☐
- Pain usually disappears in 10 minutes or less ☐

51. (a) Do you get short of breath walking with other people of your own age on level ground?

Yes ☐
No ☐

(b) Do you get more breathless than other people of your own age when walking uphill or upstairs?

Yes ☐
No ☐

(c) Do you ever have to stop walking because of breathlessness?

Yes ☐
No ☐

52. During the past month have you woken up with a feeling of tightness in your chest?

Yes ☐
No ☐

53. During the past month have you been woken by an attack of shortness of breath?

Yes ☐
No ☐

DIET

54. In a **typical week** how often do you eat these foods? **(tick (✓) ONE box for EACH type of food or drink)**

	6-7 days a week	3-5 days a week	1-2 days a week	less than 1 day a week	Rarely/ never
MEAT					
Fresh fish and shellfish					
Fish Products (eg fish fingers)					
Chicken or other poultry					
Red meat (eg lamb, beef, mince, pork)					
Offal (liver, kidney, etc.)					
Meat filled pies, sausage rolls, etc.					
VEGETABLES *(Fresh, tinned, dried, frozen)*					
Potatoes (baked, boiled, mashed)					
Raw vegetables					
Cooked vegetables					
Salad (eg lettuce, cucumber)					
FRUIT *(fresh, tinned, frozen)*					
Tomatoes					
Citrus fruits (eg oranges, lemons, grapefruit)					
Other fruit (eg apples, bananas, peaches, etc.)					
Berries					
BREAD and CEREALS					
White bread or rolls					
Brown bread or rolls					
Wholemeal / Granary bread or rolls					
Pasta					
Rice					
Pulses (lentils, peas, beans etc.)					
BISCUITS, PUDDINGS, SWEETS					
Cakes, scones, sweet pastries					
Confectionery, sweets, chocolate					
Ice-cream					
Plain biscuits					
Sweet biscuits					
OTHER FOODS					
Fried chips					
Other fried foods					
Soups					
Nuts					
Crisps					
DAIRY PRODUCTS					
Eggs					
Cheese					
Cream					
Milk					

55. Which kind of milk do you use most? **(tick (✓) ONE box only)**

- Whole milk (Full cream) ☐
- Semi-skimmed ☐
- Skimmed ☐
- Evaporated/Condensed milk ☐
- Soya/Vegetable-based milk ☐
- None ☐
- Other (please describe) _____

56. (a) Do you use butter, margarine or spread of any kind? Yes ☐

No ☐ → **(Go to Q. 57**

(b) If **yes**, please describe what brand of butter, margarine or spread you use.

_____

(c) How do you spread it? Thinly ☐ Average ☐ Thickly ☐

57. How much salt do you add to food when cooking?

A lot ☐ A little ☐ None ☐

58. How much salt do you add to food on your plate?

A lot ☐ A little ☐ None ☐

59. How many cups of coffee do you have a day? ☐ cups a day

60. How many cups of tea do you drink a day? ☐ cups a day

61. How many cups of water do you drink a day? ☐ cups a day

62. How many cups of fruit juice **do you drink a day?** ☐ cups a day

63. **(a)** Do you add sugar to hot drinks such as tea or coffee? Yes ☐

No ☐ → **(Go to Q. 64)**

(b) If **YES**, how many teaspoons of sugar do you add to each cup? ☐ teaspoons a cup

64. **(a)** Which one of the following best describes you at present? **(tick (✓) ONE box only please)**

- I eat meat (including poultry) and / or fish ☐
- I do not eat meat or fish ☐
- I do not eat any animal products ☐

(b) Do you regard yourself as vegetarian? Yes ☐

No ☐

(c) Do you regard yourself as vegan? Yes ☐

No ☐

65. **(a)** Are you on a special diet? Yes ☐

No ☐ → **(Go to Q. 66)**

(b) If **YES**, what kind of diet is it?

- Slimming - prescribed by a doctor ☐
- Slimming - decided by yourself ☐
- Diabetic ☐
- Cholesterol lowering ☐
- Other 'medical diet', please describe ☐

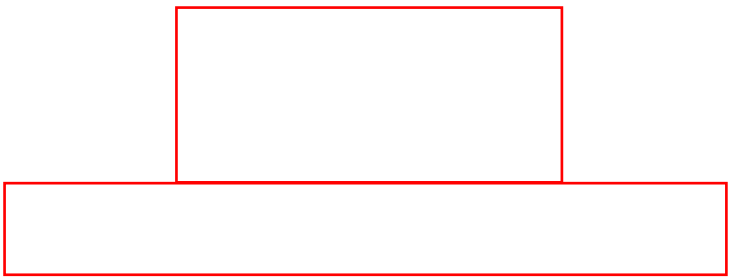
66. How long has it taken you to complete this questionnaire? ☐ mins

Thank you for your help

Please check you have answered every question,
then return this questionnaire in the reply paid envelope.

If you have any questions or difficulties with this questionnaire please contact:

Dr MS Watson
Department of Public Health
University of Aberdeen



Appendix 10 - ASCHW Clinical Examination Protocol

APRIL/MAY 1996 SS

ASCHW CLINICAL EXAMINATION PROTOCOLS MANUAL

Index

8.0 Maintenance and Checking Procedures

9.0 Incident Reports

Appendices

I	-	Examination form
II	-	Consent forms
III	-	Blood Pressure cuffs
IV	-	ECG Measurement
V	-	Universal blood and body fluid precautions.

1.0 Introduction

1.1 ASCHW

The purpose of the Aberdeen Study of Cardiovascular Health in Women (ASCHW) is to determine whether women who had a history of Pre-eclampsia and Gestational Hypertension during first pregnancies (between 1950 - 1970) are at a greater risk of developing cardiovascular disease in later life (i.e. hypertension, stroke, angina, myocardial infarction etc.).

The clinical examination of consenting participants will involve the measurement of several risk factors for cardio vascular disease, e.g. hypertension, cholesterol, smoking. These measurements are required to be performed according to standardised procedure to ensure accuracy of results and therefore accuracy of comparison between subjects. Hence the development of this protocols manual.

The ASCHW protocols manual was developed in April/May 1996 for the pilot study phase of clinical examinations commencing June 1996. It will be updated and/or modified as required prior to commencement of the Main Study Phase of clinical examinations in October 1996.

1.2 Arranging Appointments

1.2.1 For the Pilot Study

Following return by post of a completed questionnaire, women who volunteered to attend for a clinical examination are to be sent a letter with a pre-arranged appointment date and time stated. This appointment letter is to be sent 2 weeks prior to the intended clinical examination. A map of the Aberdeen Royal Infirmary complex and Foresterhill Health Centre is also to be included.

The participant may change the appointment time and date arranged for them by contacting the A.S.C.H.W. secretary at the Department of Public Health on
Tel: (01224) 663123 Ext. 52474.

1.2.2 For the Main Study

Two weeks prior to the date of the clinical examination, the sample of women selected from the 3 groups (pre-eclampsia, gestational hypertension and non-exposed) will be sent, by post, an ASCHW questionnaire along with a letter inviting them to attend for a clinical examination.

The letter, will explain the purpose of the study, and will state a pre-arranged appointment date and time. A map of the Aberdeen Royal Infirmary complex and Foresterhill Health Centre will also be included.

The participant may change the appointment date and time arranged for them by contacting the ASCHW Secretary at the Department of Public Health.

2.0 Screener Qualifications

Before the clinical examinations for ASCHW commence, the screener will have completed the following:

1) Be familiar with the ASCHW Questionnaire, consent forms and clinical examination procedures.

2) Be familiar with the equipment to be used during the Clinical Examination, and have practised using it.

3) B.P. Training

Undergone training in B.P. Measurement using test videotapes of recorded Korotkoff sounds, and through simultaneous testing with another, qualified, observer.

For this study training was undertaken in Ward 46 (ARI) Hypertension Research Clinic, using:

i) Simultaneous testing with another observer
ii) The Stuart Pharmaceuticals Ltd. test videotape - "The Measurement of B.P.", by Dr. Gareth Beevers, Reader in Medicine, University of Birmingham.

iii) The SHH/MONICA Study test videotape of recorded korotkoff sounds was also used as training. "Blood Pressure Test Series 1, 2, 3 by Dr. Caroline Morrison, Glasgow.

4) ECG Training

Training was undertaken -

i) ARI, Wards 19/20, Cardiology Unit, under the guidance of the Cardiac Technicians.

ii) Through the "Beaver" Company representative who provided training in the correct use of the HP Pagewriter 100 Cardiograph.

iii) In the correct use of the HP Pagewriter, and the correct technique for performing and ECG, through the "HP Training Video".

5) Venepuncture Training

This was achieved under the guidance of the phlebotomists on Ward 23/24/25 and 26 ARI over a period of 2 weeks. A letter of competence has been signed by Dr. I. Ross, Head of Biochemistry Department.

6) Hepatitis B Status Checked

This was done on 11/04/96 by Dr. W. Irvine at Occupational Health, University of Aberdeen.

7) Should have had a hearing test.

8) Should have had a sight test

3.0 Measurements to be Made

The following measurements are to be made at the examination (specific descriptions of each measurement are to be found at No. 6.0).

1. Height and Weight
2. Blood Prssure - with HRZS and Omron
3. ECG
4. Expired Carbon Monoxide
5. Respiratory Function Tests
6. Blood Taken for ....

4.0 Examination Flow

The clinical examination appointment is expected to take approximately 30 - 40 minutes from start to finish. The appointment should flow smoothly, and be as uninterrupted as possible. The following examination flow outline will be standard for all participants.

1. Consent must precede all procedures.
2. Height and Weight must precede B.P.
3. B.P. must precede venepuncture.

If the participant agrees to complete only part of the examination due to lack of time, or because of refusal to have certain measurements taken, the following measurements are the priorities:

1. Consent

2. Height, Weight, B.P.

3. Venepuncture.

If consent cannot be obtained then no measurements are to be made.

5.0 Procedure for Assigning ID/Reference Labels to Participants

Participants will have a screening reference number assigned to them, in numerical order of their attendance for clinical examination.

This number will be extra to their study number, and will be used to label the following:

- consent forms
- examination form(s)
- ECG trace
- Omron printouts

- Spirometry printout
- Blood tubes
- Blood request form(s)

One master copy of screening reference numbers (assigned at clinical examinations) matched with study numbers (assigned to participants sent questionnaires) will be kept.

6.0 PROTOCOLS FOR MEASUREMENT

6.1 RECEPTION

This is the initial contact the client/respondent will have with the study, therefore, it is important to create a good impression. An organised and professional manner is essential to allay anxiety in the client.

The examiner must be familiar with every aspect of the study, and must be prepared to answer any questions the participant may have.

Procedure

1) Welcome participant, do not use first name, using last name preceded by Ms./Miss/Mrs. is more professional. Reassure her she has come to the correct place. Thank her for coming - ask her to sit down.

2) Introduce yourself.

3) Check name, address, date of birth and G.P. details on lists and questionnaire (record time in and out).

4) Explain purpose of study - some participants may be confused as to why they are there. (Are they at risk of heart attack? Is there a family history of heart disease). Reassure them and explain the random nature of selection of the participants.

5). If the participant seems very anxious try to allay anxiety. Stressing the importance of the participant's help in the research project, is reassuring.

6) Explain the consent form(s) and (their) purpose. Let participant read through (them). Ensure participant realises there is no obligation to take part in the study, or to agree to all parts of the study, (but the more they feel able to co-operate, the better will be our chances of understanding heart disease as it relates to pre-eclampsia and gestational hypertension).

Ensure you both sign the consent form(s) and date them.

Affix a screening reference label to the consent form(s)

7) Go through the questionnaire with the participant and clarify any points such as missed questions or ambiguous information.

Equipment List

Questionnaire	Consent Forms
Labels	Stapler
Participant list and Study Numbers	Red Pen

6.2 Height Measurement

Purpose

The measurement of height is important to the interpretation of weight. Weight can be mathematically related to height in order to determine if an individual is overweight, given his/her height. To be effective, height must be measured directly and recorded accurately.

Procedure -

1) Height is measured in conjunction with weight; either measurement may be made first.

2) The stadiometer must be placed on a hard flat surface, with no moulding, with the base at floor level.

3) Ask participant to remove shoes and heavy outer garments and and heavy pocket contents.

4) Participant should stand on the stadiometer platform with her back to the height rule. The back of head, back, buttocks, calves and heels should be touching the height rule, feet together. Ask participant to hold head in a position where she can look straight at a spot, head high, on the opposite wall. The top of the external auditory meatus (ear canal should be level with the inferior margin of the bony orbit (cheek bone).

5) Lower the carriage and slide to the head so that hair is pressed flat.

6) The screener's eyes should be level with participants auditory meatus for the correct position from which to read height.

7) Record the height on the examination form (to the nearest cm)
e.g. if 187.4 - record as 187
if 187.5 - record as 188
if 187.6 - record as 188

8) Use a conversion table to give participant height in feet and inches if requested.

9) Do <u>not</u> record self-reported heights in ambulatory participants (mark as refusal).

If participant is non-ambulatory, note this on their examination form (and record their self-reported height).

Quality Control

1) The stadiometer should be checked daily for secure position, and contact with the floor.
2) Screener should check the accuracy of the stadiometer against a 1½ m rule. The Stadiometer should also be checked with a carpenters level to ensure vertical position.

Equipment

Stadiometer
2m metal ruler
carpenters level
conversion table

6.3 Weight Measurement

Purpose

The measurement of body weight is an important source of information for the study. Along with height (to adjust for body size), it gives an excellent indication of obesity. This characteristic of weight (obesity) relates strongly to other health characteristics such as blood pressure and blood lipids.

To use the weight information effectively, the measurement must be done precisely according to protocol and recorded carefully.

Procedure

1) Ensure that the floor surface, on which the scales rest, is hard.

2) Ask participant to remove shoes and heavy outer clothing (eg. coats etc.)

3) Before participant stands on the scale, briefly cover the solar cell and wait for the readout to go through it's sequence until it says "0.0". Now the scales are automatically zeroed.

4) Ask participant to stand still on the centre of the platform. Standing off centre may affect measurement.

5) Once the digital reading has settled, read and record exactly to 0.1 kg.

6) Do not record self-reported weights of ambulatory participants. If participant is non-ambulatory record as such on examination form (and record self-reported weight).

   If participant refuses to be weighed, document as refusal.

Quality Control

1) If scales cannot be started, or the error signs E01 - E04 are displayed - refer to the Seca 870 manual for troubleshooting guidelines.

2) Accuracy of scales may vary over time and with movement between clinical examination centres.

3) Scales should be tested every morning with a standard 5kg weight.

6.4 Body Circumference

Ratio of waist/hip circumference is, for adults, an indication of fat distribution.

A high ratio is an indicator of "android" or abdominal fat distribution, and in these patients morbidity and mortality have been found to be elevated. A low ratio is an indicator of a "gynoid" fat distribution.

6.5 Blood Pressure Measurement

Purpose

Elevated Blood Pressure, or Hypertension, is one of the risk factors of cardiovascular disease.
For the study, the measurement of Blood Pressure is an important data point. For this reason the Hawksley random zero sphygmomanometer (HRZS) is used, rather than the simpler standard mercury column sphygmomanometers, to aid in reducing observer bias.

The measurement of Blood Pressure must be carried out in a calm setting, according to a strict protocol/standardised technique, by staff trained and tested according to protocol. In 1986, the British Hypertension Study (B.H.S) published recommendations on Blood Pressure measurement. The following protocol is based on these recommendations (Petrie, J.C. et al 1987).

We shall also measure Blood Pressure later in the examination also using an Omron automated sphygmomanometer.

Procedure

1) Room temperature must be 18 - 24°C unless unavoidable, as Blood Pressure varies with ambient temperature.

2) Blood Pressure is measured in conjunction with height/weight measurement, and must follow this procedure.

3) a) Participant should have already removed heavy outer garments. If not ask participant to remove them now.

   b) An explanation of the procedure will help to allay anxiety related to an unknown, or unfamiliar, procedure.

4) Ask participant to roll up loose sleeves of blouses/shirts etc. If sleeves are too constrictive, then whole arm should be removed from sleeve. Blood Pressure cuff should not be placed over the garment. Upper arm must be bare for the Blood Pressure cuff.

5) i) Seat the participant with her right arm on the table, palm facing upwards. The right arm is used as Blood Pressure is generally higher in this arm due to he origin of innominate arteries. (Hunyor, S.N. 1990, p.97).

   ii) If the right arm is injured/diseased/missing then use the left arm after changing chairs with the participant. Document this change of protocol on the examination form.

iii) Ensure participant is seated conformably, with legs uncrossed and feet flat on floor. Adjust arm level so that antecubital fossa (elbow) is supported at level of mid-sternum (heart level) - (by altering position of body in chair).

iv) Measure upper arm circumference using tape measure and choose the correct cuff size. (See Appendix III)

Cuff Size	Max. Arm Circumference
Standard adult cuff	25-35 cm.
Large arm cuff	33-47 cm.

6) Palpate the brachial artery and place cuff around the upper right arm at approximately heart level. The lower edge of the cuff should be 2 - 3 cm above the natural crease across inner aspect of elbow. The centre of the cuff bladder - marked on cuff with X - should be placed directly over brachial artery. The cuff tubing may be placed -

a) superiorly so that it does not interfere with auscultation (British Hypertension Society recommendation).

b) with tubes inferiorly and laying symmetrically across the arm with connecting tube to sphyg away from body and tube to inflating bulb is close to body.

The cuff should be wrapped and secured firmly around the upper arm by applying pressure on the Velcro fastening fabric where it is applied to the cuff.

Record time, room temperature on examination form. Also record any unusual circumstances, eg. right arm absent.

Record any drugs patient is currently taking on examination form.

7) The British Hypertension Society recommends 3 minutes seated rest period prior to taking Blood Pressure and 30 seconds between repeated measurements.

Use this time to check through the questionnaire and attach ID screening reference to all forms (and blood tubes). Explain to participant what you are going to do with a statement such as :

"You need to have a rest for about 3 minutes with legs uncrossed before I take your blood pressure. I will be taking your blood pressure twice and will write down the average of the readings for you as a record of what your B.P. was today. The Blood Pressure machine I will use requires calculation before I get the actual B.P readings, so if you see me writing down numbers that seem strange, don't be concerned. While I'm taking your Blood Pressure, I can't hear you very well because of the stethoscope. If you

have any questions, please wait until I've finished taking your Blood Pressure and then I will answer them".

Try and avoid further discussion during the rest period unless it is needed to allay anxiety.

8) Measurement of heart rate is performed immediately prior to Blood Pressure measurement - with B.P. cuff in place and after the 3 minute rest period. Record the number of beats in 30 seconds on the examination form in the space provided.

9) Place the HRZS alongside the right arm in such a way that the mid-point of the mercury column is at eye level, and the ante cubital fossa (elbow) is at heart level (4th intercostal space - level).

10) For measurement with the HRZS follow these specific steps:-

a) Connect the cuff tubing to the RZ device.

b) Turn the diaphragm tap to "open" (to the right)/
The meniscus of mercury in an adequately filled instrument should settle at about 80 mm Hg.

c) Turn the thumb wheel at the right side of the HRZS by gently stroking it two times with the thumb of the right hand. This will cause the level of "zero" to change to a level unknown to the operator. If the wheel is not free to spin in either direction, the bellows are not completely deflated and the bellows check position (diaphragm tap) should be rechecked.

d) The cuff is inflated to above 240 mmHg and is maintained at that level for 5 seconds (by closing the inflation thumb valve) to allow the diaphragm to fill properly.

Failure to allow this interval restricts the range of zero values.

Turn the diaphragm tap to the left to "close" position.

Now measure the participant's Blood Pressure with stethoscope in position over point of maximal pulsation of brachial artery.

e) The mercury column is then allowed to fall by carefully controlling the constant release/thumb valve at) rate of 2mmHg/sec until mercury level is 4 - 6 mmHg below the diastolic reading.

f) After the SBP and DBP have been recorded by the observer any remaining pressure is released by opening the thumb valve

fully and disconnecting the tubing to the random zero device, allowing the mercury to fall to its zero level for this reading. This may take several seconds.

g) Record the SBP and DBP uncorrected on the examination form. SBP = Phase I Korotkov sounds - point where repetitive clear tapping sounds first appear for 2 consecutive beats. DBP = Phase V Korotkov - where repetitive sounds disappear.

h) Once the system has come into equilibrium the "random zero" reading, which will lie between 0 - 60 mmHg, is read from the mercury meniscus.

Record this "zero" level on the examination form beneath the uncorrected SBP and DBP.

This figure is then subtracted from the uncorrected SBP and DBP readings to give the corrected or true SBP and DBP.

11) Repeat the measurement following steps 10 a - h) above.

12) Add the 1st and 2nd SBP readings together to give a total.
Add the 1st and 2nd DBP readings together to give a total.

13) Using a calculator, calculate the mean SBP and DBP readings by dividing the total values by 2 and record these on the examination form.

14) Remove the Blood Pressure cuff and assist participant to re-dress if shirt/blouse removed.

Standard

The same person is to take BP readings from all women enrolled in the study. BP is to be taken after sitting for 3 minutes with notless than a 30 second gap between consecutive readings. H.R is to be determined immediately prior to B.P.

2 BP measurements to be taken in the same arm, and the mean taken. Korotkov phase V to be used to indicate DBP unless absent, then use phase IV. SBP is to be recorded when Korotkov phase I sounds are heard.

Observer Training

1) Hearing and sight tests to ascertain no auditory or visual impairment which could interfere with the accurate measurement of B.P.

2) Trained using the Ward 46 Video Tape. Required to achieve an accuracy of ± 2 mmHg in at least 8/10 test readings on the tapes.

Performing readings with trained supervisor on a Y tube stethoscope -the 2 measurements will be recorded and discrepancies discussed (monthly testing).

HRZS

- Will be calibrated by Medical Physics Department of ARI at start of the study and every 3 months during the study. Date checked to be taped on side of instrument.

- Any malfunction of HRZS should be reported to Hawksley & Sons, West Sussex immediately and the instrument returned for repair/replacement.

(?) Medical Physics to check.

Equipment

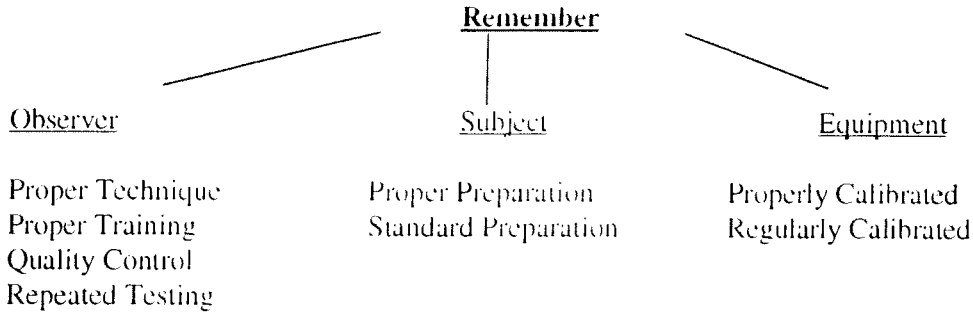
HRZS x 2
Omron HEM 705 CP X 2
Electronic Pocket Calculator
B.P. Cuffs - standard adult cuff & large arm cuff
Chair
Arm - level table
Watch with second hand or stop watch tape measure.

Information for Participant

Before attending the clinic for examination the participant should be given the following instructions which are aimed at removing many of the stimuli that can cause variation in B.P. levels.

Avoid for at least one hour prior to examination:

a) strenuous exercise
b) smoking
c) eating
d) drinking (except water)
e) prolonged exposure to extreme temperature
f) a full bladder
g) ingestion of drugs that affect B.P. If taking drugs for HT, participant should be instructed to take them at the usual time. Any drugs taken by a person should be recorded on examination form.
h) tight clothing - participant should be instructed to wear sleeveless or loose fitting blouse.



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6.6 ECG Measurement

Purpose

The ECG is an important source of information in the assessment of individuals with conditions affecting the cardiovascular system. It records, through electrodes on the body surface, an electrical picture of the heart. Comparison of these electrical events enables the heart to be "looked at" from different directions. For the purposes of this study, we shall be using the 12 lead ECG as a tool for screening for heart disease.

Procedure

The instrument used will be the Hewlett Packard Pagewriter 100 Cardiograph (Model No. HP M1772A).
Room Temperature should be maintained at a comfortable level to prevent the participant shivering or sweating. Smoking and heavy physical exercise should be avoided for 1 hour prior to the recording.
Proper participant preparation and electrode placement are the most important elements in producing a high quality ECG trace.

1) The participant should be as relaxed and comfortable as possible. Participant movement involves muscle activity which will affect the recording. Reassure the participant by explaining the procedure and ensuring she is aware that it is painless.

2) The ECG recording may be disturbed by electrical interference, whether from static, nearby electrical equipment and fixtures, or the participant herself. In order to minimise this disturbance, it is important to record the ECG in an area free from electrical interference.

3) Ensure the participant is comfortable and is lying on the examination couch located away from electrical futures and their power cords, and even away from the power cord of the cardiograph (HP user guide pg.2 - 2).

4) Ensure the cardiograph is turned on by pressing the on/standby button. The front panel lights are lit as the cardiograph performs a short power - on sequence.

5) Expose the participant's forearms, lower legs, and chest. Gently clean and abrade the surface of the skin with dry gauze.

6) Locate the 4 limb lead and 6 chest lead positions as follows, and apply disposable tab electrodes. (Also see appendix II for pictorial representation)

Limb Leads

i) Locate electrode (RA) (Red) on Right Forearm - outer aspect.
ii) Locate electrode (LA) (Yellow) on Left Forearm - outer aspect
iii) Locate electrode (LL) (Green) on Left Leg - inner or outer aspect
iv) Locate electrode (RL) (black) on Right Leg - inner or outer aspect (this is the earthing limb).

Chest Leads

i) Electrode **(V1)** - locate the angle between sternum and 2nd right rib with index and middle finger of right hand. Count down to 4th intercostal space below it. Locate V1 in the 4th intercostal space at the right sternal border.Mark with a dot.

ii) Electrode **(V2)** - locate V2 in the 4th intercostal space at the left sternal border. This should be at the same level as V1, and immediately to the left of the sternum. Mark with a dot.

iii) Electrodes **(V3 - V6)**

a) Identify the 5th intercostal space below V2 in the manner described above. Follow this space to the midsternal line and mark this location with a dot. This is the "E" point.

b) **(V6)** - 5th intercostal space, mid-axillary line. Mark with a dot.

c) **(V4)** - using a tape measure, calculate the distance from "E" point to V6. The mid point is V4. Mark with a dot (mid clavicular and 5th intercostal space)

d) **(V5)** - 5th intercostal space and mid-point between V5 and V6 (anterior - axillary)

e) **(V3)** - measure in a straight line the distance between V2 and V4. The mid-point is V3

7) Apply electrodes

8) Connect the jaws of the clips onto the metal tab of the electrode, ensuring electrode remains flat. Gently tug on the clip to ensure it is properly placed on the electrode. Don't place jaw of clips so close to the electrode that contact is made with the conductive gel. To avoid the tab-electrodes coming adrift, ensure all cables are fully supported so that they do not drag electrodes away from the participant.

9) Record an Auto ECG.

Press (Auto) on the front panel. The light above the (Auto) key flashes while the cardiograph is acquiring the ECG. When the cardiograph begins printing

the 12 lead ECG, the (Auto) light stays on. When the ECG report is finished, the light turns off.

10) Assess the ECG for AC interference, muscle tremor or baseline wander, and repeat as required.

11) Disconnect the participant from the leads and remove electrodes. Assist the participant to put clothes back on.

12) Attach a screening reference number label to the ECG.

Standard

Use the cardiograph on battery power. When not in use on patient, leave it plugged in to AC power to recharge.

The ECG is to be taken with the Filters - OFF (H.P Manual, para. 2 - 5) in order to achieve accurate ECG ST contours. In this mode the 0.15 - 150 Hz filters will be activated, instead of the 0.5 - 40 default settings when Filters - ON.\

Calibration of ECG

The machine is serviced by the medical physics department, Aberdeen Royal Infirmary at the start of the study and as required for malfunction thereafter.

Calibration is carried out automatically as each reading is made.

Training

The examiner will be trained in the recording of ECG's by the Beaver HP representative and by the cardiac technicians at Aberdeen Royal Infirmary.

The working of the ECG machine will be explained during the training session with the Beaver HP representative.

The HP training video will also be used to explain the working of the pagewriter and the technique for recording an ECG.

The HP Pagewriter user Guide is available for reference use.

Equipment

HP Pagewriter 100 Cardiograph
Patient Leads
HP Thermal ECG Paper
HP Disposable Electrodes
Tape Measure

6.7 BP - Omron HEM 705 CP

Purpose - as for HRZS

Standard - as for HRZS

Procedure based on Omron Instruction Manual except right arm will be used rather than left, as suggested in manufacturers manual. This is for same reason as highlighted in HRZS - right arm BP is generally higher due to innominate arteries. (Handbook of HT Chapter 4.)

1. Batteries should already be insitu. If not install and set date and time, as per manufacturers guidelines.

2. Printer Paper should be mounted as per manufacturers guidelines.

3. Slip cuff onto right arm (ensure sleeves are loosely rolled up, or garment is removed before measurement). Adjust cuff so lower edge is located 2 - 3 cm higher than antecubital fossa. Secure firmly around arm using the Velcro so there is no slack.

4. Ensure right arm is resting on a table top so centre of cuff is at heart level. (4th intercostal space). Use a firm block on the table, to adjust height if necessary.

5. Insert air plug of cuff into the air jack of the Omron.

6. Press sphyg/clock button and wait until buzzer emits a "pee, pee, pee ---" sound!

7. Set an inflation pressure - to 30 - 40 mmHg above palpated systolic pressure.

8. Press start button and immediately release it. BP measurement automatically begins.

9. When measurement is completed SBP and DBP are indicated at the same time on the screen. H.R. is indicated alternately to BP.

10. To print, the recording, press the "print current reading" button.

11. Press the Sphyg/Clock button to effect clock mode and complete the measurement.

12 Repeat steps 6 - 11 again and record a 2nd BP measurement.

13. Remove cuff from participant's arm and assist participant to redress if necessary.

14. Glue the 2 printouts to the examination form. (Write the values in as well incase thermal paper fades).

Equipment

2 X Omron HEM - 705CP automated digital sphygs
Omron Thermal Printer Paper
4 X Manganese Batteries
Glue

6.10 Venepuncture

Purpose

To obtain a non-fasting venous blood sample for analysis of lipids, fibrinogen, CRP, and glucose. (Serum lipids are an important risk factor for cardiovascular disease).

All assays will be performed at the Department of Biochemistry/Haematology, ARI, Foresterhill under the directions of Dr.....

This is potentially the most difficult part of the clinical examination because of the anxiety caused in most people by blood drawing and the potential for injury. However, if carefully and professionally performed, it will be safe for the participant and will provide important information for her and for the study.

The methodology to be adopted is as follows:

Procedure

1. Ensure the necessary consent form has been signed by both participant and yourself.

2. Wash hands at beginning of the work day; prior to taking blood and afterwards before seeing another patient, to minimise the risk of cross infection.

3. Explain procedure to participant for example:

   "I am going to be drawing some blood from the vein in your arm - to check your (blood cholesterol). I will just insert this little needle into your vein and shall take a small amount of blood. Do you have any questions?".

4. With coat/jacket removed, have the participant sitting comfortably in the chair with sleeve rolled up to expose the antecubital fossa, left arm or right arm (arm supported on a pillow).

5. Palpate and trace the path of the veins several times with index finger. Unlike veins, arteries pulsate, are more elastic and have a thick wall. Thrombosed veins lack resilience, feel cord-like, and roll easily.

6. Apply tourniquet to increase venous filling which will make the veins more prominent and easier to enter.

   N.B. The tourniquet should be applied 7 - 10 cm above venepuncture site. It should never be left on longer than 2 minutes. If the patient has fragile skin, or a dermatological condition, then place tourniquet over patient's blouse sleeve or use a piece of gauze so as not to pinch the skin.

7. Tapping lightly at the vein site with index and third finger a few times will cause the vein to dilate. Ask patient to make a fist.

8. Cleanse the venepuncture site with a medi- swab. Allow to dry to prevent possible haemolysis of the specimen, and a burning sensation to the patient when the venepuncture is performed.
If you need to touch the site again prior to venepuncture - ensure the site is cleansed with a medi- swab once again.

9. i) Put on gloves. Attach appropriate needle to end of vacutainer holder until it is secure.

ii) Grasp the patient's arm firmly and with your thumb or index finger of left hand, draw the skin over the venepuncture site taut. This anchors the vein and means the skin is easier to puncture because it can't move. Ensure thumb is below the venepuncture site.

iii) With the needle bevel upward, enter the vein (over the centre of the vein) in a smooth continuous motion - insert needle horizontally, ie don't angle it down or up or you may puncture the side of the vein.

iv) Ensure the patient's arm is in a flat or downward position whilst maintaining the tube below the site when the needle is in the vein.

v) Grasp the flange of the needle holder and insert a blood tube into the vacutainer. Push the tube forward until the butt of the needle punctures the stopper, exposing the full lumen of the needle.

vi) Once blood flow has commenced, do not move the position of the tube until it is withdrawn from the needle.

vii) Keep constant, slight forward pressure (in the direction of the needle) on the end of the tube. This prevents release of the shut-off valve and stopping of blood.

viii) Fill the tube until the vacuum is exhausted and blood flow ceases. It is normal for the tube not to be completely filled.

ix) When blood flow ceases, remove the tube from the holder. The shut-off valve of the vacutainer will stop blood flow from the needle butt, until the next tube is inserted (if necessary).

x) Mix blood by gently inverting the tube 5 - 6 times immediately after drawing each tube of blood. Do not mix vigorously. Put filled blood tube into a holder - don't leave it lying on a table.

xi) To obtain additional blood samples, insert next tube into holder and repeat procedure from 9 v - 9 x.

10. Release tourniquet.

11. Remove the needle, and apply pressure to the venepuncture site using a cotton ball. Ask participant to hold cotton ball firmly in place to prevent formation of a haematoma. Tape cotton ball in place or apply bandaid once bleeding has ceased.

Dispose of vacutainer sleeve and needle into sharp's container. Remove gloves and dispose into polythene bag.

Place specimen and labelled blood tubes in biohazard bag with request form.

Thank patient for her help and co-operation.

Ensure ID screening reference label is attached to
- blood tubes
- request forms
- incident form(s)

12. **<u>If Blood Sample Unobtainable</u>**

i) Move position of needle. If it has penetrated the vein too far, pull it back a bit. If it has not penetrated far enough, advance it further into the vein.

ii) Try another tube. The tube in use may not have had sufficient vacuum.

iii) Loosen the tourniquet - if it is too tight it may stop blood flow. Reapply loosely.

iv) Probing is <u>not</u> recommended as this is quite painful for the patient. Another attempt at venepuncture, in a site below the first one, is recommended.

v) A syringe and needle/butterfly may be used instead of a vacutainer, if necessary.

vi) Do not attempt venepuncture more than <u>twice</u>.

vii) If no one else is available to attempt venepuncture - mark this down on the examination form. If a person refuses to have blood taken - document this as well on the examination form.

13. **<u>Syncope</u>**

If participant looks or feels faint -

i) Have her sit down with head between knees
ii) Hold her so she doesn't fall
iii) Provide her with emesis bowl if she feels nauseated
iv) Have her remain seated until colour returns to face and she feels better
v) If continues to feel sick, take BP and H.R. If necessary, phone G.P. and/or ask for the advice of one of the medical staff. Keep participant in the clinic until she feels better. Note details on incident form.

14. **Handling Patients who are Extremely Apprehensive about Venepuncture.**
(see also Appendix 7.4)

Do not, under any circumstances force the patient to have blood taken.

It may help if veins are examined without actually drawing blood, and comments such as, "Oh, you have good veins - there should be no problem" (if veins are good), may help reassure the participant.

15. **In Event of Excessive Bleeding**

Apply pressure to the venepuncture site with a gauze pad. Bandage the pad securely in place if necessary, and leave bandage until bleeding stops. If bleeding is very excessive or persistent take participant to A & E. Record circumstances on examination and incident forms.

Staff Training
HEP. B status must be ascertained

Person performing venepuncture will have had practical and theoretical tuition, and then supervision by a qualified phlebotomist from ARI Haematology under the direction of - Dr. Ian Ross, Biochemistry and Mary Allardyce, Chief M.L.S.O. Haem.
A certificate of competence in venepuncture will be issued.

Special Procedures

* Sharps must be disposed of in appropriate sharps container
* All blood samples should be placed in biohazard bags.
* If phlebotomist suffers a needlestick injury from a contaminated needle, incident report should be completed and University Occupational Health Department should be notified to arrange for serum screening for hapatitis etc.

Equipment
Vacutainers
Gloves
tourniquet X 2
box medi. swabs
cotton balls
micropore
emesis basin
bandaids
sharps containers
blood biohazard collection bags
10 ml. syringes
20 ml. syringes
21g needles (green)
21g butterflies (green)
gloves

7.0 Participants with Special Conditions

7.1 Has Smoked Prior to Examination

If participant has smoked immediately prior to clinical examination a wait of at least 15 minutes should occur prior to taking blood pressure as smoking may cause a rise in blood pressure.

Re-arrange appointment if possible to delay the measurement of B.P.

Record on the clinical examination form the time participant last smoked.

7.2 Is Intoxicated

If participant is disruptive or is unable to give coherent responses, the appointment date and time should be rescheduled.

7.3 Is Physically Handicapped

Only perform those measurements that are able to be performed within the limitations of the individual's disability.

Note any changes of protocol on the clinical examination form, e.g. BP taken on Left arm due to absence of right arm or ECG performed whilst patient is sitting as unable to manoeuvre up onto examination couch.

7.4 Is Reluctant to have Venepuncture Performed

On no account force a participant to have blood taken -they have the right to refuse. Examining the arm for veins and offering encouragement will often persuade anxious participants. At any rate, encourage the participant to complete the other measurements involved in the examination especially, height, weight and blood pressure.

8.0 Maintenance and Checking Procedures

Daily Checks

- sign on door and waiting room
- examination room stocked with supplies of necessary equipment

All forms
- consent
- blood
- examination
- individual questionnaire

are ready.

- Room temperature 18 - 24°C
- scales in position
- stadiometer height rule in position
- adequate supplies of ECG electrodes
- blood tubes organised
- clinical examination reference labels available
- sharps container in place and biohazard bags available

Weekly Checks

- calibrate stadiometer to 150 cm using a metal height rule
- calibrate seca scales using a standard 5 kg weight
- check equipment/supplies stocks and re-order consumables as required.
- all procedures and interviews should be observed at least weekly by one of the following WCCS, MSW, BJW.

9.0 Incident Reports

An incident report form (see Appendix) is to be completed in the event of any of the following circumstances:

1. Deviations from protocol
   e.g. B.P. taken on different arm

2. Equipment Malfunction

3. Medical Problems occurring with participants or staff
   e.g. syncope, needlestick injury, haemorrhage.

4. Participants who wish to complain, who threaten the screener, or who walk out of the clinical examination.

A detailed factual account of the incident is to be documented including names, screening numbers, times, dates etc. Also record in detail what action was taken.

Copy the incident form and attach one copy to the participant's documents (if applicable), and keep one in the ASCHW clinical examination information file. (to be created).

Notify Dr's W.C.S.Smith, B.J. Wilson, and M.S.Watson of the incident. They can be contacted via telephone in the Dept. of Public Health as follows:

Dr. W.C.S. Smith	XT 53802
Dr. B.J. Wilson	53322
Dr. M.S. Watson	52494

Appendix 1 Examination Form

1. **I.D. Label**

2. **Date** ☐☐☐

   Day Month Year

3. **Location of Measurement**

   - Foresterhill Health Centre ☐
   - Other - Specify ☐

4. **Room Temperature** ☐ °C

5. **Height** ☐☐☐ Cm.

   1. Measured ☐
   2. Self reported ☐
   3. Refused ☐

6. **Weight** ☐☐☐ • ☐☐ **Kg.**

   1. Measured ☐
   2. Self reported ☐
   3. Refused ☐

7. **Have you had a cigarette within the past 24 hrs.?**

   1. YES ☐ (Go to Q8)
   2. NO ☐ (Go to Q9)

8. **What time did you have your last cigarette?**

☐☐☐☐ hrs. 1. ☐ a.m.

2. ☐ p.m.

9. **In the past 24 hrs. have you had any caffeinated beverages to drink eg., tea, coffee, coca cola?**

1. YES ☐ (Go to Q 10)

2. NO ☐ (Go to Q 11)

10. **What time did you have your last caffeine beverage?**

☐☐☐☐ hrs. 1. ☐ a.m.

2. ☐ p.m.

Blood Pressure

The participant must be allowed to have a rest period of 3 minutes prior to and during B.P. measurement. In this time the participant shall remain quiet and shall be seated with legs uncrossed and feet flat on floor.

During B.P. measurement, there should be no change in position of participant.

11. **H.R. - No Beats in 30 seconds** ☐☐

12. **Arm Circumference** ☐☐☐ Cm.

13. **Cuff Size** - 1. Standard Adult ☐

2. Large Arm Adult ☐

14. **Pulse Obliteration Pressure** ☐☐☐

	HRZS	Systolic	Diastolic
15.	First HRZS Reading (R1)		
16.	R Zero Level (RZ1)	-	-
17.	First Corrected (R1 - R21)		
18.	Second HRZS Reading (RZ)		
19	R Zero level (R22)	-	-
20.	Second Correted (R2-R22)		
21.	Sum of Correctd (R1 + R2)		
22.	Average of Corrected $\frac{(R1+R2)}{2}$		

Omron

23. First Omron Reading Glue Printout Here

Systolic .....

Diastolic.....

H.R.....

24. Second Omron Reading

Systolic.....

Diastolic.....

H.R.....

25. **Spirometry** Glue Printout Here

26. **Smokelyzer Results**

CO (ppm) .....

% CO Hb .....

27. **Venepuncture**

Position: .....

Was blood drawn: YES ☐

NO ☐

REFUSED ☐

What method: VACUTAINER ☐

BUTTERFLY ☐

SYRINGE & NEEDLE ☐

28. Note anything that deviated from standard procedure

a) Height/Weight .....

.....

b) BP.....

.....

c) ECG.....

.....

d) Venepuncture.....

.....

UNIVERSITY OF ABERDEEN
&
THE ROYAL COLLEGE OF GENERAL PRACTITIONERS

ABERDEEN STUDY OF CARDIOVASCULAR HEALTH IN WOMEN

PATIENT CONSENT FORM
[for women being invited for a clinical examination, to be enclosed with the initial questionnaire]

FORM A

NAME .....

ADDRESS .....

.....

.....

I have read the patient information sheet and understand the nature of this study. I give consent as indicated below. ***(Please score through any part to which you do not give your consent).*** I understand that I am free to withdraw from this study at any time.

PART 1

I give consent to access my medical records, for the purposes of this research project only. This includes GP records, with the permission of my current general practitioner, and details of admissions to hospitals in Scotland held on computer systems.

Signed ..... **Date** .....

PART 2

I give consent to undergo a simple medical examination which includes blood pressure recording, and ECG, a breathing test, measurement of height and weight and for a blood sample to be taken.

Signed ..... **Date** .....

UNIVERSITY OF ABERDEEN
&
THE ROYAL COLLEGE OF GENERAL PRACTITIONERS

ABERDEEN STUDY OF CARDIOVASCULAR HEALTH IN WOMEN

PATIENT CONSENT FORM
[for women invited for a clinical examination, to be completed at the time of the examination and explained by the research nurse]

FORM B

NAME .....

ADDRESS .....

.....

.....

I have read the patient information sheet and understand the nature of this study. I have discussed the study with ..... (research nurse). I give consent as indicated below. I understand that I am free to withdraw from this study at any time.

I give consent for the results of this examination to be sent to my own general practitioner.

Signed ..... **Date** .....

APPENDIX III

The choice of correct cuff is crucial to the accurate measurement of blood pressure. The British Hypertension Society recommends that the length of the bladder should be at least 80% of the arem circumference, and the bladder width 40% of arm circumference (Petrie, J.C. 1987; Perry, I.J. & Beevers, D.G. 1991, p.175).
The standard adult cuff available is 23 x 12 cm. The B.H.S now recommend a 35 x 12 cm cuff for normal or lean arms. For obese arms (circumference greater than 33 cm) a 42 x 15 cm cuff is recommended.

Baumanometer BP Inflation Bags and Cuffs.

Inflation Bags

To compress the artery during the measurement of B.P.

Cuff

To hold the inflatable latex bag on the arm during measurement of B.P.

For accurate readings the cuff must be the correct width for the arm and must impart a uniform pressure over its full width.

The cuff should be applied firmly to the arm, so the inflation bag covers the inner aspect of the arm with the centre of the bag over the brachial artery.

Calibrated V-LOK Right Cuff

This cuff features 2 white Range Lines and a White index Line to help select the correct size cuff for any limb.

To apply the cuff "cradle" the upper arm with the cuff, using it as a tape measure and observe whether the index line falls between the range lines.

If it does, the cuff is correct for that limb.

If it does not, a larger or smaller cuff should be selected.

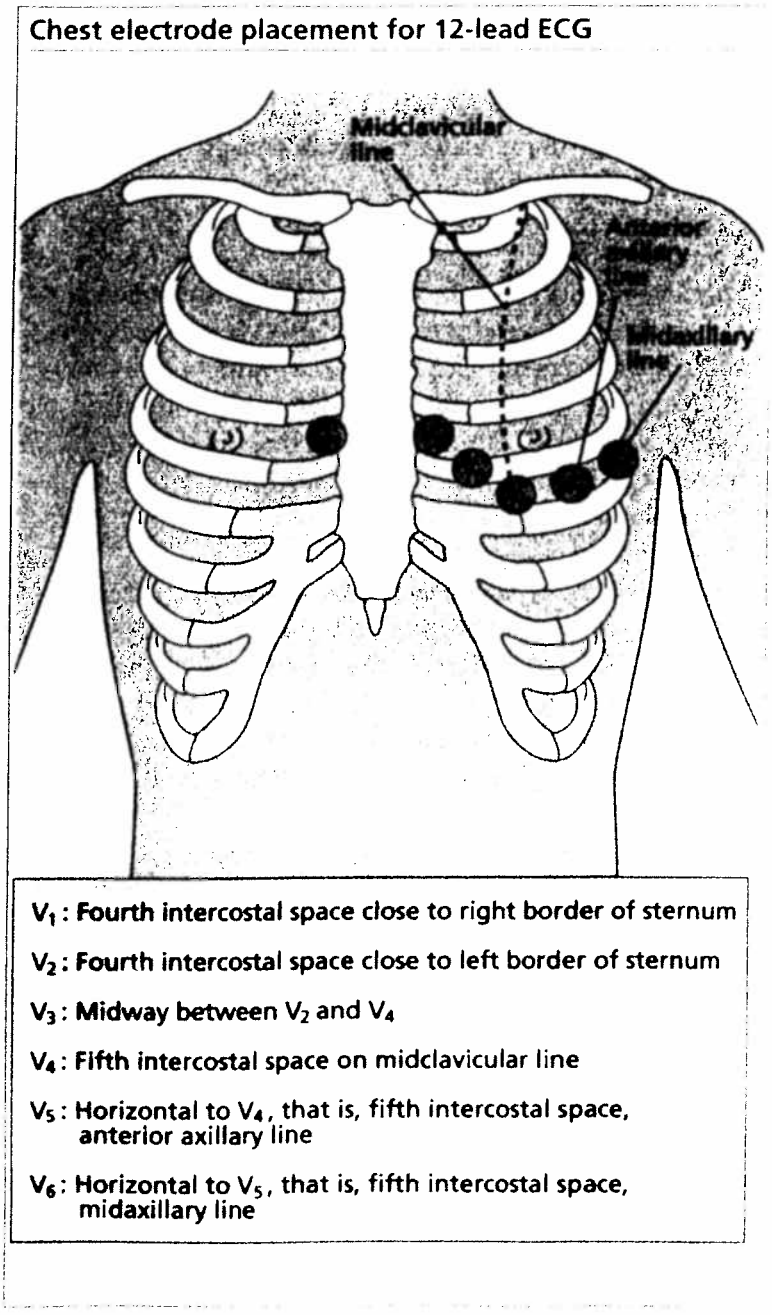
Wrap the cuff on the arm so the inflation bag covers the inner aspect of the arm with the centre of the bag over the brachial artery.

Pull it snug and press the Velcro surfaces tog.

Cuff Size	Fits Limb Circumference
Adult	25 - 35 cm
Large Arm	33 - 47 cm

APPENDIX IV

Placement of ECG Leads.



APPENDIX V

i) Universal Blood and Body Fluid Precautions.

ii) Dealing with Blood Spills.

Should be mopped up with paper towels using Sodium Hypochlorite Solution. 100 ppm (4 (0.5g) Actichlor tabs. in 1ltr. of water).

Paper towels should be disposed of in (orange) clinical waste bags.