An Assessment of the Effect of Multimorbidity on Motor-Vehicle Accident Risk

Yannick Fortin, MA

Thesis Supervisor: Dr. Daniel Krewski

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Faculty of Health Sciences
University of Ottawa
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Abstract

In North America, the last two decades saw continued increases in population multimorbidity across all age groups. This trend, which is expected to endure in the coming years, has been attributed in large part to population aging and unhealthy lifestyle choices. While the societal consequences of multimorbidity have focused primarily on the burden it imposes on the sustainability of health systems and the need to implement innovative ways to deliver care, latent costs, such as possible increases in motor-vehicle accidents (MVAs) have received relatively little attention. The principal objective of this thesis was to investigate the relationship between multimorbidity and MVAs. To complement current knowledge on the topic, we conducted observational studies based on information recorded in electronic health records (EHR). The hypothesis that increasing levels of multimorbidity would translate into increasing risk of MVA was tested in both a general population of health care recipients and in persons with epilepsy, a subgroup of individuals predisposed to comorbidities and MVAs. To gain a better understanding of morbidity ascertainment in EHR data, preliminary validation studies were performed to evaluate the performance of Elixhauser comorbidity measures for predicting hospital mortality in our data source. A systematic review of risk factors contributing to the onset and progression of epilepsy was also performed in hopes of identifying elements that would help improve the methodological design of the principal thesis study limited to persons with epilepsy. Study results confirmed the excellent performance of the Elixhauser comorbidity measures for predicting hospital mortality in the Cerner Health Facts data repository. In the general health care recipient population, a positive exposure-outcome relationship was observed between multimorbidity and MVA risk. This relationship was consistent in adults across

the lifespan and more pronounced in women than in men. In persons with epilepsy, the observed exposure-outcome relationship between multimorbidity and MVAs did not reach statistical significance. However, comorbid depression was identified as a risk factor for MVAs. Given increasing rates of multimorbidity in the general population, the findings of this thesis strongly support the need for replication and better characterization of the disease combinations that drive increases in MVA risk. Future work on this topic should also include estimates of MVA risk attributable to multimorbidity; this would inform and gauge the relevance of novel driving policies targeting individuals diagnosed with specific health conditions.

Contributions of Collaborators and Co-Authors

Comments and suggestions were received prior, during, and following the writing of the Introduction and Conclusion chapters from members of my internal thesis committee. I would like to sincerely thank my thesis supervisor Dr. Daniel Krewski, and committee members Dr. Donald R. Mattison, Dr. Deborah Cohen, and Dr. Simone Dahrouge for their contribution to these chapters.

Chapters II to VI were researched, written, and formatted specifically for publication in peer-reviewed scientific journals. In addition to the members of my internal thesis committee, the following collaborators were particularly instrumental in insuring the thesis manuscripts achieved the highest level of scientific rigour and clarity demanded for publication: Dr. James A.G. Crispo, Dr. Douglas S. McNair, Stephanie J. Walsh, and Jennifer R. Donnan. Satisfaction of the authorship requirements prescribed by the International Committee of Medical Journal Editors (ICMJE) for my co-authors are described below.

Authors

Andrea Morrissey (AM)
Don MacDonald (DM)
Donald R. Mattison (DRM)
James A.G. Crispo (JAGC)
Kayla Collins (KC)
Simone Dahrouge (SD)
Yannick Fortin (YF)
Deborah Cohen (DC)
Daniel Krewski (DK)
Douglas S McNair (DSM)
Jennifer Donnan (JD)
Lindsey Sikora (LS)
Stephanie Walsh (SW)

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A) Substantial contributions to the conception [YF, DK, JAGC] or design of the work [YF, DK, JAGC]; or the acquisition, analysis [DK, DRM, DSM], or interpretation of data for the work [YF, DRM, DSM, DC, DK, JAGC]; AND

B) Drafting the work or revising it critically for important intellectual content [YF, DRM, DSM, DC, DK, JAGC]; AND

C) Final approval of the version to be published [YF, DRM, DSM, DC, DK, JAGC]; AND

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B) Drafting the work or revising it critically for important intellectual content [YF, DRM, DSM, DC, DK, JAGC, SD]; AND

C) Final approval of the version to be published [YF, DRM, DSM, DC, DK, JAGC, SD]; AND

D) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved [YF, DRM, DSM, DC, DK, JAGC, SD].

Chapter V: ICMJE criteria for authorship

A) Substantial contributions to the conception [SW, JD, DM] or design of the work [SW, JD, DM]; or the acquisition, analysis [SW, JD, DM AM, LS, KC], or interpretation of data for the work [SW, JD, DM AM, LS, KC, YF]; AND

B) Drafting the work or revising it critically for important intellectual content [SW, JD, DM AM, LS, KC, YF]; AND

C) Final approval of the version to be published [SW, JD, DM AM, LS, KC, YF]; AND

D) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved [SW, JD, DM AM, LS, KC, YF].

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and was able to see new parts of the world. Together, these funding opportunities made the completion of my lifelong objective of pursuing doctoral studies financially possible.

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Acronyms

ACS, American Community Survey

ADHD, Attention deficit hyperactivity disorder

AED, Antiepileptic drug

AHRQ, Agency for Healthcare Research and Quality

AIDS, Acquired immune deficiency syndrome

AMD, Age-related macular degeneration

AMSTAR, Assessing the Methodological Quality of Systematic Reviews

ApoE, Apolipoprotein E

AUROC, Area under the Receiver Operating Characteristic curve

AV, Autonomous vehicle

CC, Cysticercosis

CEP-ILAE, Commission on Epidemiology and Prognosis, International League Against Epilepsy

CDC, U.S. Centers for Disease Control and Prevention

CHAMPUS, Civilian Health and Medical Program of the Uniformed Services

CI, Confidence intervals

CIHI, Canadian Institute for Health Information

CINAHL, Cumulative Index to Nursing and Allied Health Literature

CIRS, Cumulative Illness Rating Scale

CNS, Central nervous system

CSDH, Commission on the Social Determinants of Health

COPD, Chronic Obstructive Pulmonary Disease

DARE, Database of Abstracts of Reviews of Effects

DMV, Department of motor vehicles

E, Event

ECM, Elixhauser Comorbidity Measures

ED, Emergency Department

EEG, Electroencephalogram

EHR, Electronic health record

EpiGAD, The Epilepsy Genetic Association Database

FRQS, Fonds de recherche du Québec en Santé

GABBR1, Gamma-Aminobutyric acid B receptor 1

HF, Cerner Health Facts®

HHS, U.S. Department of Health & Human Services

HIPAA, Health Insurance Portability and Accountability Act

HIV, Human immunodeficiency virus infection

HL Test, Hosmer–Lemeshow goodness-of-fit test

HR, Hazard ratio

ICD-9 CM, International Classification of Diseases, Ninth Revision, Clinical Modification

ICMJE, International Committee of Medical Journal Editors

ILAE, International League Against Epilepsy

IOM, Institute of Medicine

IRR, Incidence rate ratio

MCC, Multiple chronic conditions

NA, Not applicable

NCC, Neurocysticercosis

NE, Non-event

NHIS, National Health Interview Survey

NHTSA, National Highway Traffic Safety Administration

NINDS, National Institute of Neurological Disorders and Stroke

NPHSNC, National Population Health Study of Neurological Conditions

NRC, National Research Council

NRI, Net reclassification improvement

OECD, Organisation for Economic Co-operation and Development

OGS, Ontario Graduate Scholarship

OR, Odds ratio

PHAC, Public Health Agency of Canada

PDYN, Prodynorphin

PWE, Persons living with epilepsy

PWOE, Persons without epilepsy

ROC, Receiver Operating Characteristic

RR, Relative risk

SAS, Statistical Analysis System (software)

SD, Standard deviation

SE, Standard error/Status epilepticus

SES, Socioeconomic status

SMR, Standardized mortality ratio

TB, Tuberculosis

TLE, Temporal lobe epilepsy

TRIPOD, Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis

US, United States of America

VNTR, Variant number repeat polymorphisms

WHO, World Health Organization

Chapter 1 – Introduction

Statement of the Problem

Multimorbidity, the co-occurrence of two or more chronic health conditions in an individual, is increasing in developed countries (Koné Pefoyo et al., 2015; Uijen & van de Lisdonk, 2008). Part of this increase is explained by the current population aging trend, which the United Nations (2002) has qualified as unprecedented, pervasive, enduring, and profound. As a greater proportion of adults transition to old age, the expected increase in non-communicable disease prevalence and their co-occurrence naturally follows. A second, and possibly more concerning explanation of the reported increase in population levels of multimorbidity, is the contribution of unhealthy lifestyle risk factors, including tobacco consumption, alcohol misuse, poor diets, insufficient sleep, and physical inactivity (Mendis, 2014; Mokdad, Marks, Stroup, & Gerberding, 2004; United Health Foundation, 2016). Unfortunately, these risk factors are not limited to the elderly and affect individuals of all ages. As a result, multimorbidity has increased in all age groups over the last decades and should be considered a population-wide problem (Koné Pefoyo et al., 2015; Uijen & van de Lisdonk, 2008; Ward & Schiller, 2013). Today, non-communicable diseases are the leading cause of morbidity, disability, mortality, and health care costs in the U.S. (Bauer, Briss, Goodman, & Bowman, 2014).

Given the far-reaching consequences of multimorbidity on population health and the sustainability of health systems, we asked what other latent societal cost might be incurred from increasing multimorbidity? In the last two decades, numerous studies have reported associations between chronic health conditions such as diabetes, cardiovascular diseases, neurological conditions, and increased risk of motor-vehicle accidents (MVAs) (Charlton

et al., 2010; Dobbs, 2005; Vaa, 2005; Vernon et al., 2002). We therefore hypothesized that multimorbidity would have an additive effect on MVA risk. A review of the scientific literature revealed a few studies supporting this hypothesis (Marshall & Man-Son-Hing, 2011; Papa et al., 2014). These studies, however, often based their conclusions on self-reports and sample data limited to the elderly. These limitations are problematic since self-reported data are prone to recall and response biases (Jenkins, Earle-Richardson, Slingerland, & May, 2002) and the absolute number of multimorbid individuals is greater in persons younger than 65 years compared to those above that age.

Continuing advances surrounding large electronic health record (EHR) databases now offers unique opportunities to investigate the relationship between multimorbidity and MVAs. EHR data are conducive to large population-based observational studies based on codified health services utilization activities at relatively little cost without recall and response biases (Jenkins et al., 2002). Conversely, EHR-based studies have their own set of limitations and biases. EHR repositories that comply with the U.S. Health Insurance Portability and Accountability Act (HIPAA) for instance, must adhere to strict de-identification procedures to protect the privacy and personal information of patients. Consequent to de-identification, patient records are no longer amenable to accurate data linkage with external data sources containing vital statistics, those of state Departments of Motor Vehicles (DMV), and other parallel EHR systems. These limitations are likely to translate to some level of selection bias and exposure-outcome misclassification. It is within this complex methodological context that the studies included in this thesis attempt to advance knowledge pertaining to the relationship between multimorbidity and MVAs.

In this introductory chapter, we review the scientific literature on multimorbidity and MVAs independently, then describe their demonstrated association. Moving beyond a review of studies based on the general population, we will also discuss the current literature on persons with epilepsy: a population disproportionally affected by multimorbidity and at increased risk of MVA. We conclude the chapter by presenting five knowledge gaps matched to research objectives and questions, as well as a conceptual framework based on the principles of population health and risk science.

Multimorbidity

Multimorbidity is defined as "the co-existence of two or more chronic conditions, where one is not necessarily more central than the others" (Boyd & Martin Fortin, 2010, p. 453). In a recent systematic review, Willadsen et al. (2016) explored how diseases, risk factors and symptoms were used to define multimorbidity in methodological designs. Their analysis revealed that multimorbidity was ascertained primarily from self-reports (42%), based on a range of 4 to 147 conditions, and identified mostly in general (42%) or primary care (25%) populations. In 71% of the 163 studies they reviewed, multimorbidity definitions were study specific. They always included diseases [e.g. diabetes, stroke, cancer, depression] but risk factors [e.g. hypertension, osteoporosis, hypercholesterolemia] and symptoms [e.g. back pain, visual impairment, urinary incontinence, alcohol/drug abuse, sleep disorders, dizziness, headache, tobacco abuse] were less likely assessed; 85% versus 62% respectively. The approaches used to capture and describe disease duration varied greatly. Indicators of morbidity alternated between concepts of incidence and prevalence. For instance, dichotomous indicators included 'ever/never' or 'present in the

past 12 months' or within a '2-year look back period'; indicators of chronicity included having a condition 'for at least 3 months' or 'at least 3 months in the last 12 months'.

The concept of disease severity attributed to conditions included in multimorbidity indices was generally in reference to a specific outcome; e.g. in the Charlson comorbidity index, the severity of each condition included is expressed by a relative weight based on the association between a health condition and its ability to predict mortality (Mary E. Charlson, Pompei, Ales, & MacKenzie, 1987); for the Cumulative Illness Rating Scale (CIRS) and its geriatric version (CIRS-G) the outcome of interest is physical impairment. In the Elixhauser (1998) measures of comorbidity, assessment of disease severity relies on different diagnostic codes to identify disease progression. For instance, cancer progression is separated in two groups: solid tumours without metastasis including lymphoma and metastatic cancers. Similarly, diabetes is classified by complication status: uncomplicated versus complicated.

Epidemiology of Multimorbidity

In the United States, just over half—51.9%—of the adult population is diagnosed with at least one chronic health condition (Ward & Schiller, 2013). A review of the literature reveals that epidemiology of multimorbidity is complex and complicated by methodological design choices including which diseases, symptoms, and risk factors should be included in prevalence assessments. As a result, multimorbidity prevalence has been reported to range from 12.9% to 95.1% in adults depending on the age of study participants and the number of health conditions assessed (Violan et al., 2014). An analysis of the 2010 National Health Interview Survey (NHIS) based on a prevalence assessment limited to 11 common conditions that excluded mental health disorders [hypertension,

coronary heart disease, stroke, diabetes, cancer, arthritis, hepatitis, weak or failing kidneys, chronic obstructive pulmonary disease, current asthma] revealed that 26% of U.S. adults have multiple chronic conditions (MCC) (Ward & Schiller, 2013).

Age

Multimorbidity increases with age (Barnett et al., 2012; Fortin, Bravo, Hudon, Vanasse, & Lapointe, 2005; Roberts, Rao, Bennett, Loukine, & Jayaraman, 2015; Ward & Schiller, 2013). Results from the 2010 NHIS found that 6.7%, 32.8%, and 62.5% of noninstitutionalized U.S. adults 18 to 44 years, 45 to 64 years, and 65 years and over, respectively, were multimorbid (Ward & Schiller, 2013). Likewise, a frequently cited Scottish population-based study that assessed the presence of 40 medical and mental health conditions found that 11.3%, 30.4%, and 64.9% of adults aged 25 to 44, 45 to 64, and 65 to 84 years were multimorbid (Barnett et al., 2012).

Sex

Female sex is independently associated with multimorbidity (Barnett et al., 2012; Violan et al., 2014). Women are more likely than men to have 2 to 3 chronic health conditions in the 18 to 44 age group and more likely than men to have 4 or more chronic health conditions in the 18 to 64 age group (Ward & Schiller, 2013). Above the age of 64 years, however, there is a shift with men being more likely than women to have 4 or more chronic health conditions. These differences in MCC status by age and sex categories were also reported in a Canadian study of primary care recipients (Fortin et al., 2005).

Race and Ethnicity

In Canada, those who identified as being of aboriginal descent were twice as likely to have multimorbidity as those who are not after adjusting for other covariates (Roberts et al., 2015). A study by Mathur et al. (2011) on the prevalence of cardiovascular (stroke, diabetes, heart failure, coronary heart disease, and hypertension) multimorbidity by ethnic origin showed that after adjusting for age, sex, and primary care cluster, the likelihood of multimorbidity was higher in blacks, south Asians, and other races when compared to whites.

Socioeconomic status

A recent study by Barnett et al. (2012) based on approximately 1.8 million individuals from Scotland showed that the prevalence of multimorbidity increases gradually based on deciles of increasing socioeconomic deprivation. The most deprived group of individuals became multimorbid 10 to 15 years earlier than those in the most affluent group. In a different study by Roberts (2015, p. 87), based on a geographically representative Canadian sample, "the prevalence of multimorbidity increases with age, with lower household incomes and with lower education levels within the household."

The relationship between lifestyle choices that are conducive to better health outcomes has been investigated along several dimensions. Using data from a UK household survey, Wardle and Steptoe (2003) reported that affluent individuals were not only more likely than those with lower means to exercise and eat fruit and vegetables on a daily basis, they were also more likely to be health conscious and deterministic about how their behavior may affect their long-term health outcomes. But while wealthy individuals may

be more inclined than the poor to have strong beliefs about the need to make conscious healthy lifestyle choices, SES and income are in themselves factors that limit a person's very capacity to improve their lifestyle. For instance, review of the food desert literature conducted by Walker et al. (2010) identified numerous studies that reported how SES or income are determinants of nutritional choices. Having limited means was associated with: restricted access to stores or quality food sources; the need to travel a greater distance to reach a chain store [where food is more affordable than convenience or non-chain stores]; lacking transportation to food outlets; and having greater access to fast-food restaurants. Poorer neighborhoods were also less likely than higher income neighborhoods to offer food outlet choices, house supermarkets, and offer healthy food options within their food stores.

Multimorbidity in Persons with Epilepsy

Persons living with epilepsy (PWE) have a greater disease burden than persons without epilepsy (PWOE) (Athanasios Gaitatzis, Carroll, Majeed, & Sander, 2004; A. Gaitatzis, Trimble, & Sander, 2004; Hinnell et al., 2010; Kwon et al., 2011; Rai et al., 2012; Selassie et al., 2014). Using a U.S. claims database of approximately 3 million privately insured members, Ivanova et al. (2010) concluded that insurance beneficiaries with an epilepsy diagnosis had more comorbidities and generated significantly higher direct annual costs than demographically matched PWOE. In PWE, 80% of annual per-person costs were spent on treating non-epilepsy related care. The authors also reported that mental disorders, migraines, neurological disorders [cerebral degenerations, multiple sclerosis, demyelinating diseases], heart and cerebrovascular diseases, dementia, chronic pulmonary disease, rheumatologic disease, diabetes, hemiplegia, paraplegia, renal disease, and cancers were significantly overrepresented in PWE compared to PWOE, $p<.001$. Likewise, a

Canadian population-based EHR study by Kwon et al. (2011) investigating differences in risk MVA, suicide, and assault between PWE versus PWOE reported that the former group had greater disease prevalence for each of the 30 health condition assessed.

Measuring and Adjusting for Multimorbidity

Typically, studies on multimorbidity justify their selection of admissible prevalent conditions based on study objectives (Willadsen et al., 2016). Theoretically there are thousands of possible disease combinations that can equate to multimorbidity. From a clinical and policy standpoint, however, non-random patterns of associative multimorbidity are more relevant because they are reflected in higher prevalence rates and are assumed to result from common biological mechanisms, environmental exposures, or a combination of the two. A systematic review by Prados-Torres et al. (2014)—based on the results of 14 cross-sectional studies that included a statistical assessment—identified 97 highly frequent patterns of co-occurring disease with 63 of these being combinations of three or more health conditions. Three groups of patterns stood out: 1) combinations of cardiovascular and metabolic diseases [e.g. arthritis, cardiovascular disease, diabetes, fatigue, high blood pressure, high cholesterol, and obesity]; 2) clusters including a mental health condition [e.g. dementia, depression, and hip fracture]; and 3) clusters including a musculoskeletal disorder [e.g. hypertension, osteoarthritis, and visual impairment; or arthritis and dementia]. In a study sponsored by the U.S. Centers for Disease Control and Prevention (CDC), Ward and Schiller (2013) reported that in adults 18 years and over, the most frequent disease dyad was arthritis and hypertension while the most frequent triad was arthritis, hypertension, and diabetes.

In health research, (multi)morbidity ascertainment are generally performed in four ways: manually reviewing patient charts, surveying patients directly through interviews, physical examinations and questionnaires, and interrogating electronic health data with the aid of software programs and algorithms (de Groot, Beckerman, Lankhorst, & Bouter, 2003). Each of these approaches have their advantages and limitations (Esposito, Migliaccio-Walle, & Molsen, 2013). Manually reviewing patient charts is often considered the gold standard since clinical notes offer the greatest depth and can contain information not codified in EHR data. However, this process can be time consuming, expensive, and may require clinical expertise for the accurate interpretation of chart contents. Patient surveys allow researchers to probe patients about information not contained in charts or EHR data and to clarify inconsistencies. However, surveys can be expensive, time consuming, and prone to non-response, selection bias [some patients may be more inclined to participate in a survey than others], response bias [social desirability may lead some patients to withhold sensitive information; clinical accuracy may vary based on patient characteristics], and recall bias (De Leeuw & Dillman, 2008; Jenkins et al., 2002). Obtaining valid longitudinal data from surveys is also complicated by loss to follow-up. Working with EHR data has several advantages. These include the possibility of querying large study populations at low cost with limited data acquisition time (Esposito et al., 2013). But while EHR data is theoretically standardized, coding errors are expected and coding practices can vary across time and location, possibly leading to biased study results (Benchimol et al., 2011; Iezzoni, 1997; van Walraven & Austin, 2011). In addition, policies implemented to protect the privacy and personal information of patients, such as anonymization and aggregation [e.g. replacing postal codes with broader census region

indicators] can limit the accuracy of linkage to external data sources or prevent detailed analyses (HHS, 2014; Weber, Mandl, & Kohane, 2014; West et al., 2009). Since EHR data sources are not initially created for research purposes, variables of interest may be unavailable. At times, the coding of health services utilization may be prone to systematic biases that can affect model estimates, typically leading results towards the null hypothesis.

Several methods are available for summarizing multimorbidity levels (AHRQ, 2014; Mary E. Charlson, 1993; D'Hoore, Sicotte, & Tilquin, 1993; de Groot et al., 2003; Deyo, Cherkin, & Ciol, 1992; Elixhauser et al., 1998; Ghali, Hall, Rosen, Ash, & Moskowitz, 1996; Holman, Preen, Baynham, Finn, & Semmens, 2005; Klabunde, Legler, Warren, Baldwin, & Schrag, 2007; Li, Kim, & Doshi, 2010; Romano, Roos, & Jollis, 1993; Sharabiani, Aylin, & Bottle, 2012; van Walraven, Austin, Jennings, Quan, & Forster, 2009; Yurkovich, Avina-Zubieta, Thomas, Gorenchtein, & Lacaille, 2015). Measures of comorbidity typically reflect a patient's multimorbidity status using dichotomous indicators of prevalence for multiple pre-selected health conditions (Elixhauser et al., 1998; Quan et al., 2005). Comorbidity scores or indices, such as the popular Charlson index (Mary E Charlson et al., 2008; Mary E. Charlson et al., 1987; Mary E. Charlson, Wells, Ullman, King, & Shmukler, 2014), typically summarize multimorbidity status in a single score on a continuous scale derived from the sum of prevalent conditions weighted based on disease severity. The number of indicators included in morbidity assessment tool, the source of clinical information required for implementation, the procedure used to assign weights to indicators, the study population, and outcome measure(s) selected for validation are what differentiates such tools (de Groot et al., 2003).

Motor-Vehicle Accidents in the United States

Epidemiology of MVAs

According to the most recent published estimates, there were approximately 214 million licensed drivers and 275 million registered vehicles for the 319 million US inhabitants in 2014 (NHTSA, 2016). That year, drivers travelled an estimated 3.0 billion miles [4,9 billion kilometers]. For every 100,000 licensed drivers, the annual rate of fatal crashes was 15.3. The annual rate of crash-related injuries was 1,092 per 100,000 licensed drivers. In absolute numbers, this translated to 29,989 deaths and 1,648,000 injury-related crashes. Accidents causing property damage equated to an additional 4,387,000 traffic events. Fatal, injury-related, and property damage MVAs constituted 0.5%, 27.2%, and 72.3% of the 6,064,000 MVAs in the United States in 2014, respectively. The estimated economic burden of reported and unreported crashes in the US for 2010 was 242 billion dollars.

The most recent annual report by the U.S. Department of Transportation's National Center for Statistics and Analysis showed important differences in driver-related crash involvement rates by age and sex (NHTSA, 2016). Irrespective of age group, men had higher rates of MVAs leading to fatalities, injuries, and property damage per licensed drivers then women. For fatal crashes, the MVA rate, per 100,000 licensed drivers, peaked at 48.2 for men in the 21 to 24 age range while it peaked at 19.6 for women in the 16 to 20 age range. Rates of fatal crashes decreased consistently across the lifespan for men and women drivers up to the 65 to 74 age group; in the top age category (75+) rates of fatal crashes were higher than the previous category.

The rate of injury-related crashes in drivers of both sexes peaked in the 16 to 20 age range at 3,107 and 2,850 accidents per 100,000 licenced drivers for men and women,

espectively. In men, the rates of injury-related crashes per 100,000 licensed drivers declined steadily from 3,107 to 887 in those aged 16 to 20 years compared to those over 74 years, respectively. The trend was similar in women drivers: the rates of injury-related crashes per 100,000 licensed drivers declined from 2,850 to 584 in those aged 16 to 20 years compared to those over the age 74 years, respectively.

Morbidity and MVAs

In Western countries, the link between specific health conditions and increased risk of motor-vehicle accidents and injuries is explicitly stated in existing policies upheld by transport authorities. An extensive systematic review conduced by the Monash University Accident Research Centre (Charlton et al., 2010) on the influence of health conditions on fitness to drive pooled the guidelines implemented in Australia, Canada, New Zealand, Sweden, the United Kingdom, and the state of Utah in the USA. Most jurisdictions require the disclosure of select health conditions as a requirement for obtaining or renewing a driver's license. These select health conditions are generally associated with some form of functional impairment or disability considered to pose road safety risks and may results in driving restrictions for the license holder. For instance, persons with active forms of epilepsy may become physically impaired while driving if they suffer a seizure or a loss of consciousness (Andermann, Remillard, Zifkin, Trottier, & Drouin, 1988; Hansotia, 1993; Krumholz & Hopp, 2016). Similarly, cognitive impairment resulting from treatment interventions, such as pharmacotherapy-related somnolence, may be the real or perceived hazard for road safety. As a result, several jurisdictions impose limitations on licensing based on seizure-free periods. In the state of Utah, USA, PWE can be awarded unrestricted licences if they achieve seizure-free period ranging from 3 to 12 months, may have to

submit to biannual, annual, and two-yearly reviews; and may be imposed speed, geography, and time of day driving restrictions (Utah State Driver License Medical Advisory Board, 2006; Vernon et al., 2002).

Beyond policies that explicitly control driving eligibility based on health status, the scientific literature abounds with studies linking morbidity to increased risk of MVA (Charlton et al., 2010; Classen, Crizzle, Winter, Silver, & Eisenschenk, 2012; Krauss, Krumholz, Carter, Li, & Kaplan, 1999; Orriols et al., 2014; Sagberg, 2006; Vaa, 2005; Vernon et al., 2002). To summarize the current evidence, we report the findings of two extensive systematic reviews of the literature on the topic, as well as the results of complementary meta-analyses (Charlton et al., 2010; Vaa, 2005). These systematic reviews were selected because they investigated a broad range of health conditions and were not limited to conditions acknowledged in transport authority policies.

Charlton et al. (2010) reviewed the literature to evaluate the impact of chronic illnesses and functional impairments1 on MVAs. Choosing crash involvement as their primary outcome—as opposed to driving performance or citations, which are arguable less

[1] The health conditions identified during the review were: cardiovascular disease including syncope, arrhythmias, and coronary artery disease; cerebrovascular accidents including stroke; cognitive impairments including dementia and traumatic brain injury; diabetes mellitus; epilepsy and seizure disorders; musculoskeletal disorders including rheumatoid arthritis, osteoarthritis, spinal cord injury, and amputation; neurological conditions other than epilepsy including Parkinson's disease, multiple sclerosis, cerebral palsy, and spina bifida; psychiatric illnesses including schizophrenia, depression, anxiety disorders, personality disorders, and attention deficit hyperactivity disorder (ADHD); respiratory disorders (COPD) including emphysema, chronic bronchitis and asthmatic bronchitis; sleep related disorders including sleep apnoea and narcolepsy; balance or vestibular disorders; and vision disorders including cataracts, glaucoma, age-related macular degeneration (AMD), diabetic retinopathy, refractive errors, retinitis pigmentosa, hemianopia, color vision disorders, monocular vision, corneal pathology, nystagmus, visual acuity, visual field loss, and contrast sensitivity.

serious—three experts independently categorized the evidence on MVA risk for each health condition identified in the literature. Risk categorization was estimated in terms of relative risk (RR) and based on an interpretation of the overall evidence. Once consensus was reached between the experts, each health condition or functional impairment was assigned to one of three MVA risk level: high-risk (RR>=1.1); no risk (RR≈1); and inconclusive evidence). The high-risk category was further subdivided into: slightly higher risk (RR=1.1 to 2.0), moderately higher risk (RR=2.1 to 5.0); and considerably higher risk (RR=5.0 and above). Conditions identified as having a moderately or considerably higher relative crash risk included alcohol abuse and dependence, dementia, epilepsy, multiple sclerosis, psychiatric disorders (pooled and including substance abuse), schizophrenia, depression, sleep apnoea, and cataracts. Conditions assigned to the slightly higher risk category included cardiovascular disorders, diabetes mellitus, rheumatoid arthritis (in women), osteoarthritis, neurological disorders (pooled), respiratory disorders, and vision conditions (pooled). Charlton et al. (2010) reported that the overall quality of the evidence on the association between health conditions and crash risk was modest, with only one prospective population-based study identified. Diagnostic accuracy, disease severity, disease exposure time, and the absence of control for comorbidities and driving exposure were cited as commonly unaddressed sources of bias and confounding.

In a second systematic review sponsored by the Norwegian Institute of Transport Economics, Vaa (2005) conducted a meta-analysis on the association between physical impairments, disease, ageing, and MVAs spanning the period between 1964 and 2002. The broad exposure categories included were age, sex, vision impairment, hearing impairment, arthritis/locomotor disability, cardiovascular disease, diabetes mellitus, neurological

disease, alcoholism, renal disorders, and illegal drug and medication use. The selected impairments and medical conditions were those identified as relevant in the European Union by The Council of the European Communities. Of the 62 studies included in the meta-analyses, 70.6% were based on the US population and 9.3% were based in Canada. For every broad health category considered, with the exception of renal disorder, the relative risk of being involved in a driving accident was higher in those affected by the conditions than those not affected: relative risks ranged from 1.09 to 2.00. The weighted mean relative risk of the pooled health conditions--based on 298 study results--was 1.33 (95% CI 1.28-1.37, $p<0.001$). The health condition with the highest recorded relative risk was the combination of sleep apnea and narcolepsy (RR=3.71, 2.14-6.40, $p<0.001$).

As a whole, these comprehensive studies suggest that a significant proportion of the most highly prevalent chronic health conditions in North America, e.g. cardiovascular disease, diabetes, neurological diseases, respiratory disorders, psychiatric disorders, and rheumatoid arthritis, are potential risk factors for MVAs.

Epilepsy, Driver Licensing, and MVA Risk

PWE were banned from driving when compulsory licensing policies initially came into effect (Steinwall, 1972). The purported dangers associated with driving by PWE were and continue to be based on the premise that a seizure or loss of consciousness, while driving, has a high probability of resulting in a MVA and endangers the safety of the driver and the public (Drazkowski, 2007). Risk of MVA in PWE have also been raised in persons modifying or discontinuing treatment with antiepileptic drugs (Krumholz & Hopp, 2016; Specchio & Beghi, 2004). Better treatment options to control seizures and greater understanding of the various manifestations of epilepsy eventually led to the liberalization

of driving policies, allowing PWE to drive under certain conditions (Krumholz, Fisher, Lesser, & Hauser, 1991). Currently, several developed countries have driving policies targeting PWE that include restrictions based on minimum seizure-free periods for driving admissibility (Charlton et al., 2010). In the U.S., the Epilepsy Foundation (2017) maintains a database of state driving laws detailing the requirements for periodic medical updates, seizure-free minimum periods, mandatory reporting of PWE by physicians, and whether departments of motor vehicles allow appeals for license denials. Minimum seizure-free periods range from zero to 18 months across the US states.

Regarding driver licensing, Sillanpää and Shinnar (2005) found that even in PWE who had achieved five years of seizure remission, the proportion of licensed drivers was lower than in PWOE, 73% versus 90% respectively, $p < 0.006$. A similar licensing trend was confirmed in a study by McLachlan, Starreveld, and Lee (2007). In PWE, males, those diagnosed with idiopathic epilepsy [versus cryptogenic or symptomatic etiology], those who held a job, and those without learning disabilities had a greater likelihood of being licensed to drive (Sillanpää & Shinnar, 2005).

Results from studies linking epilepsy status to MVAs are often inconsistent and methodological differences between such studies complicate the application of meta-analyses (Classen et al., 2012; Krumholz & Hopp, 2016; Naik, Fleming, Bhatia, & Harden, 2015). A few studies have reported the absence of an association between epilepsy status and increased risk of MVA when comparing PWE to PWOE (Kwon et al., 2011; McLachlan et al., 2007; Sillanpää & Shinnar, 2005). However, the weight of evidence suggests increased risk of MVA in PWE relative to PWOE (Charlton et al., 2010; Lings, 2001; Vaa, 2005). Conducting a meta-analysis based on eight studies that compared MVA

risk in persons with epilepsy, sudden disturbance of state of consciousness, and other seizures against controls from the general population, Vaa (2005) reported elevated risk of MVA in PWE relative to PWOE, RR= 1.84 (95% CI 1.68-2.02), $p < 0.05$. Likewise, a large systematic review on MVA risk from health conditions led by Charlton et al. (2010) concluded that studies investigating MVA risk in PWE versus PWOE reported a relative risk that ranged from 1.1 to over 5.0. Studies specifically investigating differences in MVA risk from multimorbidity in PWE could not be identified from the scientific literature.

Multimorbidity and MVAs

While the association between individual health conditions and MVA risk is well established (Vaa, 2005), the association between multimorbidity and MVA is much less clear (Dischinger, Ho, & Kufera, 2000; Koepsell et al., 1994; Marottoli, Cooney, Wagner, Doucette, & Tinetti, 1994; Oxley et al., 2005; Papa et al., 2014; Sims, McGwin Jr, Allman, Ball, & Owsley, 2000; Vernon et al., 2002). A systematic review conducted by Marshall and Man-Son-Hing (2011) reported a positive exposure-outcome trend between multimorbidity and MVA risk based on six studies. Of these, only two studies included drivers of all ages (Dischinger et al., 2000; Vernon et al., 2002). Young and middle age adults, who are becoming increasingly multimorbid, were underrepresented. The most recent study reporting on the relationship between multimorbidity and MVA risk was published by Papa et al. (2014). Using a cross-sectional study design, the investigators recruited 600 consecutive patients referred for care to the department of internal medicine at the University of Naples, Italy. Of these, 327 were confirmed passenger vehicles drivers. Participants took part in an interview concerning their health-related behaviors, functional and cognitive statuses, medical history, and driving record over the past 5 years. The

sample was limited to adults 40 years of age and older; younger drivers were those aged 40 to 70 years and older drivers were those over the age of 70. Driving exposure was assessed as distance traveled in kilometers per year, subsequently categorized as low [< 6,000], medium [6,000 to 12,000], or high [>12,000]. Morbidity status was assessed using the Cumulative Illness Rating Scale (CIRS), which includes 14 health conditions: cardiovascular diseases, vision and hearing issues, gastrointestinal diseases, liver, kidney, and genitourinary diseases, musculoskeletal diseases, metabolic conditions related to the endocrine system, neurological diseases, and psychiatric disorders. The authors found a marginally increased risk of MVA in older drivers [>70 years] compared to younger drivers [40 to 70 years], ($p = 0.045$). They also found that the number of current drivers diminished with increasing comorbidity; $\chi^2 = 16.206$; $p<0001$. However, this trend was only significant in the older driver category: $drivers_{\leq 70}$, $\chi^2 = 7.301$, $p = 0.462$; $drivers_{>70}$ $\chi^2 = 1.543$, $p = 0.026$. In the 40 to 70 years age group, increasing multimorbidity was significantly associated with an increase in crash percentage across tertiles [$T_1 = 10.1\% < T_2 = 26.0\% < T_3 = 37.0\%$, $\chi^2 = 5.885$, $p = 0.048$]. The same trend was could not be replicated in the older age group, where a non-significant decrease in crash percentage across increasing multimorbidity tertiles was observed [$T_1 = 32.1\% > T_2 = 27.4\% > T_3 = 24.5\%$, $\chi^2 = 0.633$, $p = 0.729$]. These findings indicate that increasing multimorbidity may result in compounded MVA risk in non-elderly adults but not necessarily in those above the age of 70 years.

Medical Interventions and MVA Risk

A common difficulty in assessing and interpreting MVA risk from morbidity is the possibly that the effects observed result not from the medical conditions themselves but from the

medical interventions used to treat them (Charlton et al., 2010). Even when a condition is being treated with drugs, one has to wonder how consistently patients comply with their treatment regimens, whether adverse reactions are related to medical treatments relevant to MVA risk, or whether adverse consequences from medical interventions interfere with driving abilities and habits. In the Charlton (2010) systematic review cited earlier, the evidence on MVA risk resulting from medical interventions is largely inconclusive. Exceptions include treatments for sleep apnea and cataracts. In the case of benzodiazepines for the treatment of psychiatric disorders (pooled conditions) and antidepressant-tricyclics for treating depression, there appears to be observed increased risk of crash on those treated compared to those untreated but methodological limitations preclude a proper separation between disease and treatment exposure (Dobbs, 2005).

Thesis Framework

Knowledge Gaps

This thesis addresses five related and highly relevant knowledge gaps. These priority research topics are summarized below and are the basis for the thesis chapters.

Chapter II (Manuscript 1): The growing number and size of EHR data repositories, as well as the advantages of this form of health information sparked my interest in the Cerner Health Facts (HF) database. HF is a large EHR repository containing health services utilization data from more than 37 million unique individuals distributed across the four US census regions. HF contains anonymized and standardized diagnostic, pharmacy, procedural, and demographic information on Americans of all ages, sex, race, and socio-economic status who visited over 400 inpatient, outpatient, and emergency department care

settings. HF therefore has incredible potential for the investigation of health problems and epidemiological questions. A review of the literature revealed, however, that none of the commonly used measures of multimorbidity had been either developed or validated with HF data. Without empirical evidence of predictive ability and accuracy, the use of risk adjustment instruments validated in other data sources remained questionable in HF.

Chapter III (Manuscript 2): Measures of multimorbidity perform best under specific conditions. These conditions typically include: the length of a patient's history examined for the presence or absence of recorded diagnoses (lookback period), and the manner by which morbidity prevalence is summarized. For example, a lookback period can be limited to a single health care encounter or it can include encounters from previous episodes of health services utilization. When summarizing the multimorbidity status of a person, recorded health conditions can be reported as the sum of coexisting conditions, they can be treated as a series of distinct dichotomous indicators [present vs. absent], or they can be pooled into a weighted score that accounts for the relative severity of each condition. To obtain optimal results from the use of measures of multimorbidity in a specific data source, the consequences of making the above methodological choices should be evaluated empirically. In HF, the consequences resulting from these methodological choices had not been evaluated.

Chapter IV (Manuscript 3): Several studies have identified health conditions as risk factors for MVAs. However, findings on the possible relationship between multimorbidity and MVA were scarce, mostly representative of the elderly population, and often based on survey data which are prone to specific forms of bias. An investigation on the hypothesized

exposure-outcome relationship between multimorbidity and MVA conducted with EHR data, inclusive of all adults of driving age, would make a novel contribution to the existing literature.

Chapter V (Manuscript 3): Epilepsy is the quintessential example of a health condition associated with driving restrictions and adverse driving outcomes. Aside from books written by clinicians, there is a paucity of systematic and peer-reviewed syntheses describing risk factors associated with the onset and progression of epilepsy. In the context of this thesis, such a synthesis of the literature becomes a useful tool for theorizing which demographic, socioeconomic, and biological factors might be associated with the acquisition of a driver's license, driving, and MVA risk in PWE.

Chapter VI (Manuscript 5): PWE are not only at increased risk of MVA, they are also disproportionally multimorbid compared to PWOE. While MVA studies involving PWE might control for comorbid health conditions, multimorbidity status has never been targeted specifically as a risk factor for MVA in that population.

Research Objectives and Questions

The knowledge gaps described above were translated into sets of research objectives complemented with specific research questions. Work conducted to advance the research objectives, A to E, is described in separate thesis chapters.

Objectives A (Manuscript 1):

To conduct an external validation and compare the performance of the Quan and the Agency for Healthcare Research and Quality (AHRQ, version 3.7) Elixhauser Comorbidity Measures (ECM) for predicting inhospital mortality of all-causes during an index encounter and at 1-year, in HF.

Question A1: What is the discrimination and calibration performance of the Quan Enhanced ICD-9 and the AHRQ version 3.7 ECMs when predicting inhospital mortality from all-causes at the index encounter and after one year of follow-up in HF?

Question A2: Based on the predictive performance metrics obtained during the external validation procedures, which of the ECMs, Quan versus AHRQ, is a better tool for risk adjustment in HF?

Objectives B (Manuscript 2):

First, to identify the optimal look back period (index encounter alone versus 1 year versus 2 years) for the Quan ECM when predicting all-cause inhospital mortality and inhospital mortality at 1 year in HF. Second, to ascertain which comorbidity summary method (the binary, total, or weighted) best predicts the mortality outcomes.

Question B1: Using the best performing ECM variant identified in *Objective 1*, which lookback period has the best discrimination performance when predicting inhospital mortality in HF: the index encounter alone, the index encounter with one year of lookback, or the index encounter with 2 years of lookback?

Question B2: Using the best performing ECM variant identified in *Objective 1*, which comorbidity summary method has the best discrimination performance for predicting inhospital mortality in HF: the original ECM binary indicators, the sum of all comorbidities, or the weighted comorbidity score?

Objectives C (Manuscript 3):

First, to conduct a case-control study that examines whether there is an exposure-response relationship between multimorbidity and MVA occurrence. Second, to investigate if sex and age modify the effect of the relationship between multimorbidity and MVA risk.

Question C1: Does the relationship between multimorbidity and MVA risk follow an exposure-response curve?

Question C2: Does age modify the relationship between multimorbidity and MVA risk?

Question C3: Does sex modify the relationship between multimorbidity and MVA risk?

Objective D (Manuscript 4):

To systematically review the literature on risk factors for the onset and progression of epilepsy.

Question D1: What are the risk factors for the onset and natural progression of epilepsy?

Objectives E (Manuscript 5):

First, to evaluate if increasing multimorbidity is associated with MVA risk in PWE. Second, to investigate if individual comorbidities are independently associated with MVAs in PWE.

Question E1: Does multimorbidity modify the risk of MVAs in PWE?

Question E2: Which, if any, comorbid health conditions in PWE are associated with MVA risk?

Conceptual Model

The research questions, methodologies, interpretation and discussion of findings presented in this thesis were informed by a combination of the principles of population health and risk management science. The *Integrated Framework for Risk Management and Population Health* (henceforth the integrated framework) proposed by Krewski et al. (2007) provides a cohesive and comprehensive tool that integrates the fundamental principles of these two disciplines (figure 1.1).

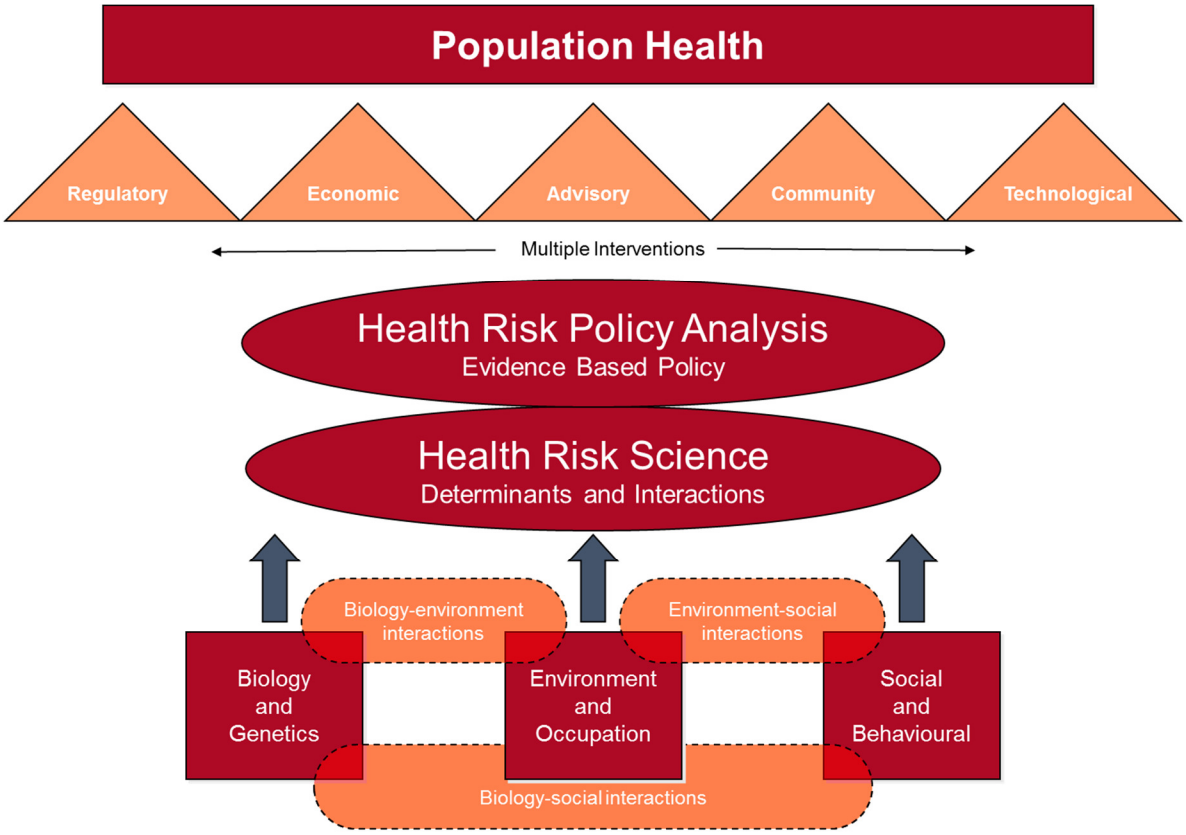

Figure 1.1. Integrated framework for risk management and population health. Adapted from Krewski et al. (2007) with permission to reproduce granted by Taylor & Francis.

According to the Public Health Agency of Canada (2012, pp. 1-2), population health is "an approach to health that aims to improve the health of the entire population and to reduce health inequities among population groups. In order to reach these objectives, it looks at and acts upon the broad range of factors and conditions that have a strong influence on our health." Population health is principally concerned with addressing health inequities between individuals (Epp, 1986; Young, 2004) that are believed to result from the interaction of a complex set of social and other health determinants (Evans, Barer, Marmor, & Moss, 1995; Marmot & Wilkinson, 2006). In the integrated framework, these interacting health determinants are broadly categorized as biological, environmental and occupational,

and socio-behavioral. Related work by the WHO's Commission on the Social Determinants of Health suggests that health inequities also result from distal causes, termed structural determinants, that interact and contribute to the stratification of populations by socio-economic status, gender and ethnicity (CSDH, 2008; Solar & Irwin, 2010). Structural determinants of health, which include governance structures, macro-economic/social/public policies, and prevailing socio-cultural norms and values, are identified in the top portion of the framework by Krewski et al. (2007). These conditions modulate the ability of individuals to obtain higher levels of educational attainment, make occupational gains, and increase their income. Structural determinants of health, particularly socio-economic status, have a direct and indirect influence on proximal and intermediary determinants of health as they often impact material circumstances such as access to safe housing, food security, and working conditions (Marmot, 2001; Marmot & Wilkinson, 2006). Together, distal, intermediate, and proximal determinants of health result in differential rates of physical and psychological health condition following a social gradient (Evans et al., 1995; Marmot, 2001; Marmot, Friel, Bell, Houweling, & Taylor, 2008; Marmot, Rose, Shipley, & Hamilton, 1978; Marmot et al., 1991; Marmot & Wilkinson, 2006). The decreasing proportion of multimorbid individuals across increasing socioeconomic strata described earlier is an example of the compounding effects of health determinants (Barnett et al., 2012; Roberts et al., 2015).

Evidence suggests that health inequities are best addressed with multi-level, multi-sectorial intervention strategies (Edwards & McDowell, 1998; Edwards, Mill, & Kothari, 2004) that are theoretically informed (Carpiano & Daley, 2006; Krieger, 2001). The integrated framework supplements the foundations of the population health approach by

incorporating elements of health risk science and health risk policy analysis. By doing so, the model moves beyond the population health focus, which privileges the promotion of positive health determinants, and attempts to identify and propose management strategies targeting the sources of exposure that confer specific health risks to individuals.

The focus of this thesis can be subsumed under the health risk science component of the integrated framework. More specifically, the work conducted was a risk assessment of the consequences of multimorbidity on motor-vehicle accidents. Throughout the thesis, the term accident is used in lieu of crash or collision. Even so, my intent was to investigate those accidents that are avoidable, those not attributable to chance alone. The U.S. National Research Council's (NRC) (1983) framework for risk assessment, which influenced the development of the integrated framework, lists four components of risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization. The hazard of interest in this thesis was multimorbidity and the principal risk of focus was MVA occurrence. Regarding the assessment of a dose-response relationship, this thesis reports on whether increasing levels of multimorbidity translate into a hypothesized increased risk of MVA. By reporting on multimorbidity prevalence in the sample, the thesis provides a relative exposure assessment in U.S. adults. This exposure assessment also included stratified analyses by demographic indicators: age and sex. Risk characterization pools and weights the evidence of the three risk assessment dimensions described.

A good risk characterization will restate the scope of the assessment, express results clearly, articulate major assumptions and uncertainties, identify reasonable alternative interpretations, and separate scientific conclusions from policy judgments.

A risk characterization of the consequences of multimorbidity is provided in the discussion sections of the individual chapters, as well as in the overall discussion in chapter 7.

Thesis Chapters

Chapters II to VI represent independent studies conducted as part of this thesis. The reporting format of each chapter reflects the editorial requirements of the peer-reviewed academic journal where the study manuscript was submitted for publication.

Chapter II: External validation and comparison of two variants of the Elixhauser comorbidity measures for all-cause mortality

- Objectives A
- Status: Published in the journal *PLOS ONE* in March 2017.

Chapter III: Optimal look back period and summary method for Elixhauser comorbidity measures in a U.S. population-based electronic health record database

- Objectives B
- Status: Published in *Open Access Medical Statistics* in January 2017.

Chapter IV: An exposure–response relationship between multimorbidity and motor-vehicle accidents

- Objectives C
- Status: Published in the *Journal of Transport & Health* in February 2017.

Chapter V: A systematic review of the risks factors associated with the onset and natural progression of epilepsy

- Objectives D
- Status: Published in *NeuroToxicology* in March 2016.

Chapter VI: Association between multimorbidity and motor-vehicle accidents in persons with epilepsy

- Objectives E
- Status: Unpublished as of September 2017.

Chapter VII: Discussion and conclusion

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Chapter 2 - External Validation and Comparison of Two Variants of the Elixhauser Comorbidity Measures for All-Cause Mortality

Yannick Fortin[1,2], James A.G. Crispo[1,2,3], Deborah Cohen[2,4,5], Douglas S McNair[6], Donald R. Mattison[1,7], Daniel Krewski[1,2,7]

Authors Note

1. McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada. 2. School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada. 3. Fulbright Canada Student, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 4. Canadian Population Health Initiative (CPHI), Canadian Institute for Health Information (CIHI), Ottawa, Ontario, Canada. 5. Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. 6. Cerner Corporation, Kansas City, Missouri, USA. 7. Risk Sciences International, Ottawa, Ontario, Canada.

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Abstract

Assessing prevalent comorbidities is a common approach in health research for identifying clinical differences between individuals. The objective of this study was to validate and compare the predictive performance of two variants of the Elixhauser comorbidity measures (ECM) for inhospital mortality at index and at 1-year in the Cerner Health Facts® (HF) U.S. database. We estimated the prevalence of select comorbidities for individuals 18 to 89 years of age who received care at Cerner contributing health facilities between 2002 and 2011 using the AHRQ (version 3.7) and the Quan Enhanced ICD-9-CM ECMs. External validation of the ECMs was assessed with measures of discrimination [c-statistics], calibration [Hosmer–Lemeshow goodness-of-fit test, Brier Score, calibration curves], added predictive ability [Net Reclassification Improvement], and overall model performance [generalized R^2]. Of 3,273,298 patients with a mean age of 43.9 years and a female composition of 53.8%, 1.0% died during their index encounter and 1.5% were deceased at 1-year. Calibration measures were equivalent between the two ECMs. Calibration performance was acceptable when predicting inhospital mortality at index, although recalibration is recommended for predicting inhospital mortality at 1 year. Discrimination was marginally better with the Quan ECM compared the AHRQ ECM when predicting inhospital mortality at index (c_{QuaN} =0.887, 95% CI: 0.885 - 0.889 vs. c_{AHRQ}=0.880, 95% CI: 0.878 - 0.882; p <.0001) and at 1-year (c_{QuaN} =0.884, 95% CI: 0.883 - 0.886 vs. c_{AHRQ}=0.880, 95% CI: 0.878-0.881, p <.0001). Both the Quan and the AHRQ ECMs demonstrated excellent discrimination for inhospital mortality of all-causes in Cerner Health Facts®, a HIPAA compliant observational research and privacy-protected

data warehouse. While differences in discrimination performance between the ECMs were statistically significant, they are not likely clinically meaningful.

Introduction

With data on over 47 million unique patients who received care at nearly 500 US care facilities since 2000, the Cerner Health Facts® (HF) electronic health record database is a rich source of data available for epidemiological and health services research (B.R.I.D.G.E. to Data, 2014). In addition to demographic and payer data, HF contains longitudinal diagnostic, procedure, pharmacy, and laboratory information on individuals receiving care within Cerner data networks.

To date, the predictive performance of commonly used comorbidity risk adjustment methods have yet to be corroborated in HF. Measures of comorbidity are useful tools for controlling for variation in overall patient health or adjusting for case-mix in epidemiological studies using electronic health data (Fischer et al., 2015; Schneeweiss & Maclure, 2000; Schneeweiss et al., 2001; van Gestel et al., 2012). They are also used in observational drug effectiveness, health services, and outcomes studies when the unit of analysis cannot be appropriately randomized (Bosetti et al., 2015; French, Campbell, Spehar, & Angaran, 2005; Glynn, Gagne, & Schneeweiss, 2012; Holmes, Luo, Kuo, Baillargeon, & Goodwin, 2013; Suh, Hay, Johnson, & Doctor, 2012). Measures of patient comorbidity have shown to be good predictors of short- and long-term mortality, hospital costs, length of stay (LOS), and readmission (Chu, Ng, & Wu, 2010; Hall, 2006; Sharabiani et al., 2012; Yurkovich et al., 2015). Failure to take patient comorbidity into account may lead to biased analyses, possibly due to confounding or systematic differences in health

status among populations. Validated comorbidity measures may be used to address this issue.

In its simplest form, measures of comorbidity are aggregates of diagnostic codes used to identify the prevalence of predetermined health conditions in individuals documented in health data sources such as electronic health records. Of the many comorbidity measures validated for use with electronic health data, the original Elixhauser (1998) comorbidity measures (ECM) are frequently reported as having greater predictive performance for short- and long-term mortality than competing models (Chu et al., 2010; Lix, Quail, Teare, & Acan, 2011; Sharabiani et al., 2012; Stukenborg, Wagner, & Connors, 2001). The ECM target 30 medical, psychiatric, and lifestyle-related health conditions that are negatively associated with adverse health outcomes: congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension (un/complicated), paralysis, neurological disorders, chronic pulmonary disease, uncomplicated diabetes, complicated diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease without bleeding, aids/HIV, lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression. A few years after the publication of the original ECM, Quan et al. (2005) and the Agency for Healthcare Research and Quality (AHRQ) (2014) separately developed revised ECM variants, with Quan and colleagues reporting enhanced predictive performance for inhospital mortality compared to both the original ECM and the AHRQ ECM (version 3.0). Studies have not examined whether the Quan variant is superior to the most recent AHRQ ECM (version

3.7) at predicting inhospital mortality and inhospital mortality at 1-year despite differences in the ICD-9-CM codes used to identify prevalent health conditions by each variant. The AHRQ ECM also differs from the Quan ECM by the exclusion of diagnostic codes making up a cardiac arrhythmia health condition group. Neither the Quan nor the AHRQ ECMs have been validated in HF.

The objectives of this study were to conduct an external validation and compare the performance of the Quan and AHRQ (version 3.7) ECMs for predicting inhospital mortality of all-causes at index and at 1-year in HF.

Methods

Data Source

Study data were derived from inpatient and emergency care encounters in Cerner Health Facts® (Kansas City, MO, USA), an administrative health database compliant with the US Health Insurance Portability and Accountability Act (HIPAA). Approximately 500 health care facilities have contributed patient-level clinical encounter data to HF since January 2000. Data contributors range in size from those with fewer than five beds to those with over 500 and are located throughout the U.S. with a greater proportion situated in the Northeastern region of the United States (Taylor, 2014). University affiliated teaching hospitals comprise 40% of data contributors and they contribute more than 60% of all health encounters. Contributing health care facilities are categorized by teaching status, population density, bed size, and census region. HF data includes diagnoses recorded during emergency department (ED) visits, outpatient care, and hospitalizations, pharmacy orders, surgical procedures, laboratory and microbiology tests, and clinical procedures (B.R.I.D.G.E. to Data, 2014).

This study was approved by the Office for Research Ethics and Integrity at the University of Ottawa.

Study Population and Index Encounter

Individuals 18 to 89 years of age at the time of an ED or inpatient encounter at any HF contributing facility between January 2002 and December 2012 were eligible for inclusion. One ED or inpatient encounter was randomly selected between January 1st, 2002 and December 31st, 2011 as the index encounter for each individual. Outpatient visits were excluded as possible index encounters since deaths, the study outcome, are relatively infrequent during outpatient care (Keyes et al., 2008; Raymond, Grossman, Weaver, Toti, & Winikoff, 2014). Persons younger than 18 years were excluded due to the relatively lower prevalence of Elixhauser health conditions and mortality in this population. Individuals 90 years or older are assigned to a single category in HF in order to comply with HIPAA requirements and were excluded to ensure age remained continuous in our analyses. Care recipients who transferred to or from any other health facility during the index encounter were excluded to avoid cases with higher potential for missing information (van Walraven et al., 2009). Patient characteristics included sex, age at the index encounter, health insurance status, and race restricted to Caucasians, African Americans, Hispanics, and Asians. Health insurance status was categorized using AHRQ recommendations (Barrett, Lopez-Gonzalez, Hines, Andrews, & Jiang, 2014), including private, Medicaid, Medicare, uninsured [self-pay], other (TRICARE-CHAMPUS, international plan, research funded, Title V, worker's compensation), or missing. For reasons unknown, some HF contributing health care facilities voluntarily withhold

information on the health insurance status of their patients, which leads to a significant proportion (>40%) of missing values.

Elixhauser Comorbidity Measures and Variants

The original ECM (1998) comprises binary indicators for the diagnosis of 30 clinical conditions, each defined by a combination of codes according to the International Classification of Disease, Ninth Edition (ICD-9) (CDC, 2009a). Two variants of the original ECM were compared with the study sample; the AHRQ's latest comorbidity software (version 3.7) (AHRQ, 2014) and Quan et al.'s (2005) Enhanced ICD-9-CM classification of comorbidities. The presence or absence of ECM comorbidities was assessed by examining the ICD-9-CM diagnostic codes recorded during the index encounter.

Outcomes

The primary study outcomes were inhospital mortality of any causes during the index encounter and at 1-year. Inhospital mortality at 1-year was defined as a death recorded in a discharge abstract for an ED visit or an inpatient admission during the year that followed the admission date of the index encounter. Deaths recorded during the index encounter were therefore included in the mortality at 1-year outcome.

Data Analysis

The prevalence of comorbidities was described with counts and percentages while frequency differences between the ECMs were compared with McNemar's test (McNemar, 1947). To quantify the size and the clinical importance of the observed differences in the

prevalence of comorbidities across ECMs, we derived Cohen's h (Cohen, 1988). Multiple logistic regression was used to predict the risk of mortality outcomes and output overall measures of model performance. External validation of the ECMs in HF was accomplished by deriving measures of calibration and discrimination for every predictive model, outcome, and sample combination considered (Collins et al., 2014; Moons, Altman, Reitsma, & et al., 2015). Model discrimination was assessed using the Area under the Receiver Operating Characteristic (ROC) curve (AUROC), an indicator of the ability of the ECMs to discriminate between the mortality statuses (Gonen, 2006; Iezzoni, 1997). The AUROC is often referred to as the concordance index number (c-statistic) and ranges between 0.5 [no discrimination] and 1.0 [perfect discrimination], with values above 0.7, 0.8, and 0.9 considered reasonable, strong, and exceptional, respectively (Hosmer Jr, Lemeshow, & Sturdivant, 2013). The discrimination performance of each ECM was compared to 1) a baseline model, and 2) the competing ECM. Predictors in the baseline model were limited to sex and age at the index encounter to align with prior ECM validation and comparison studies (Li et al., 2010; Zhu & Hill, 2008). Differences in the AUROC between the fitted models were tested using the ROC and ROCCONTRAST statements in SAS (Gonen, 2006). The ROCCONTRAST option is an algorithm based on the non-parametric Mann-Whitney statistics developed by DeLong et al. (1988) for comparing the significance of differences between correlated ROC curves.

Model calibration measures included the Hosmer–Lemeshow goodness-of-fit test, which evaluates the degree of agreement between the predicted and observed risk of inhospital mortality (Kramer & Zimmerman, 2007). The Hosmer–Lemeshow goodness-of-fit test outputs a Pearson chi-square score with a corresponding p-value: rejection of the

null hypothesis indicates an imperfect correlation between predicted and observed values. Calibration plots displaying predicted inhospital mortality probabilities on the x-axis and observed inhospital mortality frequencies on the y-axis were generated to visually inspect calibration performance across risk deciles. The plots were enhanced using a smoothing spline function. Brier scores, which equate to the mean squared difference between predicted probabilities and observed outcomes, were included as measures of model accuracy [with lower Brier scores reflecting greater accuracy] (Brier, 1950). Explained variation was reported in terms of the generalized R^2.

It has been argued that the AUROC can be of limited value when comparing small incremental differences between predictive models (Cook, 2010). To quantify the net improvement in predictive ability of the ECM that achieved the highest level of discrimination over the ECM with the lowest level of discrimination, we computed the net reclassification improvement (NRI) measure (Pencina, D'Agostino, & Steyerberg, 2011; Pencina, D'Agostino, & Vasan, 2008). Category-free NRI (NRI>0) assesses whether individuals are reclassified correctly in a prognosis model compared to a reference model. NRI>0 is a quantification of the net correct changes in model-based probabilities for both events [where improvement equates to increased probabilities of the outcome] and non-events [where improvement equates to decreased probabilities of the outcome] (Pencina, D'agostino, & Vasan, 2010, p. 14). The NRI was implemented without risk categories because this approach allows for universal comparisons, it is robust against changing event-rates, and it was the most objective approach available in light of the insufficient evidence for meaningful risk categories for all-cause mortality in the literature (Pencina et al., 2011). NRI>0 values were computed using a SAS macro developed by Kennedy et al. (2010) and

are reported with the percentage of events and non-events correctly reclassified. Statistical analyses were completed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Risk Groups

Recent history of hospitalization or emergency department use is associated with increased risk of hospital readmission and death (Lanièce et al., 2008; van Walraven et al., 2010). To further explore the utility of the ECMs, measures of discrimination and calibration performance were generated for both high and low risk patient groups. Individuals with evidence of one or more inpatient stay in the 12 months preceding the index encounter, or three or more emergency department visits in the 3 months preceding the index encounter, were defined as high risk. Patients that did not satisfy the high-risk criteria were assigned to the low risk group.

Sensitivity Analyses

Admissible index encounters in this study included ED visits and inpatient stays. It is reasonable to hypothesize that persons admitted for inpatient stays would generally be at greater risk of inhospital death than persons visiting the emergency department. To investigate potential differences in ECM performance by index encounter type, complimentary validation analyses were performed on index encounters recorded as ED visits and inpatient stays separately.

Results

We identified 3,273,298 unique individuals who satisfied our inclusion criteria and received care at a HF care facility between 2002 and 2011. Mean age was 43.9 years and

women were the majority (53.8%) (Table 2.1). Individuals were primarily Caucasians (72.3%), with others identified as African American (21.7%), Hispanic (4.5%), or Asians (1.5%). Index encounters were reported by health care institutions from the four US census regions: Northeast (36.1%), Midwest (19.8%), South (32.9%), and West (11.2%). Privately insured individuals comprised 48.3% of non-missing payer class cases. Most patients in the sample were classified as low risk (92.0%). Approximately two-thirds of index encounters were ED visits (67.4%). A total of 31,298 (1.0%) and 50,215 (1.5%) inhospital deaths of all-cause were recorded during the index encounter and at 1-year, respectively. As expected, high risk patients had a greater frequency of inhospital mortality than low risk patients at index [1.9% vs 0.9%, χ^2 (1, N = 3,273,298) = 2,792.1, p<.0001], and at 1 year [4.2% vs 1.3%, χ^2 (1, N = 3,273,298) = 13,509.1, p<.0001].

Table 2.1 Patient Demographic and Index Encounter Characteristics, N = 3,273,298

Characteristics	N (%)
Sex	
Female	1,761,525 (53.8)
Male	1,511,773 (46.2)
Age (Years)	
Mean ± SE	43.9 ± 0.01
Race	
Caucasian	2,366,665 (72.3)
African American	711,051 (21.7)
Hispanic	146,877 (4.5)
Asian	48,705 (1.5)
Insurance Status	
Private	795,449 (24.3)
Medicare	370,701 (11.3)
Medicaid	248,009 (7.6)
Uninsured	378,536 (11.6)
Other	139,745 (4.3)
Missing	1,340,858 (41.0)
Risk Group	
Low	3,010,916 (92.0)
High	262,382 (8.0)
Inhospital Mortality	
Deaths	31,298 (1.0)
Inhospital Mortality at 1-Year	
Deaths	50,215 (1.5)
Care Setting, Index Encounter	
ED Visit	2,204,680 (67.4)
Inpatient Stay	1,068,618 (32.6)
Census Region	
Northeast	1,180,270 (36.1)
Midwest	648,644 (19.8)
South	1,077,965 (32.9)
West	366,419 (11.2)

ED=Emergency department. SE=Standard error.

In descending order, hypertension, uncomplicated diabetes, chronic pulmonary disease, and fluid and electrolyte disorders were the most prevalent conditions identified by both ECMs (Table 2.2). Excluding HIV/AIDS, differences in prevalence between the ECMs for every health condition group were statistically significant based on McNemar's test, $p<0.0001$. However, for most of the conditions assessed, the variation in prevalence between the ECMs differed by less than 1%, with the greatest differences observed for deficiency anemia (2.58%) and psychoses (1.22%). According to the interpretation criteria suggested by Cohen (1988), only the deficiency anemia group demonstrated a small ($h=0.203$) practically meaningful difference in prevalence by ECM.

Table 2.2. Prevalence of Comorbid Conditions by ECM Variant, N = 3,273,298

Condition	Quan, N (%)	AHRQ, N (%)	McNamar's Test *P Value*	Cohen's h
Hypertension	572,139 (17.48)	573,457 (17.52)	<.0001	0.001
Chronic Pulmonary Disease	256,170 (7.83)	248,676 (7.60)	<.0001	0.009
Diabetes Uncomplicated	226,807 (6.93)	227,815 (6.96)	<.0001	0.001
Fluid and Electrolyte Disorders	187,321 (5.72)	186,282 (5.69)	<.0001	0.001
Cardiac Arrhythmia	174,656 (5.34)	na	na	na
Depression	113,659 (3.47)	89,410 (2.73)	<.0001	0.043
Congestive Heart Failure	99,280 (3.03)	90,775 (2.77)	<.0001	0.015
Alcohol Abuse	89,460 (2.73)	86,307 (2.64)	<.0001	0.006
Hypothyroidism	85,493 (2.61)	83,926 (2.56)	<.0001	0.003
Obesity	79,680 (2.43)	80,996 (2.47)	<.0001	0.003
Other Neurological Disorders	76,237 (2.33)	97,360 (2.97)	<.0001	0.040
Drug Abuse	61,260 (1.87)	59,029 (1.80)	<.0001	0.005
Renal Failure	60,238 (1.84)	57,231 (1.75)	<.0001	0.007
Solid Tumor without Metastasis	56,376 (1.72)	56,519 (1.73)	<.0001	0.000
Valvular Disease	51,250 (1.57)	21,907 (0.67)	<.0001	0.087
Peripheral Vascular Disorders	41,651 (1.27)	43,410 (1.33)	<.0001	0.005
Diabetes Complicated	34,016 (1.04)	34,111 (1.04)	<.0001	0.000
Liver Disease	31,307 (0.96)	21,910 (0.67)	<.0001	0.032
Psychoses	29,656 (0.91)	69,664 (2.13)	<.0001	0.102
Coagulopathy	27,019 (0.83)	27,330 (0.83)	<.0001	0.001
Rheumatoid Arthritis/collagen	24,143 (0.74)	22,407 (0.68)	<.0001	0.006
Metastatic Cancer	22,836 (0.70)	23,004 (0.70)	<.0001	0.001
Weight Loss	21,219 (0.65)	19,429 (0.59)	<.0001	0.007
Pulmonary Circulation Disorders	21,084 (0.64)	20,894 (0.64)	<.0001	0.001
Deficiency Anemia	19,745 (0.60)	104,246 (3.18)	<.0001	0.203*
Paralysis	13,707 (0.42)	19,001 (0.58)	<.0001	0.023
Blood Loss Anemia	10,884 (0.33)	24,487 (0.75)	<.0001	0.058
Peptic Ulcer Disease excl. bleeding	8,251 (0.25)	507 (0.02)	<.0001	0.076
Lymphoma	6,778 (0.21)	6,920 (0.21)	<.0001	0.001
AIDS/HIV	4,246 (0.13)	4,246 (0.13)	1.000	0.000

* Small effect size according to the interpretation criteria suggested by Cohen (1988). NA, not applicable.

Table 2.3 reports the performance measures of discrimination and calibration for the study sample and by patient risk groups. When predicting inhospital mortality during the index encounter, the Quan model (c=0.887, 95% CI: 0.885 - 0.889) had negligible but significantly higher discrimination than the AHRQ (c=0.880, 95% CI: 0.878 - 0.882; p <.0001) and baseline (c=0.820, 95% CI: 0.818 - 0.822; p <.0001) models. Similar results were obtained for predicting inhospital mortality at 1-year, the discrimination performance of the Quan model (c=0.884, 95% CI: 0.883 - 0.886) marginally exceeded the discrimination performance of the AHRQ (c=0.880, 95% CI: 0.878 - 0.881) and baseline (c=0.826, 95% CI: 0.824 - 0.827) models, p <.0001. Model discrimination for the mortality outcomes remained strong (AUROC>0.8) and the observed advantage of the Quan ECM over the AHRQ ECM was confirmed in both risk group samples. ROC plots displaying the minor discrimination advantage of the Quan ECM over the AHRQ ECM are provided in Figures 1 and 2.

There were no differences in Brier scores between competing ECMs, irrespective of the predicted outcome. The Brier scores were consistently lower when predicting inhospital mortality at index than at 1 year. These findings might indicate that the ECMs have better calibration when predicting the former outcome than when predicting the latter. The calibration plots reported in Figures 3 and 4 show good agreement between predicted and observed risk of inhospital mortality at index. However, the level agreement between the predicted and observed risk of inhospital mortality at 1 year were less satisfactory, suggesting the need for recalibration. As the observed risk of mortality at 1 year increased, the ECMs increasingly over-predicted the outcome. Results from the Hosmer–Lemeshow goodness-of-fit test indicated imperfect agreement between expected and observed risk,

irrespective of the ECM-outcome combination assessed. This is expected given the large study sample and previously reported simulation results from Kramer et al. (2007) showing the Hosmer-Lemeshow test to be particularly sensitive to sample size: even with a minor deviation (0.4%) from perfect fit between expected and observed risk, studies with sample sizes of 50,000 or more observations rejected the null hypothesis 100% of the time.

Explained variation (generalized R^2) was consistently higher, by approximately 1 to 2% with the Quan ECM compared to the AHRQ ECM across patient groups and mortality outcomes. Measures of discrimination (AUROC), calibration (Brier scores), and overall performance (generalized R^2) were consistently better in the low risk patient group compared to the high-risk patient group.

Net reclassification improvements were observed by the Quan ECM over the AHRQ ECM for the full sample, in high and low risk patients, and in patients with index encounter limited to inpatient stays. However, the magnitude of these improvements was low to moderate, between 0.35 to 0.62, on a possible NRI range of -2 to 2. The positive NRI scores observed, and the apparent greater predictive performance of the Quan ECM, were driven principally by improvements in model specificity (the correct reclassification of non-events). In every sample-outcome combination examined, the percentage of events correctly reclassified by the Quan ECM was negative, possibly indicating reduced sensitivity compared to the AHRQ ECM. In the sample limited to persons whose index encounter was an emergency department visit, this reduced sensitivity combined with minimal improvement in specificity by the Quan ECM compared to the AHRQ ECM resulted in negative NRI.

Table 2.3. Measures of Discrimination and Calibration Performance by ECM and Mortality Outcome

		External Validation			
		Inhospital Mortality at Index		Inhospital Mortality at 1 Year	
		Quan	AHRQ	Quan	AHRQ
All Patients N =3,273,298	AUROC [a] (95% CI)	0.887 (0.885,0.889) [G]	0.880 (0.878,0.882) [G]	0.884 (0.883,0.886) [G]	0.880 (0.878,0.881) [G]
	HL Test [b]	485.5*	459.8*	890.1*	879.1*
	Brier Score [c]	0.009	0.009	0.014	0.014
	R^2 [d]	24.9	23.1	25.1	24.0
	NRI>0 [e] (95% CI)	0.6115 (0.6006,0.6224)*		0.5234 (0.5149,0.5318)*	
	Reclassification, E - NE [F]	-18% - 79%		-27% - 80%	
	Deaths (%)	31,298 (1.0)		50,215 (1.5)	
High Risk Patients [f] N =262,382	AUROC [a] (95% CI)	0.870 (0.865,0.874) [G]	0.861 (0.857,0.866) [G]	0.834 (0.830,0.837) [G]	0.830 (0.826,0.833) [G]
	HL Test [b]	106.6*	96.7*	271.5*	261.1*
	Brier Score [c]	0.018	0.018	0.037	0.037
	R^2 [d]	22.7	21.4	20.7	20.0
	NRI>0 [e] (95% CI)	0.4725 (0.4450,0.5000)*		0.3566 (0.3384,0.3747)*	
	Reclassification, E - NE [F]	-15% - 62%		-28% - 64%	
	Deaths (%)	5,035 (1.9)		11,043 (4.2)	
Low Risk Patients [f] N =3,010,916	AUROC [a] (95% CI)	0.886 (0.884,0.889) [G]	0.879 (0.877,0.881) [G]	0.885 (0.883,0.886) [G]	0.880 (0.878,0.882) [G]
	HL Test [b]	378.0*	410.6*	619.4*	616.2*
	Brier Score [c]	0.008	0.008	0.012	0.012
	R^2 [d]	24.8	22.9	25.0	23.8
	NRI>0 [e] (95% CI)	0.6183 (0.6064,0.6302)*		0.5384 (0.5288,0.548)*	
	Reclassification, E - NE [F]	-18% - 80%		-27% - 80%	
	Deaths (%)	26,263 (0.9)		39,172 (1.3)	

* P-value < 0.001. E= Events. NE=Non-events.

[a] Area under the Receiver Operating Characteristic (ROC) curve (AUROC). AUROC is a measure of discrimination ranging from 0.5 (zero discrimination) to 1.0 (perfect discrimination).

[b] Pearson chi-square value derived from the Hosmer–Lemeshow goodness-of-fit test (Hosmer Jr et al., 2013).

[c] Measure of predictive accuracy, greater accuracy is reflected by lower score.
[d] Generalized R-squared, explained variation, displayed in percentage.
[e] Category-free net reclassification improvement using the AHRQ ECM as the reference model.
[f] E – NE, percentage of events (E) and non-events (NE) correctly reclassified by the Quan ECM compared to the AHRQ ECM. [g] AUROC curve differed significantly from the baseline model limited to age and sex ($p < 0.0001$), and from the competing ECM ($p < 0.0001$). Differences between AUROC curves were evaluated with the Mann-Whitney U test approach developed by DeLong et al. (1988). In the unstratified sample, the baseline model had an AUROC of 0.820 (95% CI 0.818-0.822) for inhospital mortality at index, and 0.826 (95% CI 0.824-0.827) for inhospital mortality at 1 year. For high risk patients, the baseline model had an AUROC of 0.770 (95% CI 0.764-0.775) for inhospital mortality at index, and 0.755 (95% CI 0.751-0.759) for inhospital mortality at 1 year. For low risk patients, the baseline model had an AUROC of 0.821 (95% CI 0.819-0.823) for inhospital mortality at index, and 0.828 (95% CI 0.826-0.830) for inhospital mortality at 1 year.
[f] High risk patients had one or more inpatient stay in the 12 months preceding the index encounter or three or more emergency department visits in the 3 months preceding the index encounter. Patients that did not satisfy the high-risk criteria were assigned to the low risk group.

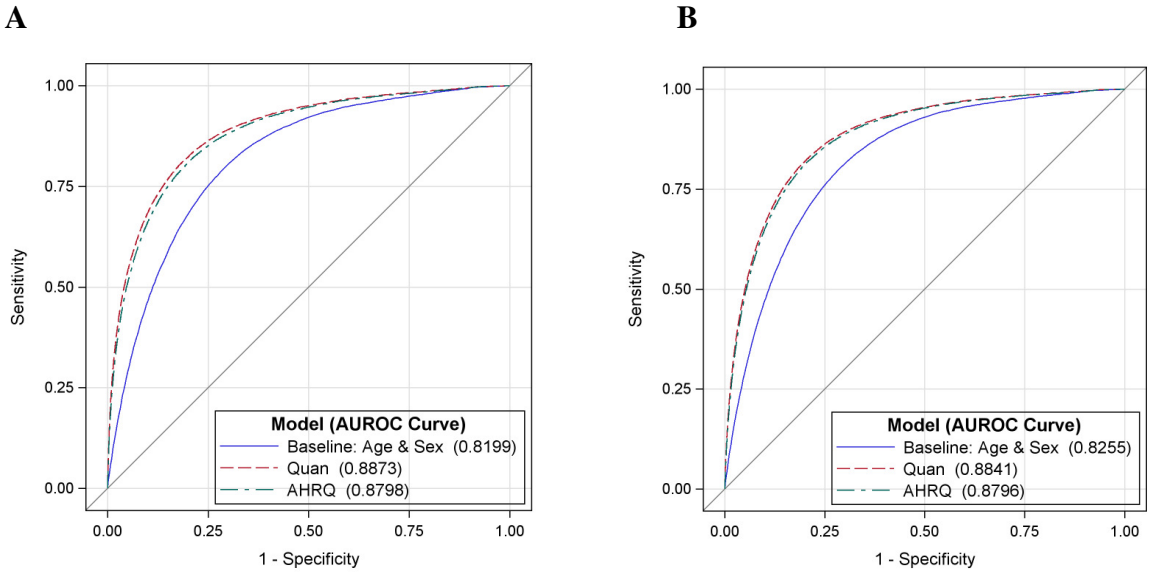

Fig 2.1. AUROC comparisons by ECM for predicting inhospital mortality at index [A] and at 1 year [B].
Abbreviations: AUROC, area under the receiver operating characteristic; ROC, receiver operating characteristic.

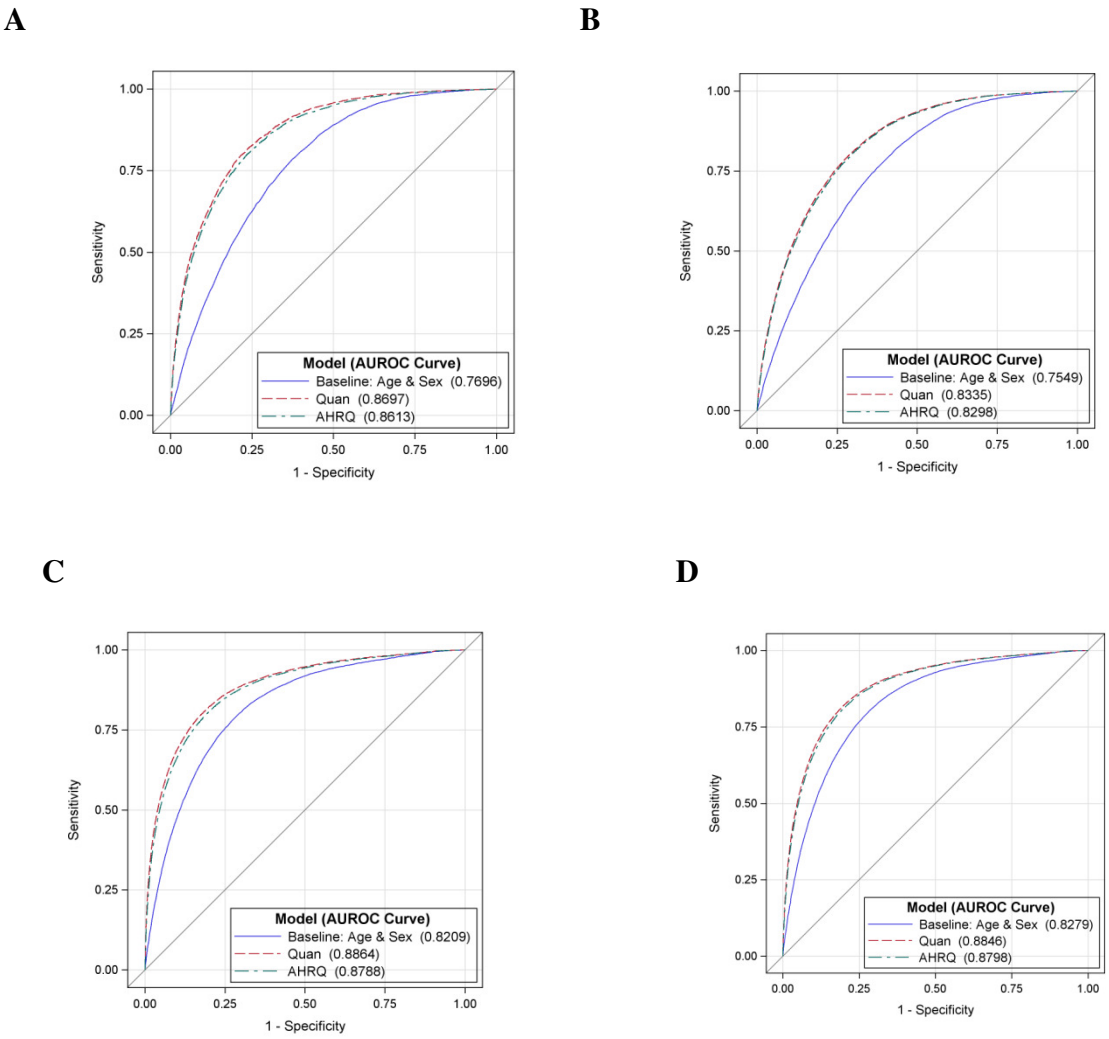

Fig 2.2 AUROC comparisons by ECM for predicting inhospital mortality at index [A] and at 1 year [B] in high risk patients, and inhospital mortality at index [C] and at 1 year [D] in low risk patients.

High risk patients had one or more inpatient stay in the 12 months preceding the index encounter or three or more emergency department visits in the 3 months preceding the index encounter. Patients that did not satisfy the high-risk criteria were assigned to the low risk group.

Abbreviations: AUROC, area under the receiver operating characteristic; ROC, receiver operating characteristic.

A **B**

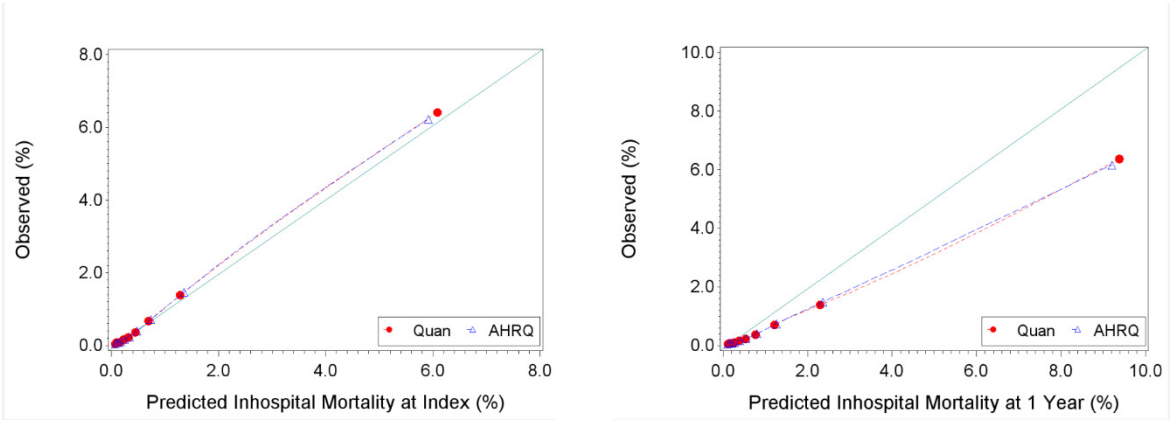

Fig 2.3. Observed versus predicted risk of inhospital mortality [A] at index and [B] at 1 Year.

Perfect calibration is represented by the full line with a slope of 1 starting at the origin.

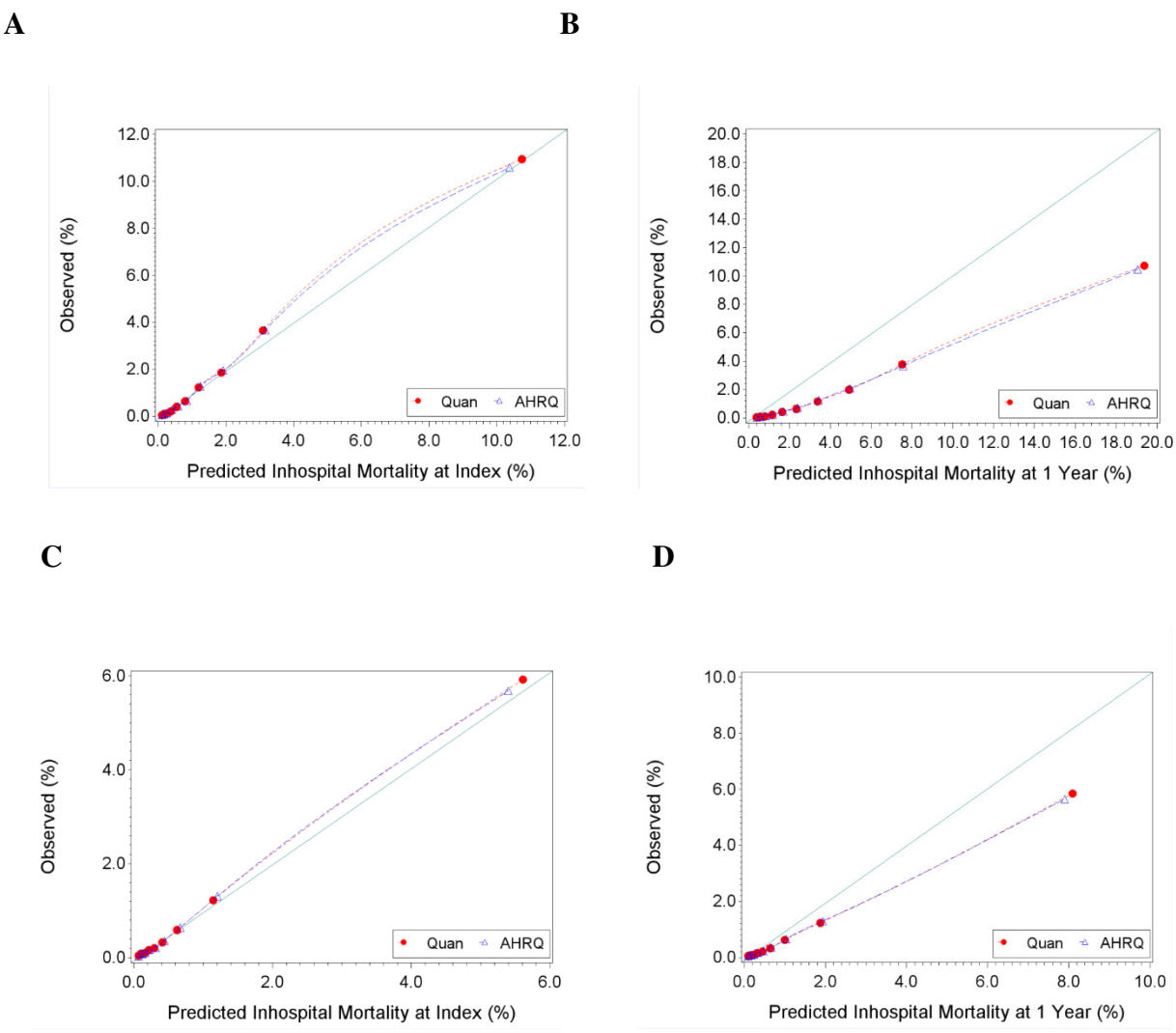

Fig 2.4. Observed versus predicted risk of inhospital mortality at index [A] and at 1 year [B] for high risk patients, and inhospital mortality at index [C] and at 1 year [D] for low risk patients. Perfect calibration is represented by the full line with a slope of 1 starting at the origin. High risk patients had one or more inpatient stay in the 12 months preceding the index encounter or three or more emergency department visits in the 3 months preceding the index encounter. Patients that did not satisfy the high-risk criteria were assigned to the low risk group.

Sensitivity analyses

Results from the sensitivity analyses are available as Appendix A. As hypothesized, patients whose index encounter was an inpatient stay had a greater risk of inhospital mortality at index [2.4% vs 0.3%, $\chi 2$ (1, N = 3,273,298) = 33,138.7, p<.0001], and at 1

year [3.6% vs 0.6%, $\chi 2$ (1, N = 3,273,298) = 43,585.6, p<.0001] than patients whose index encounter was an ED visit. Performance measures in the analyses stratified by index encounter type mimicked the trends reported for the unstratified sample, except for explained variation which was 48 to 69 percent lower in the ED visit sample than in the inpatient sample. Measures of discrimination (AUROC) and calibration (Brier scores) were superior in the inpatient sample compared to the ED visit sample.

Discussion

We conducted an external validation and compared the ability of the Quan and AHRQ ECMs to predict inhospital mortality at index and at 1-year in the Cerner HF database. In a prior study, the Quan ECM demonstrated superior predictive performance over the AHRQ version 3.0 ECM for inhospital mortality at index in a Canadian population with universal health coverage (Quan et al., 2005). The current study expands on prior findings and demonstrates the performance advantage of the Quan ECM over the AHRQ version 3.7 ECM for inhospital mortality at index and at 1-year in Cerner Health Facts®. This is the first study to evaluate any diagnostic-based risk adjustment methods in HF and to confirm the excellent discrimination performance of both the Quan and AHRQ ECMs in a multi-payer US health data source. While significant, increased discrimination performance of the Quan ECM over the AHRQ ECM did not exceed 1% for any of the mortality outcomes after the inclusion of baseline variables age and sex. It is therefore unlikely that the observed differences between the ECMs are clinically meaningful. The marginal performance improvement in discrimination and explained variance observed between the ECMs may be a consequence of the large sample available for analysis and might not be reproducible in smaller HF subsets or patient subpopulations. In this study,

evidence of superior predictive performance by the Quan ECM was demonstrated in an undifferentiated patient population, in patient groups stratified by risk of hospital readmission and death, and in patients stratified by their index encounter type [ED visits and inpatient stays].

Visual inspection of the calibration plots for the Quan and AHRQ ECMs revealed noticeable levels of disagreement between predicted and observed risk of inhospital mortality at 1 year. Lower calibration performance appeared more pronounced in the high risk patient group compared to the low risk patient group. To improve accuracy, we recommend that the ECMs be recalibrated specifically for predictions of inhospital mortality at 1 year in HF. The observed over-prediction of inhospital mortality at 1 year by the ECMs likely results from a combination of factors ranging from suboptimal parameter section to outcome misclassification.

The ICD-9 codes used to assess the prevalence of comorbid conditions by the competing ECMs resulted in minimal variations in disease frequencies; prevalence differed by less than 1% for the majority of conditions. The exclusion of cardiac arrhythmia from the AHRQ ECM may be responsible for the observed predictive performance differences. In the Quan ECM, cardiac arrhythmia was the fifth most prevalent condition and was significantly associated with increased odds of inhospital mortality at index and at 1-year in the adjusted models (Appendix B).

This study has limitations. Like other EHR-derived data warehouse used for observational research that comply with the U.S. HIPAA law and regulations, HF adheres to de-identification procedures that prevent further linkage to registries such as the National Death Index and other health organizations outside the same HIPAA-covered entity. Since

deaths were limited to those recorded during inpatient care and within HIPAA-covered networks, some misclassification of mortality at 1-year is to be expected from the deaths that occurred outside these settings. The patient de-identification process also implies that the diagnoses and combination of ICD codes used for estimating ECM prevalence could not be validated using chart re-abstraction methodology leaving doubts about their sensitivity and specificity in HF. Limiting the assessment of morbidities to a single index encounter, as opposed to including a look back period in the assessment of a patient's health, likely resulted in the misclassification of previously diagnosed health conditions as absent. Including a look back periods of one to two years generally improves the detection of prevalent health conditions (Preen, Holman, Spilsbury, Semmens, & Brameld, 2006; Zhang, Iwashyna, & Christakis, 1999). One explanation for this improvement is that look back periods limit bias in discharge abstract coding whereby secondary health conditions tend to be under recorded in patients treated for severe acute conditions and vice versa (Elixhauser et al., 1998; Hughes, Iezzoni, Daley, & Greenberg, 1996). A look back period was not included in this study to increase the comparability of results with the original Quan (2005) paper and because our research group is currently conducting a parallel study to test the consequences of varying look back periods in HF.

HF was not primarily designed for research purposes (B.R.I.D.G.E. to Data, 2014). Study findings are therefore subject to the same risks, biases, and limitations typically associated with research based on electronic health data (Esposito et al., 2013; van Walraven & Austin, 2011). These include potential for selection bias, missing or incomplete documentation, coding errors, misclassifications of diagnostic codes, record linkage errors due to interoperability issues, and duplication. Finally, recorded comorbid

conditions could not be separated from conditions resulting from complications in care. Thus, it was impossible to evaluate the effects of excluding complications of care from our models.

The Quan and the AHRQ (version 3.7) ECMs were found to be practically equivalent in discriminating between short- and long-term inhospital mortality outcomes in HF. While ECM calibration measures were satisfactory for predicting inhospital mortality at index, recalibration of the ECMs is recommended to improve the predictive accuracy for inhospital mortality at 1 year. These diagnostic-based risk adjustment tools should enhance capacity for conducting quality observational studies and health services research using Health Facts® data.

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Appendix A

Table 2.1S. Measures of Discrimination and Calibration Performance for Inhospital Mortality by Index Encounter Type, ED Visits and Inpatient Stays

		External Validation			
		Inhospital Mortality at Index		Inhospital Mortality at 1 Year	
		Quan	AHRQ	Quan	AHRQ
ED N =2,204,680 (67.4%)	AUROC [a] (95% CI)	0.816 (0.811,0.822) [g]	0.813 (0.807,0.818) [g]	0.839 (0.835,0.842) [g]	0.838 (0.834,0.842) [g]
	HL Test [b]	48.6*	46.8*	79.5*	76.0*
	Brier Score [c]	0.003	0.003	0.005	0.005
	R^2 [d]	11.0	10.7	14.8	14.7
	NRI>0 [e] (95% CI)	-0.5131 (-0.5335,-0.4927)*		-0.3639 (-0.3778,-0.3499)*	
	Reclassification, E - NE [F]	-59% - 8%		-63% - 26%	
	Deaths (%)	6,051 (0.27)		12,053 (0.55)	
IS 1,068,618 (32.6%)	AUROC [a] (95% CI)	0.862 (0.860,0.864) [g]	0.849 (0.847,0.852) [g]	0.851 (0.849,0.853) [g]	0.843 (0.841,0.845) [g]
	HL Test [b]	417.0*	397.3*	924.5*	895.7*
	Brier Score [c]	0.021	0.021	0.031	0.032
	R^2 [d]	23.1	20.9	22.8	21.4
	NRI>0 [e] (95% CI)	0.5033 (0.4908,0.5157)*		0.4242 (0.4142,0.4343)*	
	Reclassification, E - NE [F]	-5% - 55%		-13% - 55%	
	Deaths (%)	25,247 (2.36)		38,162 (3.57)	

* P-value < 0.001. ED = Index encounter is an emergency department visit. IS = Index encounter is an inpatient stay. E= Events. NE=Non-events.

[a] Area under the Receiver Operating Characteristic (ROC) curve (AUROC). AUROC is a measure of discrimination ranging from 0.5 (zero discrimination) to 1.0 (perfect discrimination).

[b] Pearson chi-square value derived from the Hosmer–Lemeshow goodness-of-fit test (Hosmer Jr et al., 2013).

[c] Measure of predictive accuracy, greater accuracy is reflected by lower score.

[d] Generalized R-squared, explained variation, displayed in percentage.

[e] Category-free net reclassification improvement with the AHRQ ECM as the reference model.
[f] E – NE, percentage of events (E) and non-events (NE) correctly reclassified by the Quan ECM compared to the AHRQ ECM.
[g] AUROC curve differed significantly from the baseline model limited to age and sex ($p < 0.0001$), and from the competing ECM ($p < 0.0001$). Differences between AUROC curves were evaluated with the Mann-Whitney U test approach developed by DeLong et al. (1988). For ED encounters, the baseline model had an AUROC of 0.804 (95% CI 0.799-0.810) for inhospital mortality at index, and 0.826 (95% CI 0.822-0.829) for inhospital mortality at 1 year. For IS encounters, the baseline model had an AUROC of 0.752 (95% CI 0.749-0.754) for inhospital mortality at index, and 0.754 (95% CI 0.752-0.756) for inhospital mortality at 1 year.

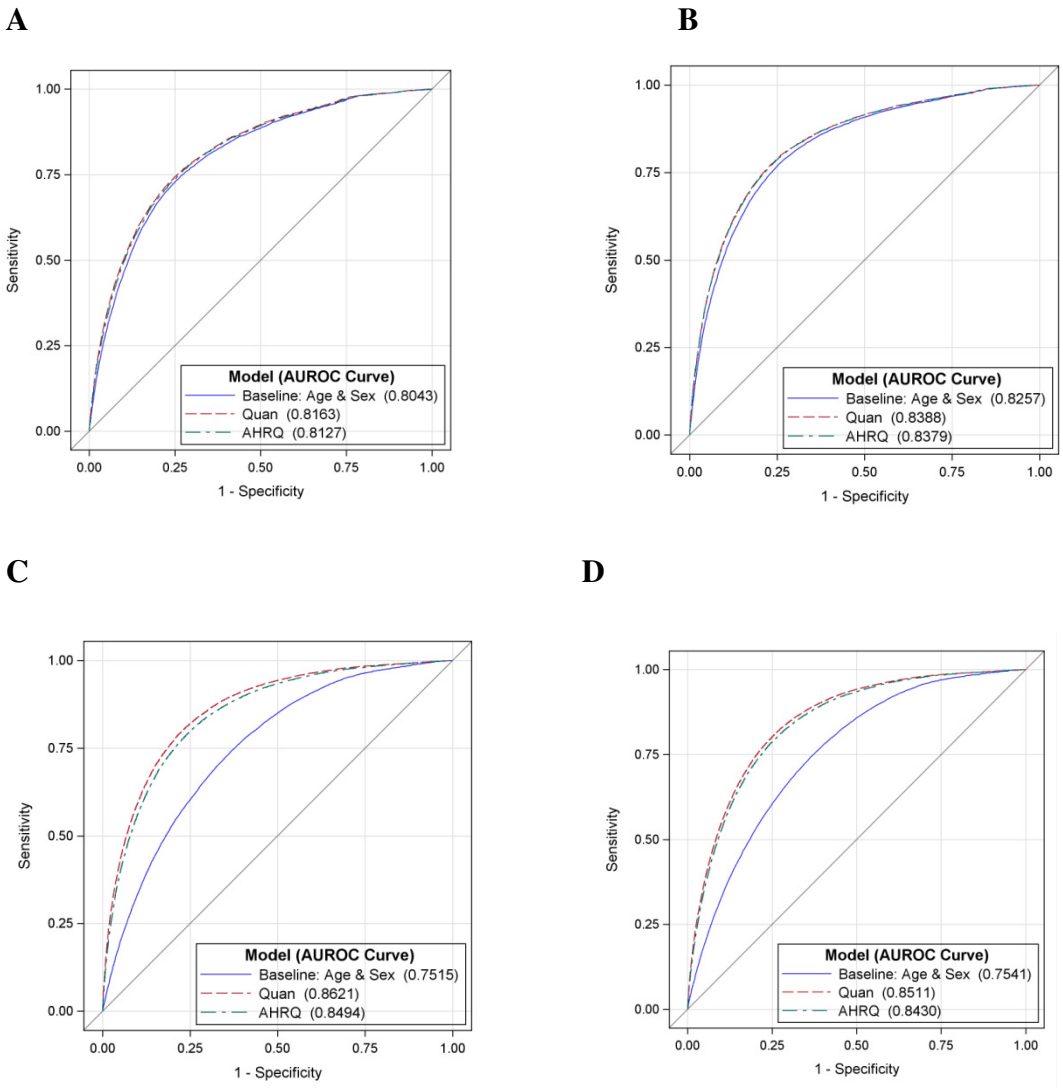

Fig 2.1S. ROC comparison by ECM for predicting inhospital mortality at index [A] and at 1 Year [B] for index encounters limited to emergency department visits, and inhospital mortality at index [C] and at 1 Year [D] for index encounters limited to inpatient stays. **Abbreviations**: AUROC, area under the receiver operating characteristic; ROC, receiver operating characteristic.

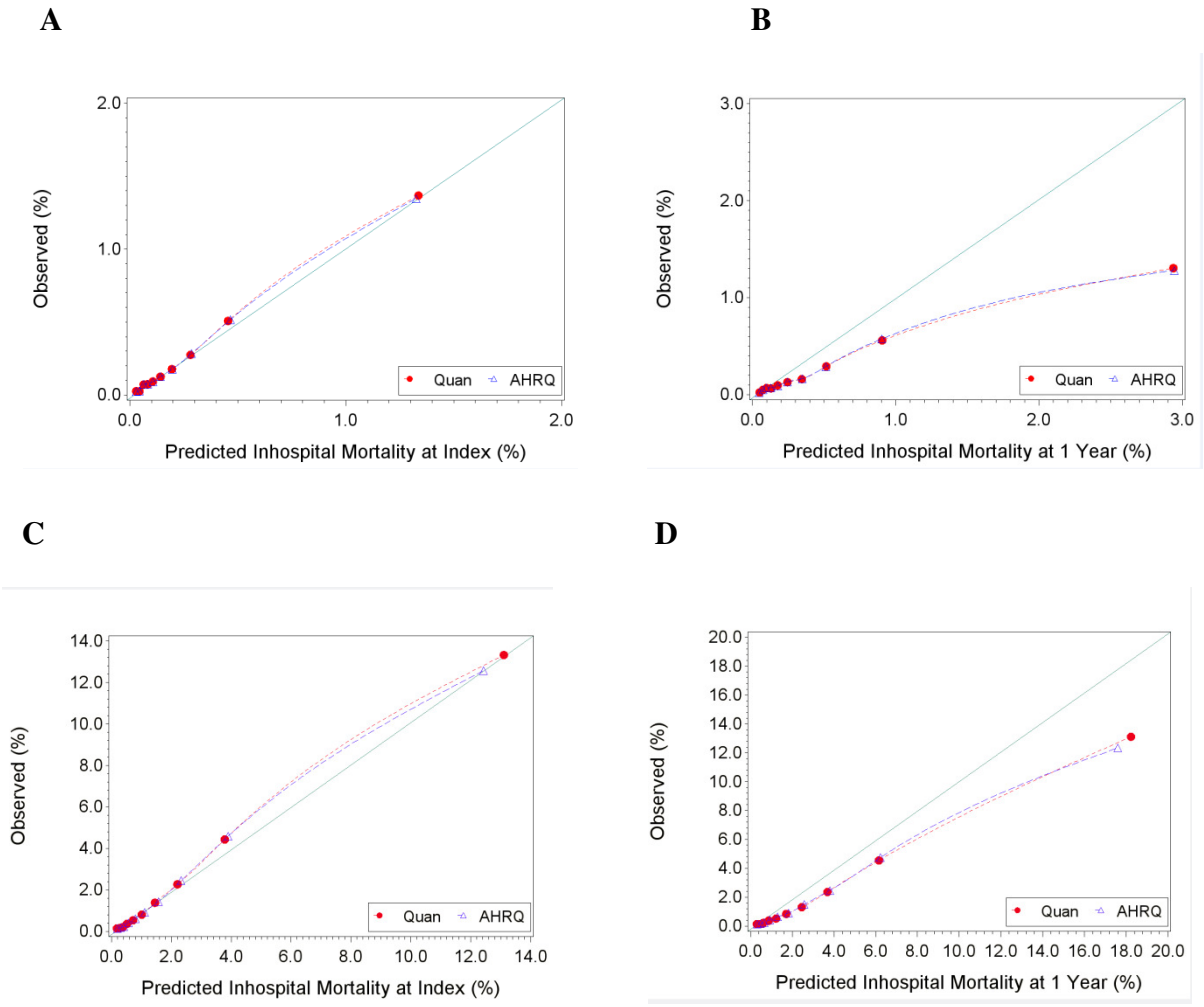

Fig 2.2S. Observed versus predicted risk of predicting inhospital mortality at index [A] and at 1 Year [B] for index encounters limited to emergency department visits, and inhospital mortality at index [C] and at 1 year [D] for index encounters limited to inpatient stays. Perfect calibration is represented by the full line with a slope of 1 starting at the origin.

Appendix B

Table 2.2S. Adjusted Odds Ratios of Elixhauser Conditions for Inpatient Mortality at Index and at 1-Year by ECM Variant, N = 3,273,298.

	Adjusted Odds Ratio (95% CI, p<0.05)			
	Inpatient Mortality at Index		Inpatient Mortality at 1-Year	
Condition	**Quan**	**AHRQ**	**Quan**	**AHRQ**
Congestive Heart Failure	2.29 (2.22-2.37)	2.66 (2.57-2.75)	2.29 (2.23-2.35)	2.55 (2.49-2.62)
Cardiac Arrhythmia	1.81 (1.76-1.87)	Not applicable	1.51 (1.47-1.54)	Not applicable
Valvular Disease	0.73 (0.69-0.77)	0.88 (0.82-0.95)	0.84 (0.81-0.88)	Not-significant
Pulmonary Circulation Disorders	1.51 (1.42-1.62)	1.58 (1.48-1.68)	1.37 (1.29-1.44)	1.54 (1.47-1.63)
Peripheral Vascular Disorders	1.42 (1.35-1.50)	1.54 (1.47-1.62)	1.41 (1.35-1.47)	1.49 (1.43-1.55)
Hypertension Combined	0.54 (0.52-0.55)	0.55 (0.54-0.57)	0.64 (0.62-0.65)	0.65 (0.63-0.66)
Paralysis	3.40 (3.16-3.66)	3.39 (3.18-3.61)	2.97 (2.78-3.17)	2.86 (2.71-3.02)
Other Neurological Disorders	3.77 (3.63-3.91)	2.12 (2.04-2.20)	2.90 (2.81-3.00)	1.85 (1.80-1.92)
Chronic Pulmonary Disease	1.09 (1.05-1.12)	1.17 (1.13-1.21)	1.35 (1.31-1.38)	1.41 (1.38-1.45)
Diabetes Uncomplicated	0.87 (0.84-0.90)	0.88 (0.85-0.91)	Not-significant	Not-significant
Diabetes Complicated	0.71 (0.65-0.77)	0.71 (0.66-0.77)	1.09 (1.03-1.15)	1.09 (1.03-1.15)
Hypothyroidism	0.63 (0.60-0.67)	0.67 (0.64-0.71)	0.72 (0.69-0.75)	0.74 (0.71-0.77)
Renal Failure	1.77 (1.70-1.85)	1.85 (1.77-1.93)	2.03 (1.97-2.10)	2.03 (1.96-2.10)
Liver Disease	3.69 (3.50-3.90)	2.72 (2.54-2.90)	3.57 (3.41-3.74)	3.12 (2.95-3.29)
Peptic Ulcer Dis. excl. bleeding	0.39 (0.32-0.49)	Not-significant	0.63 (0.54-0.73)	Not-significant
AIDS/HIV	3.22 (2.72-3.82)	3.77 (3.19-4.45)	3.91 (3.41-4.48)	4.34 (3.80-4.97)
Lymphoma	2.04 (1.83-2.27)	2.13 (1.92-2.38)	2.86 (2.63-3.11)	2.90 (2.67-3.15)
Metastatic Cancer	3.22 (3.03-3.42)	3.35 (3.16-3.56)	3.50 (3.33-3.67)	3.60 (3.43-3.77)
Solid Tumor without Metastasis	1.58 (1.50-1.66)	1.60 (1.52-1.68)	1.95 (1.87-2.03)	1.95 (1.87-2.03)

Rheumatoid Arthritis/collagen	Not-significant	Not-significant	1.20 (1.12-1.29)	1.17 (1.08-1.26)
Coagulopathy	2.74 (2.61-2.87)	3.35 (3.19-3.51)	2.39 (2.29-2.49)	2.73 (2.62-2.85)
Obesity	0.88 (0.82-0.94)	Not-significant	0.88 (0.83-0.93)	0.91 (0.86-0.96)
Weight Loss	2.53 (2.41-2.66)	2.63 (2.5-2.78)	2.35 (2.25-2.46)	2.40 (2.29-2.51)
Fluid and Electrolyte Disorders	3.20 (3.11-3.29)	3.60 (3.51-3.71)	2.44 (2.39-2.50)	2.63 (2.57-2.70)
Blood Loss Anemia	Not-significant	0.84 (0.75-0.95)	Not-significant	Not-significant
Deficiency Anemia	0.43 (0.38-0.48)	0.66 (0.63-0.69)	0.67 (0.62-0.73)	0.89 (0.86-0.92)
Alcohol Abuse	Not-significant	1.13 (1.06-1.20)	1.15 (1.10-1.21)	1.19 (1.13-1.26)
Drug Abuse	Not-significant	1.27 (1.15-1.40)	Not-significant	1.23 (1.13-1.33)
Psychoses	0.73 (0.65-0.82)	0.64 (0.58-0.70)	Not-significant	0.79 (0.74-0.85)
Depression	0.68 (0.64-0.73)	0.75 (0.70-0.81)	0.80 (0.76-0.84)	0.86 (0.82-0.91)

* Odds ratios are adjusted for baseline variables sex and age.

Chapter 3 - Optimal Look Back Period and Summary Method for Elixhauser Comorbidity Measures in a U.S. Population-Based Electronic Health Record Database

Yannick Fortin[1,2], James A.G. Crispo[1,2,3], Deborah Cohen[2,4,5], Douglas S McNair[6], Donald R. Mattison[1,7], Daniel Krewski[1,2,7]

Authors Note

1. McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada. 2. School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada. 3. Fulbright Canada Student, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 4. Canadian Population Health Initiative (CPHI), Canadian Institute for Health Information (CIHI), Ottawa, Ontario, Canada. 5. Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. 6. Cerner Corporation, Kansas City, Missouri, USA. 7. Risk Sciences International, Ottawa, Ontario, Canada.

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Abstract

Background

Comorbidity risk-adjustment tools are widely used in health database research to control for clinical differences between individuals, but they need to be validated a priori. This study aimed to identify the optimal parameters for predicting all-cause inhospital mortality using Quan's enhanced Elixhauser comorbidity measures (ECMs) in the US-based Cerner Health Facts® (HF) electronic health record database.

Methods

Health care recipients aged 18–89 years between 2002 and 2011 were included. Prevalent comorbidities recorded, 1) during the index encounter; 2) in the prior year; and 3) in the prior 2 years were identified using the ECMs. Multiple logistic regression models, with inhospital mortality at index and at 1 year as the predicted outcomes, were fitted with comorbidities summarized as binary indicators, total counts, or weighted scores for the three look back periods. Baseline variables included sex and age. The receiver operating characteristic (ROC) curves of the competing models were compared with a non-parametric Mann–Whitney U test to identify the optimal parameters.

Results

A sample of 3,273,298 unique health care recipients were included, of whom 31,298 (1.0%) and 50,215 (1.5%) died during the index encounter and within the 1-year follow-up, respectively. Models of comorbidity based on binary and weighted indicators had near-identical performance and were statistically better than the models based on total counts ($p < 0.0001$). Discrimination of inhospital mortality was highest with a look back period limited to the index encounter, while inhospital mortality at 1 year was best predicted with 1 year of look back ($p < 0.0001$).

Conclusion

In Cerner HF, the binary and weighted methods for summarizing the Quan ECM were the best predictors of all-cause inhospital mortality at index and at 1 year. Observed differences in predictive performance between models with diagnostic ascertainment periods of up to 2 years of look back were statistically significant but not practically important.

Introduction

Risk-adjustment measures of patient comorbidity are commonly used in health database research and are associated with short- and long-term mortality, hospital costs, inpatient length of stay (LOS), physician visits, and hospital readmissions.[1–9]

The strong discriminatory performance of two Elixhauser comorbidity measure (ECM) variants, by Quan et al. [10] and the Agency for Healthcare Research and Quality (AHRQ),[11] for predicting inhospital mortality was recently confirmed in the Cerner Health Facts® (HF) database.[12] HF is a longitudinal electronic health record (EHR) data source populated by health care centers located across the continental US in compliance with the US Health Insurance Portability and Accountability Act (HIPAA). HIPAA-compliant data repositories must adhere to strict patient de-identification procedures to ensure the privacy and protection of personal information.[13] These operational constraints preclude any possibility of subsequent data linkage to national registries such as the National Death Index or to other health provider data sources that are not covered under a common HIPAA network. EHR databases such as HF are therefore limited in their ability to fully capture the utilization of health services of their constitutive patients, possibly leading to missing information about health outcomes and health service use happening outside their privacy network. How this potential missing information affects the performance of comorbidity risk assessment tools in HF and similar health data sources deserves investigation, if only for the interpretation of studies derived from them.

Selecting an appropriate ascertainment look back period (henceforth, look back) is a standard decision researchers have to make prior to relying on comorbidity risk-adjustment tools. A look back period is the length of a patient's medical history available for the assessment of prevalent comorbidities. When look back is expanded to include health encounters preceding an index

encounter, additional diagnoses, possibly unreported during the index, are more likely to be detected. One reason cited for expanding the look back period beyond a single health encounter is to limit discharge coding bias, whereby existing and less serious chronic health conditions are less likely to be recorded within EHRs during acute health encounters and vice versa.[1,14] In a recent systematic review, Yurkovich et al[15] concluded that combining health data from outpatient and inpatient encounters yields comorbidity indices with better predictive performance for mortality outcomes than inpatient data alone. Evidence also suggests that longer look back is associated with comorbidity indices with better predictive performance for a wide array of health outcomes.[4,16] However, performance increases beyond 1 year of look back may be insignificant.[17] In HF and similar sources of health data in which patient follow-up cannot be confirmed with complete accuracy, the selection of an optimal look back period should be confirmed through empirical investigation.

The comorbidity status of patients, inferred from the health conditions recorded in EHRs, can be summarized in several ways. Unlike the Charlson[8] comorbidity index and its variants,[18–21] which summarize overall comorbidity in a single score on a continuous scale, ECMs consist of 30 binary indicators.[1,10] This makes ECMs impractical when conducting association studies or when matching cases to controls based on health status. Fortunately, several approaches are available for improving the manageability of ECMs. The simplest method is to count the total number of prevalent comorbidities identified during the look back period (henceforth, the total method). Comorbidities can also be assigned relative weights based on the strength of their association with an outcome of interest, e.g., inhospital mortality. Once these relative weights are derived, they can be added to produce a single comorbidity score for each patient. The ECM point system developed and validated by van Walraven et al[22] (henceforth, the weighted method) is based on this approach

but has yet to be validated in a US health data source. The principal and arguably questionable assumption of the total method is that every ECM health condition has the same strength of association with the outcome of interest. The weighted method addresses this limitation by producing a weighted comorbidity score that accounts for the relative ability of each ECM condition to predict an outcome.

Alternative methods for summarizing overall comorbidity in patients result in comorbidity risk-adjustment tools with divergent predictive performances.[16] In a recent meta-analysis, Sharabiani et al[16] tested the discrimination performance of comorbidity measures for predicting short- and long-term outcomes with different comorbidity summary methods. When predicting inpatient and short-term mortality (<30 days), model performance ranked in increasing order from the binary method to the total method and then to the weighted method. For predicting long-term outpatient mortality (>30 days), the performance of comorbidity summary methods ranked differently. They improved from the total method to the weighted method and then to the binary method. The predictive performance of competing ECM summary methods has not been compared in the HF database, and it is unclear if one approach outperforms the others in this type of data source.

The primary objective of this study was to identify the optimal look back period (index encounter alone versus 1 year versus 2 years) for the Quan ECM when predicting all-cause inhospital mortality and inhospital mortality at 1 year in HF. The secondary objective was to ascertain which comorbidity summary method, the binary, total, or weighted, best predicts the mortality outcomes.

Methods

Source of health data

The study is based on EHRs from the Cerner HF (Kansas City, MO, USA) data repository and relies on inpatient, outpatient, and emergency care encounters recorded between January 2000 and December 2012. Cerner is a global provider of health informatics solutions, and HF is managed in accordance with the HIPAA. To date, >500 health care facilities have contributed patient-level data to HF, including details on hospital admissions, diagnoses, medication orders, laboratory tests, medical procedures, and surgical interventions. [23] Data-contributing health care facilities are located in all US census regions and are categorized by teaching status, urban/rural setting, and bed size. Participating data sources are primarily located in the Northeast census region (36%) and ~60% of HF health encounters are recorded by university-affiliated teaching hospitals. Permission to access and analyze HF data was granted by Cerner Corporation, Kansas City, MO, USA.

HIPAA compliance by the Cerner Corporation ensures complete de-identification and anonymization of HF patients. Ethical approval for this study was granted by the University of Ottawa's Office for Research Ethics and Integrity who deemed patient consent unnecessary due to the deidentification process.

Study population

Individuals aged 18–89 years with one or more inpatient or emergency department (ED) visits between January 2002 and December 2011 were admissible for inclusion in the study. For each admissible patient, a single health care encounter was selected at random and assigned as the index encounter. Random selection of the index encounter was completed to limit systematic information bias while allowing for the possibility of look back and follow-up time. The study inclusion dates were selected to ensure index encounters had 2 years of available look back time and 1 year of

follow-up. Individuals younger than 18 years were excluded due to the low prevalence of ECM conditions and mortality in this age group. Individuals aged 90 years or older were excluded because age is treated as a continuous variable in this study and age values are pooled in a single category beyond 89 years in HF due to HIPAA requirements. To avoid bias resulting from missing information, we excluded index encounters in which individuals were admitted from or transferred to an outside health care facility.[22] Individual characteristics included sex (male and female), race limited to the four highest frequency categories (Caucasian, African American, Hispanic, and Asian), and age captured during the index encounter. Primary health insurance status at the index encounter was classified based on recommendations from the AHRQ [24] as private, Medicaid, Medicare, uninsured/self-pay, other Tricare (formerly known as the Civilian Health and Medical Program of the Uniformed Services [CHAMPUS]), (international plan, research funded, Title V, worker's compensation), or missing. An important proportion of health insurance status values were expected to be missing since data contributors often elect to retain this type of information from being transferred to external data repositories such as HF.

ECMs

Quan et al's[10] enhanced International Classification of Diseases, Ninth Edition (ICD-9), ECM was selected to identify the prevalence of 30 health conditions. This choice was based on prior evidence of superior performance by this ECM for predicting inhospital mortality in HF compared to version 3.7 of the AHRQ ECM.[25] The Quan ECM relies on specific combinations of ICD-9 diagnostic codes to identify cases of congestive heart failure, cardiac arrhythmia, valvular disease, pulmonary circulation disorders, peripheral vascular disorders, hypertension (un/complicated), paralysis, neurological disorders, chronic pulmonary disease, uncomplicated diabetes, complicated diabetes, hypothyroidism, renal failure, liver disease, peptic ulcer disease without bleeding, AIDS/HIV,

lymphoma, metastatic cancer, solid tumor without metastasis, rheumatoid arthritis/collagen vascular diseases, coagulopathy, obesity, weight loss, fluid and electrolyte disorders, blood loss anemia, deficiency anemia, alcohol abuse, drug abuse, psychoses, and depression, from electronic health data.[26,27]

Look back periods

To test the consequences of varying the diagnostic ascertainment look back period on the predictive performance of the ECM, prevalent health conditions were identified during the index encounter alone (index only), during the index encounter and any encounter recorded in the preceding year (1-year look back), and during the index encounter and any encounter recorded during the previous 2 years (2-year look back). Prior studies have reported that when the objective is to predict mortality, disease prevalence captured from multiple health care settings generally performs better (higher c-statistic values) than disease prevalence assessments limited to a single health care setting.[4,15,28,29] For this reason, diagnostic ascertainment in this study included information recorded in inpatient, outpatient, and emergency care settings.

ECM summary methods

The overall comorbidity status of patients was summarized using three approaches. The binary method reflected the original Elixhauser format, and the 30 health conditions assessed were coded as binary indicators (present or absent). In the total method, each health condition identified was assigned a value of 1 and a total count was derived to produce a continuous variable ranging from 0 to 30. For the weighted method, the van Walraven (VW) [22] point system was implemented and relative weights were calculated based on HF data. The VW point system is principally founded on the methodology from the Framingham Heart Study for compiling risk score for developing

coronary heart disease over time.[30] To begin, a random number generator based on the Bernoulli distribution was used to divide the HF encounters into two subsamples. The first dataset (derivation) was reserved to generate the VW weights and the second dataset (validation) was retained to conduct the comparative statistical analyses. In the VW approach, backward stepwise logistic regression was used to predict the outcome of interest (e.g., inhospital mortality) using the ECM binary indicators as parameters. Conditions significantly associated ($p < 0.05$) with the dependent in the best-fitted model were retained and parameter estimates were divided by the absolute value of the parameter with the lowest admissible estimate. ECM conditions not significantly associated with the dependent were assigned a weight of zero. A weighted summary score was then compiled for each patient by adding the relative weight of each positively identified health condition during the diagnostic ascertainment step. Since this study has three look back periods and two outcomes, six sets of VW weights were generated.

Statistical analysis

The study outcomes were all-cause inhospital mortality during the index encounter and at 1 year. Inhospital mortality at 1 year was defined as a death recorded during an HF encounter (inpatient stay or emergency visit) in the 365 days that followed the admission date of the index encounter. Deaths occurring during the index encounter are therefore included in the inhospital mortality at 1-year outcome. Because deaths occurring in outpatient settings are rare relative to those occurring in acute care settings,[31,32] they were excluded from the study. Patient demographic and index encounter characteristics for the derivation, validation, and complete datasets are reported as counts and percentages for categorical variables and as mean and standard error (SE) values for continuous variables. Observed differences between the derivation and validation datasets were compared with Pearson's chi-squared test for the categorical variables and with Student's t-test for

the continuous variables. Multiple logistic regression was used to fit the six combinations of look back and comorbidity summary method and to predict the mortality outcomes. Since the weights required by the VW point system were produced from the derivation dataset, the comparative analyses were conducted with the validation dataset as opposed to the complete sample. The baseline model was limited to sex and age at index to allow for comparisons with prior studies.[4,25,33] Statistical analyses were completed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA), which allowed for concordance index (c-statistic) values to be outputted from the logistic regression function using the receiver operating characteristic (ROC) option.[34] Interpretation of the c-statistics follows recommendations by Hosmer Jr, Lemeshow, and Sturdivant, [35] whereby values >0.7 are considered reasonable, those >0.8 are strong, and those >0.9 are exceptional. Differences in the capacity of each model to discriminate between the mortality outcomes were compared using the ROCCONTRAST option, which relies on a variation of the non-parametric Mann–Whitney U test developed by DeLong et al.[36]

Results

A dataset based on the inclusion of 3,273,298 unique health care recipients was randomly parsed to create a derivation and a validation dataset containing 1,637,572 and 1,635,726 patients, respectively (Table 3.1). In the complete dataset, the majority were females (53.8%) and Caucasians (72.3%). The mean age was 41.1 years (SE = 0.01), and 31,298 (1.0%) deaths of any cause were recorded during the index. At 1 year, 50,215 (1.5%) deaths were recorded. A larger percentage of index encounters originated from health care facilities located in the Northeast (36.1%) census region compared to the Midwest (19.8%), South (32.9%), and West (11.2%). Forty-one percent of health insurance statuses were missing (41.0%), and the privately insured

(24.3%) made up the majority of non-missing values. The observed differences between the derivation and validation samples were not significant (see table 1).

The prevalence of the health conditions ascertained ranked consistently across all look back periods and was led by hypertension (17.5–19.5%), chronic pulmonary disease (7.8–9.2%), diabetes without complications (6.9–7.8%), fluid and electrolyte disorders (5.7–7.0%), and cardiac arrhythmia (5.3–6.2%; Table 3.2). The greatest increase in prevalence between the index encounter and 2 years of look back were for hypertension (2.0%), chronic pulmonary disease (1.3%), and fluid and electrolyte disorders (1.3%). The adjusted odds and relative weight of each health condition derived during the implementation of the VW point system are reported in Table 3.3 for inhospital mortality and in Table 3.4 for inhospital mortality at 1 year. In the models retained for predicting inhospital mortality, uncomplicated diabetes and blood loss anemia were excluded for all look back periods, while the rheumatoid arthritis/collagen disease group was excluded from the models based on and 2 years of look back. The parameters retained in the models predicting inhospital mortality at 1 year differed. Valvular disease was excluded across all look back periods, while diabetes with complications and alcohol abuse were excluded from the 1- and 2-year look back models. Relative points (weights) attributed to health conditions ranged from -6 to 11 across the three look back periods when predicting inhospital mortality, and neurological disorders, metastatic cancer, and fluid and electrolyte disorders had the largest weights. For inhospital mortality at 1 year, health conditions exhibited a broader range of points, from -11 to 27, across the look back periods, with liver disease, lymphoma, and metastatic cancer having the largest weights.

Model performance comparisons based on the validation dataset showed that irrespective of the look back period and the outcome predicted, the combination of the baseline variables with

any of the summary methods improved on the predictive performance of the baseline model alone ($p < 0.0001$) (Table 3.5). For inhospital mortality, the average performance improvement on the baseline model across the look back periods was 6.6%, 3.4%, and 6.4% for the binary, total, and weighted summary methods, respectively. For inhospital mortality at 1 year, the equivalent improvements in c-statistics were 5.9%, 3.7%, and 5.7%.

For both mortality outcomes, the predictive performance of models improved consistently and significantly in the following order of summary method for every look back period: total < weighted < binary. Irrespective of the look back period and outcome, the predictive performances of the binary and weighted summary methods were nearly identical ($0.882 \leq$ c-statistics ≤ 0.887), varying by less than a percent in direct comparisons. The most noticeable performance improvement across the look back periods was the outperformance of the total method by the binary and weighted methods, which averaged approximately 3% for inhospital mortality at index and ≈2% for inhospital mortality at 1 year. The c-statistic confidence intervals of every direct comparison between the binary and the weighted methods overlapped, yet differences in model performance between the methods were statistically significant ($p < 0.0001$).

When predicting inhospital mortality, the best performing look back period across all summary methods was the diagnostic assessment limited to the index encounter alone. For predictions of inhospital mortality at 1 year, the best look back period was the index encounter supplemented with 1 year of look back. While the differences in predictive performance across look back periods for each summary method were statistically different, performance improvements were negligible and rarely exceeded more than two-tenths of a percent. ROC curves are available in Appendix A (Figures S1 and S2).

Table 3.1. Patient demographic and encounter characteristics, for the complete, derivation, and validation datasets

Variable	*Complete* *N =3,273,298 (%)*	*Derivation* *N =1,637,572 (%)*	*Validation* *N =1,635,726 (%)*	*p value*[A]
Sex				*0.366* [B]
Female	1,761,525 (53.8)	881,667 (53.8)	879,858 (53.9)	
Age (Years)				0.706 [C]
Mean ± SE	44.1 ± 0.01	44.0 ± 0.01	44.1 ± 0.01	
Race				0.468 [B]
Caucasian	2,366,665 (72.3)	1,183,791 (72.3)	1,182,874 (72.3)	
African American	711,051 (21.7)	355,705 (21.7)	355,346 (21.7)	
Hispanic	146,877 (4.5)	73,765 (4.5)	73,112 (4.5)	
Asian	48,705 (1.5)	24,311 (1.5)	24,394 (1.5)	
Health Insurance Status				0.685 [B]
Private	795,449 (24.3)	397,520 (24.3)	397,929 (24.3)	
Medicare	370,701 (11.3)	185497 (11.3)	185204 (11.3)	
Medicaid	248,009 (7.6)	124,091 (7.6)	123,918 (7.6)	
Uninsured	378,536 (11.6)	189,729 (11.6)	188,807 (11.5)	
Other	139,745 (4.3)	69,905 (4.3)	69,840 (4.3)	
Missing	1,340,858 (41.0)	670,830 (41.0)	670,028 (41.0)	
Census Region				0.229 [B]
Northeast	1,180,270 (36.1)	589,807 (36.0)	590,463 (36.1)	
Midwest	648,644 (19.8)	325,141 (19.9)	323,503 (19.8)	
South	1,077,965 (32.9)	539,459 (32.9)	538,506 (32.9)	
West	366,419 (11.2)	183,165 (11.2)	183,254 (11.2)	
Inhospital Mortality				0.351 [B]
Deaths	31,298 (1.0)	15,740 (1.0)	15,558 (1.0)	
Inhospital Mortality at 1-Year				0.185 [B]
Deaths	50,215 (1.5)	25,269 (1.5)	24,946 (1.5)	

[A] *p value* resulting from the significance tests used to evaluate the difference between the derivation and validation subsamples. [B] Statistical significance derived using Pearson's chi-squared test. [C] Statistical significance derived using Student's t-test.
Abbreviation: SE, Standard error.

Table 3.2. Prevalence of comorbid conditions by look back period, N = 3,273,298

Health Condition(s)	Index Only, N (%)	1 Year Look Back, N (%)	2 Year Look Back, N (%)
Congestive heart failure	99,280 (3.03)	109,970 (3.36)	116,581 (3.56)
Cardiac arrhythmia	174,656 (5.34)	191,000 (5.84)	202,319 (6.18)
Valvular disease	51,250 (1.57)	58,506 (1.79)	63,974 (1.95)
Pulmonary circulation disorders	21,084 (0.64)	24,790 (0.76)	27,212 (0.83)
Peripheral vascular disorders	41,651 (1.27)	49,317 (1.51)	54,798 (1.67)
Hypertension combined	572,139 (17.48)	611,354 (18.68)	638,363 (19.50)
Hypertension uncomplicated	518,529 (15.84)	558,185 (17.05)	586,568 (17.92)
Hypertension complicated	55,303 (1.69)	62,760 (1.92)	67,135 (2.05)
Paralysis	13,707 (0.42)	15,417 (0.47)	16,675 (0.51)
Other neurological disorders	76,237 (2.33)	84,644 (2.59)	90,360 (2.76)
Chronic pulmonary disease	256,170 (7.83)	281,398 (8.60)	300,230 (9.17)
Diabetes, uncomplicated	226,807 (6.93)	245,625 (7.50)	256,680 (7.84)
Diabetes, complicated	34,016 (1.04)	40,131 (1.23)	44,068 (1.35)
Hypothyroidism	85,493 (2.61)	96,038 (2.93)	103,358 (3.16)
Renal failure	60,238 (1.84)	66,706 (2.04)	70,142 (2.14)
Liver disease	31,307 (0.96)	36,958 (1.13)	41,044 (1.25)
Peptic ulcer disease, excluding bleeding	8,251 (0.25)	10,142 (0.31)	11,719 (0.36)
AIDS/HIV	4,246 (0.13)	4,921 (0.15)	5,235 (0.16)
Lymphoma	6,778 (0.21)	7,506 (0.23)	7,958 (0.24)
Metastatic cancer	22,836 (0.70)	24,646 (0.75)	25,405 (0.78)
Solid tumor without metastasis	56,376 (1.72)	63,399 (1.94)	67,709 (2.07)
Rheumatoid arthritis/collagen disease	24,143 (0.74)	27,417 (0.84)	29,763 (0.91)
Coagulopathy	27,019 (0.83)	31,378 (0.96)	34,258 (1.05)
Obesity	79,680 (2.43)	90,225 (2.76)	98,747 (3.02)
Weight loss	21,219 (0.65)	26,262 (0.80)	29,644 (0.91)
Fluid and electrolyte disorders	187,321 (5.72)	211,182 (6.45)	228,697 (6.99)
Blood loss anemia	10,884 (0.33)	12,742 (0.39)	14,262 (0.44)
Deficiency anemia	19,745 (0.60)	24,617 (0.75)	28,171 (0.86)
Alcohol abuse	89,460 (2.73)	96,224 (2.94)	101,830 (3.11)
Drug abuse	61,260 (1.87)	68,894 (2.10)	75,069 (2.29)
Psychoses	29,656 (0.91)	33,619 (1.03)	36,329 (1.11)
Depression	113,659 (3.47)	130,320 (3.98)	143,078 (4.37)

Table 3.3. Adjusted Odds of inhospital mortality and relative points by health condition(s) and look back period, N = 1,637,572

Health Condition(s)	Index Only, OR (CI)	Points	1 Year Look Back, OR (CI)	Points	2 Year Look Back, OR (CI)	Points
Congestive Heart Failure	3.33 (3.17-3.50)***	9	3.13 (2.98-3.30)***	8	3.04 (2.89-3.19)***	9
Cardiac Arrhythmia	2.87 (2.75-3.00)***	8	2.77 (2.65-2.89)***	7	2.68 (2.57-2.80)***	8
Valvular Disease	0.87 (0.81-0.95)***	-1	0.83 (0.77-0.89)***	-1	0.80 (0.74-0.86)***	-2
Pulmonary Circulation Disorders	1.38 (1.25-1.52)***	2	1.31 (1.19-1.43)***	2	1.29 (1.18-1.41)***	2
Peripheral Vascular Disorders	1.98 (1.84-2.14)***	5	1.68 (1.56-1.81)***	4	1.55 (1.44-1.66)***	4
Hypertension	0.85 (0.82-0.89)***	-1	0.86 (0.82-0.89)***	-1	0.85 (0.82-0.89)***	-1
Paralysis	3.54 (3.20-3.92)***	9	3.12 (2.82-3.44)***	8	2.86 (2.60-3.16)***	9
Neurological Disorders	4.20 (3.99-4.42)***	11	3.73 (3.55-3.93)***	9	3.55 (3.38-3.73)***	11
Chronic Pulmonary Disease	1.25 (1.19-1.31)***	2	1.16 (1.10-1.21)***	1	1.13 (1.08-1.19)***	1
Diabetes without complications	E	.	E	.	E	.
Diabetes with complications	0.68 (0.61-0.77)***	-3	0.64 (0.57-0.71)***	-3	0.64 (0.58-0.71)***	-4
Hypothyroidism	0.79 (0.73-0.86)***	-2	0.80 (0.74-0.87)***	-2	0.79 (0.73-0.85)***	-2
Renal Failure	1.85 (1.74-1.97)***	5	1.67 (1.57-1.78)***	4	1.65 (1.56-1.76)***	4
Liver Disease	3.50 (3.24-3.78)***	9	2.99 (2.77-3.22)***	7	2.80 (2.60-3.01)***	9
Peptic Ulcer Disease excluding bleeding	0.49 (0.36-0.67)***	-5	0.51 (0.39-0.66)***	-5	0.51 (0.41-0.64)***	-6
AIDS/HIV	1.77 (1.39-2.25)***	4	1.66 (1.32-2.09)***	3	1.66 (1.33-2.08)***	4
Lymphoma	2.73 (2.32-3.21)***	7	2.29 (1.96-2.68)***	6	2.15 (1.84-2.50)***	6
Metastatic Cancer	3.62 (3.31-3.97)***	9	3.73 (3.42-4.08)***	9	3.78 (3.46-4.13)***	11
Solid Tumor without Metastasis	2.20 (2.04-2.38)***	6	1.88 (1.75-2.03)***	4	1.80 (1.67-1.94)***	5
Rheumatoid Arthritis/collagen	1.15 (1.00-1.31)*	1	E	.	E	.
Coagulopathy	2.87 (2.67-3.08)***	8	2.52 (2.35-2.69)***	6	2.38 (2.23-2.55)***	7
Obesity	0.60 (0.54-0.66)***	-4	0.59 (0.54-0.65)***	-4	0.60 (0.55-0.65)***	-4
Weight Loss	2.84 (2.64-3.05)***	8	2.51 (2.35-2.69)***	6	2.44 (2.28-2.61)***	7
Fluid and Electrolyte Disorders	3.74 (3.60-3.90)***	10	3.58 (3.44-3.73)***	9	3.45 (3.32-3.59)***	10
Blood Loss Anemia	E	.	E	.	E	.
Deficiency Anemia	0.47 (0.40-0.56)***	-5	0.55 (0.48-0.63)***	-4	0.53 (0.46-0.60)***	-5
Alcohol Abuse	0.82 (0.76-0.90)***	-1	0.86 (0.79-0.94)***	-1	0.89 (0.82-0.96)**	-1
Drug Abuse	0.57 (0.50-0.65)***	-4	0.52 (0.46-0.60)***	-4	0.51 (0.45-0.58)***	-6
Psychoses	0.73 (0.62-0.87)***	-2	0.72 (0.62-0.84)***	-2	0.73 (0.63-0.84)***	-3
Depression	0.59 (0.54-0.65)***	-4	0.54 (0.50-0.59)***	-4	0.52 (0.47-0.56)***	-6

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Abbreviations: CI, 95% confidence intervals; E, eliminated from the model; OR, odds ratio.

Table 3.4. Adjusted odds of inhospital mortality at 1-year and relative points by health condition(s) and look back period, N = 1,637,572

Health Condition(s)	Index Only, OR (CI)	Points	1 Year Look Back, OR (CI)	Points	2 Year Look Back, OR (CI)	Points
Congestive Heart Failure	3.32 (3.19-3.45)***	24	3.11 (2.98-3.23)***	13	3.01 (2.89-3.13)***	15
Cardiac Arrhythmia	2.40 (2.31-2.49)***	17	2.30 (2.22-2.39)***	10	2.24 (2.16-2.32)***	11
Valvular Disease	E	.	E	.	E	.
Pulmonary Circulation Disorders	1.24 (1.15-1.34)***	4	1.24 (1.15-1.33)***	2	1.22 (1.14-1.31)***	3
Peripheral Vascular Disorders	2.00 (1.88-2.13)***	14	1.77 (1.67-1.87)***	7	1.65 (1.56-1.74)***	7
Hypertension	1.05 (1.02-1.09)**	1	1.09 (1.06-1.13)***	1	1.10 (1.06-1.13)***	1
Paralysis	3.22 (2.94-3.52)***	23	2.86 (2.62-3.13)***	12	2.67 (2.45-2.90)***	13
Neurological Disorders	3.20 (3.06-3.35)***	23	2.93 (2.80-3.06)***	13	2.78 (2.66-2.90)***	14
Chronic Pulmonary Disease	1.56 (1.51-1.62)***	9	1.45 (1.40-1.50)***	4	1.41 (1.36-1.46)***	5
Diabetes without complications	1.15 (1.10-1.20)***	3	1.10 (1.06-1.15)***	1	1.08 (1.04-1.12)***	1
Diabetes with complications	1.09 (1.01-1.19)*	2	E	.	E	.
Hypothyroidism	0.89 (0.84-0.95)***	-2	0.92 (0.87-0.97)**	-1	0.90 (0.85-0.95)***	-1
Renal Failure	2.14 (2.03-2.24)***	15	1.88 (1.79-1.97)***	7	1.83 (1.75-1.92)***	8
Liver Disease	3.46 (3.24-3.69)***	25	2.94 (2.77-3.12)***	13	2.74 (2.58-2.90)***	14
Peptic Ulcer Disease excluding bleeding	0.76 (0.62-0.93)**	-5	0.77 (0.65-0.91)**	-3	0.76 (0.65-0.89)***	-4
AIDS/HIV	2.24 (1.85-2.70)***	16	2.00 (1.67-2.40)***	8	1.97 (1.65-2.35)***	9
Lymphoma	3.92 (3.47-4.43)***	27	3.46 (3.08-3.89)***	15	3.26 (2.91-3.66)***	16
Metastatic Cancer	3.93 (3.65-4.22)***	27	4.04 (3.77-4.34)***	16	4.07 (3.79-4.36)***	19
Solid Tumor without Metastasis	2.77 (2.61-2.94)***	20	2.41 (2.28-2.56)***	10	2.31 (2.18-2.44)***	11
Rheumatoid Arthritis/collagen	1.30 (1.18-1.44)***	5	1.29 (1.17-1.42)***	3	1.22 (1.12-1.34)***	3
Coagulopathy	2.58 (2.43-2.75)***	19	2.33 (2.20-2.47)***	10	2.22 (2.10-2.35)***	11
Obesity	0.58 (0.54-0.63)***	-11	0.59 (0.55-0.64)***	-6	0.60 (0.56-0.65)***	-7
Weight Loss	2.68 (2.52-2.86)***	20	2.38 (2.24-2.52)***	10	2.28 (2.15-2.41)***	11
Fluid and Electrolyte Disorders	2.87 (2.77-2.96)***	21	2.78 (2.70-2.88)***	12	2.71 (2.62-2.80)***	13
Blood Loss Anemia	1.22 (1.07-1.39)**	4	1.16 (1.03-1.31)*	2	1.12 (1.00-1.26)*	2
Deficiency Anemia	0.73 (0.65-0.82)***	-6	0.83 (0.75-0.91)***	-2	0.80 (0.73-0.87)***	-3
Alcohol Abuse	0.91 (0.85-0.98)*	-2	E	.	E	.
Drug Abuse	0.61 (0.55-0.68)***	-10	0.59 (0.53-0.65)***	-6	0.59 (0.54-0.65)***	-7
Psychoses	0.85 (0.75-0.96)*	-3	0.84 (0.75-0.94)**	-2	0.85 (0.76-0.94)**	-2
Depression	0.70 (0.65-0.75)***	-7	0.68 (0.63-0.72)***	-5	0.65 (0.61-0.69)***	-6

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

Abbreviations: CI, 95% confidence intervals; E, eliminated from the model; OR, odds ratio.

Table 3.5. Predictive performance by mortality outcome, look back period, and comorbidity summary method, N = 1,635,726

Model	c-statistic (95% CI)		
	Index Only	**Index + 1 Year Look back**	**Index + 2 Year Look back**
Inhospital Mortality			
Baseline: Age & Sex	0.820 (0.818-0.822)	0.820 (0.818-0.822)	0.820 (0.818-0.822)
Baseline & Binary Method	0.887 (0.885-0.890)[a]	0.886 (0.883-0.888)[a,b]	0.884 (0.882-0.887)[a-c]
Baseline & Total Method	0.856 (0.853-0.859)[a,d]	0.854 (0.851-0.856)[a,b,d]	0.851 (0.849-0.854)[a-d]
Baseline & Weighted Method	0.886 (0.884-0.888)[a,d,e]	0.884 (0.882-0.885)[a,b,d,e]	0.883 (0.881-0.885)[a-e]
Inhospital Mortality at 1-Year			
Baseline: Age & Sex	0.826 (0.824-0.827)	0.826 (0.824-0.827)	0.826 (0.824-0.827)
Baseline & Binary Method	0.884 (0.882-0.886)[a]	0.886 (0.884-0.888)[a,b]	0.885 (0.883-0.887)[a-c]
Baseline & Total Method	0.861 (0.859-0.863)[a,d]	0.864 (0.862-0.866)[a,b,d]	0.863 (0.862-0.866)[a-d]
Baseline & Weighted Method	0.882 (0.880-0.884)[a,d,e]	0.883 (0.881-0.885)[a,b,d,e]	0.883 (0.881-0.885)[a-e]

Notes: c-statistic differences were evaluated using the non-parametric Mann–Whitney U statistical method for comparing ROC curves developed and described by DeLong et al.[36] [a]Reference = baseline: age and sex, statistically significant, $p < 0.0001$. [b]Reference = index only, statistically significant, $p < 0.0001$. [c]Reference = index + 1-year look back, statistically significant, $p < 0.0001$. [d]Reference = baseline and binary method, statistically significant, $p < 0.0001$. [e]Reference = baseline and total method, statistically significant, $p < 0.0001$.
Abbreviations: CI, 95% confidence interval; ROC, receiver operating characteristic.

Discussion

The goal of this study was to advance methodologies for conducting observational studies founded on privacy-protected data warehouses. More specifically, we aimed to identify the optimal look back period and comorbidity summary method for the Quan ECM when predicting inhospital mortality at index and inhospital mortality at 1 year in Cerner HF. We found that the optimal comorbidity risk-adjustment parameters differed minimally across the mortality outcome. The Quan ECM model based on the binary method with diagnostic ascertainment limited to the index encounter performed the best for predicting inhospital mortality. When predicting inhospital mortality at 1 year, the binary method with 1 year of look back had the highest c-statistic. A recent study by Thompson et al[37] conducted using the AHRQ National Inpatient Sample and the Maryland State Inpatient Database showed that the binary method (*c* □□0.809, 95% CI: 0.808–0.810) for the original Elixhauser comorbidities performed slightly better than the VW method (*c* □□0.802, 95% CI: 0.801–0.804), albeit the cardiac arrhythmia group was excluded from both models. During the validation of the original VW point system, van Walraven et al[22] observed a similar but inverse performance between the binary (*c* □□0.760, 95% CI: 0.756–0.764) and weighted (*c* □□0.763, 95% CI: 0.759–0.766) methods when predicting inhospital mortality for a Canadian population. Our findings pertaining to the best method for summarizing Elixhauser conditions fit somewhere between the above studies. While the binary method was statistically superior, when holding the look back period constant, we found that improvements in predictive performance between the binary and weighted methods were not likely clinically important. As for the total method, it performed significantly worse on average than the other methods. Relatively lower performance by the total method was recently demonstrated[37] and was expected because it is

unrealistic to assume that every ECM condition has an equivalent relationship to the outcome of interest.

This study asked if the length of the ascertainment look back period affected the capacity of models to discriminate between mortality statuses. Previous studies had shown that longer look back periods are better predictors of long-term mortality and that look back periods limited to the index encounter are better predictor of inhospital mortality at index.[4,16,17] In this study, every direct comparison between look back periods proved highly statistically different (p □□0.0001), yet varying the look back period appeared practically irrelevant. For inhospital mortality, we observed statistically significant decreases in predictive performance with increasing look back. For predicting inhospital mortality at 1 year, the 1-year look back option was statistically the best option. Complementary results from sensitivity analyses based on 3-, 4-, and 5-year look back periods (not reported) failed to demonstrate any improvement in predictive performance and did not challenge the main study findings. Within comorbidity summary methods, the statistically significant difference in predictive performance between the look back periods are not likely to have any clinical relevance since they rarely exceeded half a percent. In this study, mortality outcomes were selected because they are the most commonly used end points in validation studies of comorbidity measures and allow for cross-study comparisons.[15] However, alternative outcomes, such as hospital readmissions, have been shown to be better predicted by longer look back periods and would require additional validation.[17]

While implementing the VW point system, we observed an inverse relationship between several comorbidity groups and the mortality outcomes. This led to ECM conditions having negative weights. Notably, more than one-third of the Quan ECM, including valvular disease, hypertension, diabetes with complications, hypothyroidism, peptic ulcer disease without bleeding,

obesity, depression, psychoses, drug abuse, alcohol abuse, and deficiency anemia, had negative weights when predicting inhospital mortality at the index with 1 year of look back. According to Elixhauser et al,[1] conditions negatively associated with mortality possibly reflect the fact that during acute encounters, conditions possibly considered irrelevant to the provision of care are less frequently recorded. In other words, conditions negatively associated with mortality may not be protective as much as they are the result of a combination of clinical relevance and inconsistent data collection. It could also be hypothesized that comorbidities such as drug and alcohol abuse, psychoses, and depression are less likely recorded in medical records because they are stigmatized conditions with a lower likelihood of voluntary disclosure by health care recipients.

The strengths of this study include its broad geographic coverage, numerous contributing health care facilities, and the large and diverse population of US health care recipients in the data source. This afforded the selection of a study sample with complete demographic profiles and available diagnostic information without compromising study power. While studies with enormous sample sizes are prone to being overpowered, the resulting resource utilization consequences are somewhat inconsequential and ethical concerns are irrelevant in administrative database research. The ability to ascertain diagnoses across multiple care settings in HF, i.e., outpatient clinics, ED visits, hospital care, is likely to have improved the accuracy and completeness of individual comorbidity profiles. The study design was based on random encounters over episodes of care. Episodes of care were initially defined by Solon et al[38] as the grouping of health services data from one or more health encounters related to the management of a principal health condition or problem. In the context of validating measures of comorbidity without selecting a primary health condition of interest, as was the case for this study and those to which it should be compared,[22,39] the episode of care approach not only increases complexity but

also raises methodological concerns. For instance, in highly comorbid individuals, the aggregation of a larger number of health encounters into a single episode of care is likely to lead to increased opportunities for identifying prevalent health conditions, when compared to people with lower overall morbidity and narrower episodes of care. This situation could result in greater exposure misclassification based on the characteristics of the episode of care itself. The reader is referred to the seminal paper by Wingert et al[40] for further discussion of the theoretical motives supporting the episodes of care methodology.

This study is also the first to validate the performance of the VW approach using the Quan ECM in a US data source. Our findings highlight the relevance of internal validation prior to selecting comorbidity risk-adjustment parameters. In HF, the choice of look back period is not as critical as the choice of comorbidity summary method compared to other data sources. While the total summary method should be avoided, the consequences of limiting ECM diagnostic ascertainment to the index encounter, the least complex and resource-intensive approach available, is not likely to practically affect the performance of the Quan ECM in HF. We also confirmed the practical equivalence of the weighted and binary methods for predicting inhospital mortality outcomes. This highlights a real advantage for future epidemiological studies since weighted scores are much easier to manipulate, interpret, and could help avoid problems related to overfitting that arise during regression analyses when too many variables are included in a model.[22]

Limitations of this study included our inability to separate conditions present on admission from complications in care typically identified using diagnostic-type indicators. In HF, the diagnostic-type indicator was not consistently available, which prevented further investigation of this parameter. Thus, we could not test the hypothesis by Quan et al[10] that including conditions emerging from complications in care is likely to benefit predictions for long-term mortality but

not necessarily inhospital mortality. In HF, care recipients are tracked as they seek care from Cerner participating institutions. However, not all US health care institutions are Cerner clients and data contributors. Even in cases where patients received care from two Cerner health facilities, it would only be possible to track patients across time if these facilities were covered under the same privacy (HIPAA) network. Likewise, care recipients in HF may have the option of seeking health services from non-Cerner-affiliated health facilities. In such instances, the clinical encounter data would not be captured in HF and details about health services participation, including diagnoses and health outcomes, would be lost. These limitations are characteristic of observational research conducted with HIPAA-compliant administrative databases and necessitate consideration in experimental design. Notably, evidence of mortality had to be limited to deaths captured in Cerner hospitals since mortality status could not be verified against other sources of vital statistics through data linkage. Therefore, deaths were certainly underrepresented, and this likely introduced some biases. Another possible source of confounding relates to how health care organizations elect to record the discharge outcome of people transferred to hospice care.[41] Findings from Kozar et al[41] based on data from US Trauma Quality Improvement Program centers suggest that transfers to hospice care assign a survivor status to patients and that in some cases, the more appropriate discharge status might be deceased. The authors also found that patients with two or more comorbidities were more likely to be coded as hospice care transfers than inhospital deaths.

Results of this study must be contrasted against the possibility of lead time and retention biases, which could vary by condition, by condition latency or intermittency, by condition severity, by services rendered, by age, by health insurance status, and other factors.[42,43] People with certain conditions or comorbidities could theoretically expedite or delay seeking care and experience different lead times till their first encounter with an HIPAA-covered entity source institution in

HF. Such factors could crucially affect whether one will or will not have, 1) antecedent encounters in the data warehouse, at 1 year or other look back intervals, and 2) subsequent encounters, at 1 year or other follow-up times, wherein mortality or comorbidities can be ascertained.

Often, comparative studies of comorbidity indices or measures are performed in a population defined by a specific primary diagnosis, e.g., cancer,[44–46] from which comorbid conditions are defined. This study is aligned with the seminal Quan et al[10] study and was conducted with an undifferentiated patient general population. For this reason and until evidence to the contrary is available, it is advised that VW-based weights be rederived for each study population based on a different primary diagnosis. We completed secondary database research in a data source primarily designed for documenting clinical practice, health services, and billing.[23] Hence, our results are subject to the typical biases and limitations accompanying administrative database research,[47,48] which include risks of missing clinical and demographic information, the misclassification of diagnoses during data abstraction, linkage errors related to interoperability issues, and record duplication.

Finally, we confirmed the excellent predictive performance of the Quan ECM for predicting inhospital mortality and inhospital mortality at 1 year in Cerner HF, a large longitudinal US multi-payer health database that complies with US HIPAA regulations and limitations. The performance of the Quan ECM expressed as binary indicators and the weighted scores were practically equivalent and both surpassed the total method. Differences in diagnostic ascertainment look back period up to 2 years were statistically but not clinically associated with significant differences in predictive performance for inhospital mortality.

Acknowledgments

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Disclosure

YF, JAGC, and DC report no competing interests. DSM is the president of Cerner Math Inc. and has ownership interest in the Cerner Corporation. This paper reflects the opinions of the authors and not necessarily those of the Canadian Institute for Health Information or the Cerner Corporation. DRM serves as chief medical officer of Risk Sciences International (RSI), a company formed in partnership with the University of Ottawa in 2006. RSI undertakes risk assessment work for public and private sector clients in Canada and abroad. RSI has not conducted prior work on the subject of the present research paper. DK is chief risk scientist and CEO of RSI. Since 2002, DK has held a Natural Sciences and Engineering Research Council of Canada (NSERC) Industrial Research Chair in Risk Science, through a peer-reviewed university–industry partnerships program administered by NSERC. The scientific opinions and conclusions expressed in research publications by the chair are the responsibility of the chair alone. The authors report no other conflicts of interest in this work.

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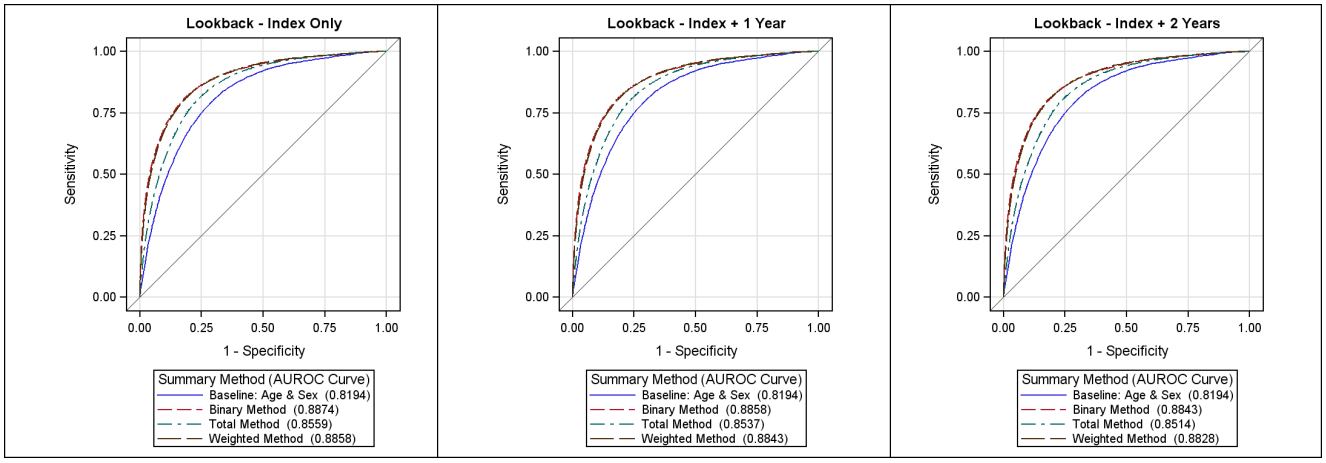
Appendix A

In-Hospital Mortality



In-Hospital Mortality at 1-Year

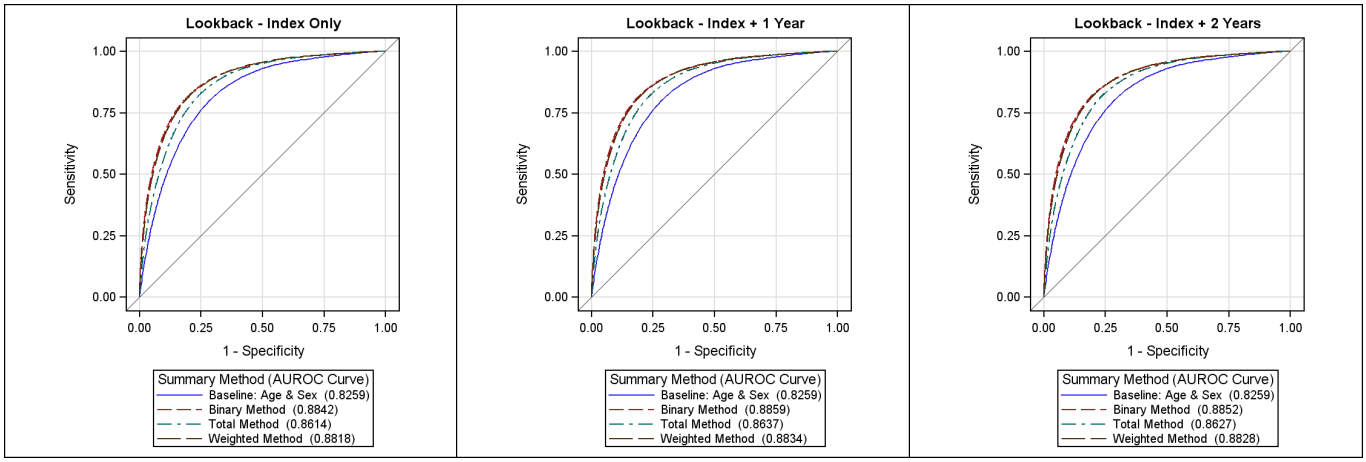
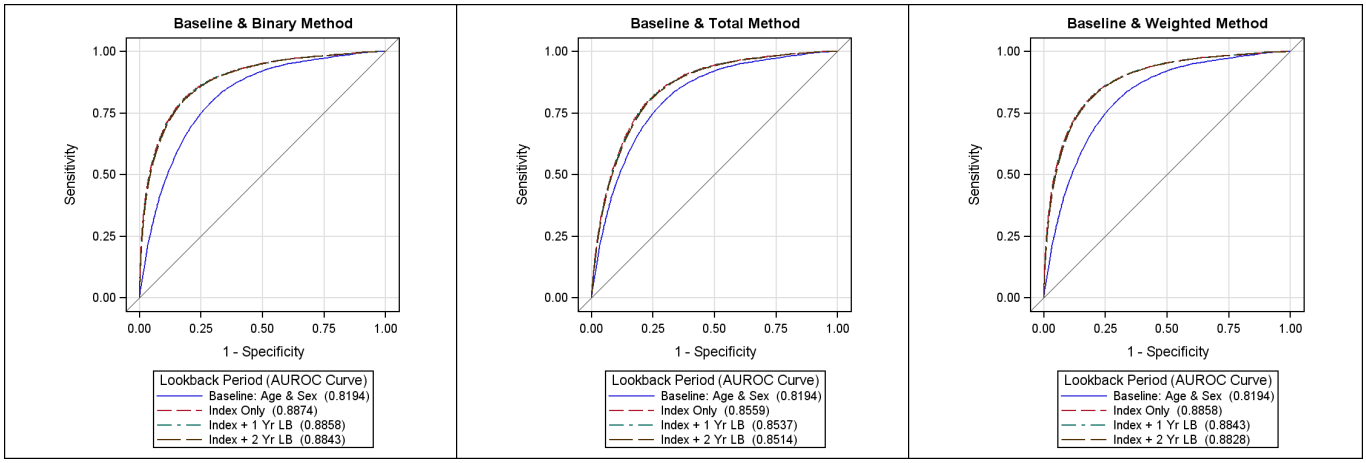


Figure 3.1S. Comparisons of Receiver Operating Characteristic Curves across Comorbidity Summary Methods by Mortality Outcome and Look Back Period.
Abbreviation: AUROC, Area under the receiver operating characteristic curve.

In-Hospital Mortality



In-Hospital Mortality at 1-Year

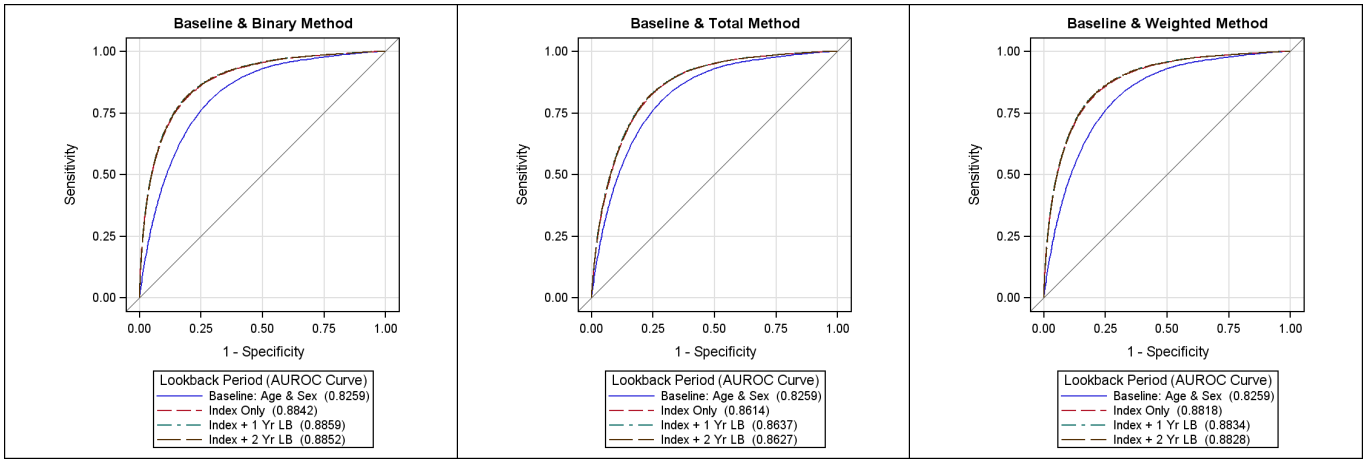


Figure 3.2S. Comparisons of Receiver Operating Characteristic Curves across Look Back Periods by Mortality Outcome and Comorbidity Summary Method.
Abbreviation: AUROC, Area under the receiver operating characteristic curve; LB, Look Back.

Chapter 4 - An Exposure–Response Relationship between Multimorbidity and Motor-Vehicle Accidents

Yannick Fortin[1,2], James A.G. Crispo[1,2,3], Deborah Cohen[2,4,5], Simone Dahrouge[6,7], Douglas S McNair[8], Donald R. Mattison[1,9], Daniel Krewski[1,2,9]

Authors Note

1. McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada. 2. School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada. 3. Fulbright Canada Student, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 4. Canadian Population Health Initiative (CPHI), Canadian Institute for Health Information (CIHI), Ottawa, Ontario, Canada. 5. Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. 6. C.T. Lamont Primary Health Care Research Center, Bruyère Research Institute, Ottawa, Ontario, Canada. 7. Department of Family Medicine, University of Ottawa, Ottawa, Canada. 8. Cerner Corporation, Kansas City, Missouri, USA. 9. Risk Sciences International, Ottawa, Ontario, Canada.

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Abstract

Objective

Several health conditions are independently associated with an increased risk of experiencing a motor-vehicle accident (MVA). The objective of this study was to investigate the possibility of an exposure–response relationship between multimorbidity and MVAs using electronic health records.

Methods

Driver-related MVA cases recorded between 2002 and 2012 were identified in Cerner Health Facts®, a national electronic health record database in the United States. Cases were matched to five controls from the same health care facility on age, sex, and index date (± 2 years). Multimorbidity was defined as the total number of morbidities per patient, based on the prevalence of 13 predefined health conditions that were retrospectively assessed during the previous 2 years. The risk of MVA for individuals with increasing multimorbidity, relative to no morbidity, was estimated using conditional logistic regression. Additional analyses were conducted to evaluate possible effect modification by sex and age.

Results

A total of 74,167 unique MVA cases were matched to 370,835 controls: 59.1% of study participants were males and the mean age was 37.0 ± 0.0 years. Multimorbidity, having 2 or more health conditions, was more frequent in cases (8.0%) than in controls (5.6%), $\chi 2$ (1, N = 445,002) = 585.9, p<.0001. A positive association was detected between increasing multimorbidity and MVA risk. Relative to no morbidity, the odds of MVA increased steadily with an increasing number of prevalent morbidities–from 1.11 (95% CI 1.06-1.16) with two concurrent health

conditions to 3.53 (95% CI 2.69-4.64) with six or more health conditions. Increasing MVA risk with increasing multimorbidity was more pronounced in women than men.

Conclusions

This study found an overall increased risk of MVA with increasing multimorbidity, which was reproduced across sex and age categories. The important public health implications of these findings warrant replication with additional adjustment for driving habits.

Keywords: Comorbidity; multimorbidity; chronic disease; crash risk; motor-vehicle accidents; automobile driving

Introduction

In several Western countries, pre-existing morbidity is a determinant of driving eligibility and restrictions (Charlton et al., 2010; Vaa, 2005; Vernon et al., 2002). Such restrictions−including limits on speed, geography, or time of day−are typically imposed on individuals who declare the presence of select health conditions to their licensing authority and are often based on the premise that certain health conditions and their treatment may result in physical or cognitive impairments that increase the risk of having a motor-vehicle accident (MVA) (Johansson et al., 1996; OECD, 2001). Prior studies have identified a number of health conditions as independent predictors of MVAs, including alcohol abuse and dependence, schizophrenia, sleep apnoea/narcolepsy, vision impairment, dementia, epilepsy, multiple sclerosis, cardiovascular diseases, diabetes mellitus, psychiatric disorders, and neurological illnesses (Charlton et al., 2010; Dobbs, 2005; Vaa, 2005).

Multimorbidity is typically defined as the co-occurrence of 2 or more chronic health conditions (Boyd & Martin Fortin, 2010). Intuitively, it seems reasonable to expect that persons diagnosed with multiple health conditions independently associated with an increased MVA risk would be at a higher risk of a vehicular crash than those without multimorbidity. In a population-level study based on the assessment of 40 medical and mental health conditions, Barnett et al. (2012) found that 11.3%, 30.4%, and 64.9% of adults aged 25 to 44, 45 to 64, and 65 to 84 years, respectively, were multimorbid. In addition to the high prevalence of multimorbidity in developed countries, there is evidence that multimorbidity has increased for all age groups over the last decades (Koné Pefoyo et al., 2015; Uijen & van de Lisdonk, 2008) and it is expected to continue increasing in the coming years (Anderson, 2012). Older age, female sex, and lower socioeconomic status are associated with greater multimorbidity (Marengoni et al., 2011; Roberts et al., 2015; Uijen & van de Lisdonk, 2008). However, multimorbidity is not limited to the elderly, and affects

a proportion of working adults who often drive to maintain employment and participate in social functions. Describing the relationship between increasing multimorbidity and risk of MVAs is therefore an important public health research priority.

A systematic review of epidemiological studies on the relationship between multimorbidity and MVA risk (Dischinger et al., 2000; Koepsell et al., 1994; Marottoli et al., 1994; Oxley et al., 2005; Sims et al., 2000; Vernon et al., 2002) concluded that the risk of MVA is higher with increasing multimorbidity (Marshall & Man-Son-Hing, 2011). Only two of the six studies on crash risk retained by the systematic review were inclusive of drivers of all-ages (Dischinger et al., 2000; Vernon et al., 2002) which limit the representativeness of young and middle age adults. As is often the case, the other studies targeted older adults. More recently, Papa et al. (2014) confirmed the positive association between multimorbidity and MVAs in adults 40 to 70 years but not in those over the age of 70 years. The latter were significantly more likely to lower or abandon their driving activities with increasing multimorbidity while the younger age group did not. Although these finding were based on a cross-sectional study design and self-reports, the authors controlled for driving exposure, categorized morbidity exposure with the validated Cumulative Illness Rating Scale (de Groot et al., 2003; Miller & Towers, 1991), and investigated the possibility of a dose-response effect between multimorbidity and MVA risk. Few studies have investigated changes in MVA risk with each additional health condition. Overall, there is a need for additional research on this topic, particularly whether an exposure-response relationship exists between multimorbidity and MVA in adults across the lifespan.

The primary objective of this case-control study was to examine whether there is an exposure-response relationship between multimorbidity and MVA occurrence. A secondary

objective was to investigate if sex and age modify the effect of the relationship between multimorbidity and MVA risk.

Methods

Data Source

Electronic health records from the Cerner Health Facts® (HF) (Kansas City, MO) database recorded between January 2000 and December 2012 were the basis for this study and accounted for care administered to 36.7 million Americans at health care facilities dispersed across the four U.S. census regions [Northeast, Midwest, South, and West]. HF contains longitudinal health service utilization information on individuals seen in outpatient and acute care settings, including services for the insured and uninsured. Outpatient clinics offering generalist and specialist care include standalone physician offices and clinics integrated within larger health care centers. Available information included demographic characteristics, diagnoses, laboratory tests, clinical procedures, and medication orders (hospital pharmacies only). This study was approved by the Office for Research Ethics and Integrity at the University of Ottawa.

Study Population

Individuals 16 to 89 years of age with complete demographic information [sex, age, race] were eligible for inclusion in our study. Patients over the age of 89 years were excluded because the age variable is no longer continuous after 90 years in HF and must be pooled into a single category to comply with HIPAA regulations.

Cases Ascertainment

Cases were health care recipients with a primary or secondary diagnostic code for a driver-related MVA according to the International Classification of Diseases, Ninth Revision, Clinical

Modification (ICD-9-CM) (Kwon et al., 2011) (Appendix A). Health encounters were assessed for MVAs from January 2002 onwards to allow for 2 years of pre-incident assessment of morbidity. For patients with multiple MVAs, the earliest encounter was selected as the index encounter. Although the total number of MVAs per study participant was also considered as a possible continuous dependent variable, this outcome was not included in our analyses because differentiating between independent MVA events in EHR data are of questionable accuracy, particularly when such events are separated by short amounts of time.

Control selection

Cases were matched to five controls from the same treating health care facility on sex, age, and index encounter year. To complete the match, the characteristics of cases and their referent MVA encounter were linked to every available health encounter without a recorded MVA code on age, sex, hospital identification number, and encounter year [± 2]; for each case, five controls matching the criteria were selected at random. Controls selected as part of a matched case-control set were subsequently excluded from further matching. Cases were excluded as possible controls.

Exposure Assessment

The exposure of interest, multimorbidity, was defined as the co-occurrence of two or more prevalent health conditions based on a pre-defined list of 13 condition groups that are considered leading causes of disability, health expenditures, and mortality in the U.S. (Bauer et al., 2014; CDC, 2009b, 2013). They include: cardiovascular disorders; dementia; diabetes; chronic pulmonary disease; rheumatic disease; epilepsy; multiple sclerosis; Parkinson's disease, psychiatric disorders excluding substance abuse, sleep disorders, vision-related conditions, hypothyroidism, and cancer. In addition, the select health conditions had to be significantly

associated ($p<0.05$) with increased odds of MVA according to comprehensive systematic reviews and meta-analyses by Vaa (2005), Dobbs et al. (2005), or Charlton et al. (2010). ICD-9-CM codes used to identify prevalent health conditions are listed in Appendix A. To improve the detection of existing health conditions and limit exposure misclassification, diagnoses recorded during the index encounter or during health encounters in the two years preceding the index encounter admission date were reviewed. A binary indicator was created for each of the 13 conditions assessed and the sum of the binary indicators of prevalent conditions was compiled for each patient. An ordinal measure of multimorbidity status was then created by categorizing total morbidity into seven categories [No morbidity, 1 condition, 2 conditions, 3 conditions, 4 conditions, 5 conditions, and 6 or more conditions].

Given the widely recognized relationship between MVAs and elevated blood alcohol content (NHTSA, 2016), indicators of substance and alcohol abuse were created from recorded diagnoses during the lookback period. Having a history of drug misuse, including alcohol abuse, has been associated with significantly higher risk MVAs (Charlton et al., 2010; Gjerde, Normann, Christophersen, Samuelsen, & Mørland, 2011; Koepsell et al., 1994; Vaa, 2005; Vernon et al., 2002). Risk of MVA in substance abusers was also found to be particularly pronounced in drivers with restricted licences due to existing medical conditions when compared to drivers without medical restrictions (Vernon et al., 2002).

Demographic Characteristics and Other Covariates

Race was categorized as Caucasian, African American, Hispanic, Asian, and other. Health insurance status—our proxy for socioeconomic status—was categorized according to a model proposed by the U.S. Agency for Healthcare Research and Quality (Barrett et al., 2014) using the following categories: private, Medicaid, Medicare, self-pay/uninsured, other (TRICARE-

CHAMPUS, international plan, research funded, Title V, worker's compensation), and missing. In HF, data contributing hospitals and clinics at times elect—for privacy reasons—to withhold the transfer of information on health insurance status. This results in missing values for approximately 27% of HF health encounters. Based on consultations with the Cerner Corporation, a number of health care facilities do not share data on health insurance payer class. This is likely attributable to policies aimed at protecting the privacy and personal information of patients. In this study, since cases and controls are matched on health facility ID, the misclassification of health insurance status is expected to be equivalent between the group and therefore, nondifferential.

Three variables were derived to measure factors that could affect the identification of prevalent health conditions in our sample: the total number of health care encounters (including the index) available for morbidity assessment (henceforth referred to as total encounters); the actual number of days between the index admission and the earliest recorded admission within the lookback period (henceforth referred to as confirmed lookback); and the sum of inpatient days (including the index) identified in the lookback period (henceforth referred to as inpatient days). Indicators describing the context of care for the index encounters are reported in Table 4.1.

Statistical analysis

Categorical variables for patient characteristics and morbidity prevalence are described by frequency distributions and compared using the Pearson Chi-square (χ^2) test. Continuous variables are presented with means ± standard deviations and compared with Student's t-test. To prevent correlations between the independent variables from biasing the model parameter estimates, correlations between covariates were verified with the Spearman's rank correlation approach. A single model parameter, the one with the strongest association with the outcome, was retained in the fully adjusted model if a high degree of multicollinearity (≥ 0.8) was detected with another

independent variable. This was done to prevent model instability and to reduce the likelihood of incorrect model predictions (Grewal, Cote, & Baumgartner, 2004; Holland, 2014; Vatcheva, Lee, McCormick, & Rahbar, 2016). Statistical tests were two-tailed with a significance level of 0.05. Crude and adjusted odds of the exposure by MVA status were computed using conditional multiple logistic regression. Suspected confounders were assessed with the change in estimate method using a 5% cut off (Greenland, 1989): only empirically confirmed confounders were included in the adjusted model. Crude and adjusted odds ratios of the relationship between multimorbidity status and MVA involvement were generated for the full sample, then stratified by sex, and by age group strata [16-24 years, 25-44 years, 45-64 years, and 65 years and older]. To investigate possible effect modification by sex and age, interaction terms—sex*multimorbidity and age*multimorbidity—were derived and tested using bivariate and multivariate logistic regression models. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity Analyses

Elvik (2011) suggested that some drivers might knowingly avoid seeking care to prevent the diagnosis of health conditions that would jeopardize their ability to maintain driving eligibility (see Vernon et al. (2002) for a review of morbidity disclosure avoidance in drivers). This behaviour would also result in the misclassification of morbidity status. We hypothesize that persons whose care was limited to the outpatient setting in our sample might have greater opportunity for non-disclosure of health conditions than patients admitted for acute care, where a more comprehensive medical history would be taken within a clinical context. Analyses were therefore repeated on the subsets of the sample whose care was limited to outpatient settings.

Results

Of the 11,847,268 available health services recipients 16 to 89 years of age with complete demographic profiles, 74,167 MVA cases were identified and matched (1:5) to 370,835 controls (Table 4.1). Individuals involved in MVAs were most often male (59.1%) and of younger age—68.2% were 44 years of age or less. MVA cases and controls varied significantly by race and health insurance status, with those covered under private insurance showing an increased but expected higher frequency of crashes compared to other groups. Cases had significantly more health encounters, total inpatient days, and longer confirmed lookback days than controls.

Table 4.1: Patient and care setting characteristics, N = 445,002.

	MVA Status		
Variables	***Crash N =74,167(%)***	***No Crash N =370,835(%)***	***P Value***
Sex			*Na*
Female	182,076 (40.9)		
Male	262,926 (59.1)		
Age at Index			
Mean ± SD	37.0 ± 0.0		*Na*
Age Category			
16 to 24	130,746 (29.4)		*Na*
25 to 44	172,788 (38.8)		
45 to 64	110,214 (24.8)		
65 and Older	31,254 (7.0)		
Race			*<.001* [C]
Caucasian	55,593 (75.0)	271,703 (73.3)	
African American	13,986 (18.9)	70,120 (18.9)	
Hispanic	2,194 (3.0)	12,132 (3.3)	
Asian	576 (0.8)	3,843 (1.0)	

	MVA Status		
Variables	***Crash N =74,167(%)***	***No Crash N =370,835(%)***	***P Value***
Other	1,818 (2.5)	13,037 (3.5)	
Health Insurance Status			*<.001* [C]
Private	32,648 (44.0)	130,923 (35.3)	
Medicare	2,689 (3.6)	26,831 (7.2)	
Medicaid	5,056 (6.8)	40,185 (10.8)	
Uninsured	8,828 (11.9)	51,897 (14.0)	
Other	4,130 (5.6)	22,020 (5.9)	
Missing	20,816 (28.1)	98,979 (26.7)	
Total Encounters			*<.001* [S]
Mean ± SD	3.6 ± 6.6	2.8 ± 4.9	
Confirmed Lookback Days			*<.001* [S]
Mean ± SD	183 ± 257	113 ± 205	
Inpatient Days			*<.001* [S]
Mean ± SD	2.2 ± 11.2	1.5 ± 13.5	
Census Region			*Na*
Northeast	188,436 (42.3)		
Midwest	595,62 (13.4)		
South	173,376 (39.0)		
West	23,622 (5.3)		
Missing	6 (0.0)		
Teaching Status			Na
Non-teaching	121,404 (27.3)		
Teaching	323,598 (72.7)		
Population Density			Na
Rural	3,684 (0.8)		
Urban	441,312 (99.2)		

Na: Not applicable, perfect matches between cases and controls result in p-values of 1. C= Pearson Chi-Square test. S= Student's t-test.

Health care encounters in our sample were recorded at 158 facilities located mostly in the Northeast (42.3%) and South (39.0%) census regions of the U.S. The majority of index encounters were located in urban settings (99.2%) and recorded at teaching facilities (72.7%).

Of the 13 preselected health conditions examined, seven were significantly more prevalent, one (cancer) was significantly less prevalent, and five showed no difference in prevalence in the crash versus non-crash group, respectively (Table 4.2). Overall, cardiovascular disorders (7.9%), chronic pulmonary disease (5.6%), diabetes (5.3%), and psychiatric disorders (4.2%) were the most prevalent conditions identified in the sample, all of which were significantly more frequent in MVA cases than controls. Recorded diagnoses of both alcohol (7.8% vs 2.5%, $p < .001$) and drug (4.2% vs 2.1%, $p < .001$) abuse were more prevalent in MVA cases than in controls.

Table 4.2: Prevalence of health conditions by MVA involvement, N = 445,002: Cases = 74,167; Controls = 370,835.

Health Condition	*Crash (74,167) n, (%)*	*No Crash (370,835) n, (%)*	*P value*	
Total number of health conditions (Mean +/- SD)	0.36 +/- 0.80	0.30 +/- 0.67	<0.001	@
Cardiovascular Disorders	6,762 (9.1)	28,273 (7.6)	<0.001	*
Dementia	219 (0.3)	1,257 (0.3)	0.059	
Diabetes Mellitus	4,689 (6.3)	18,773 (5.1)	<0.001	*
Chronic Pulmonary Disease	4,963 (6.7)	19,844 (5.4)	<0.001	*
Rheumatic Disease	418 (0.6)	1,960 (0.5)	0.232	
Epilepsy	728 (1.0)	2,884 (0.8)	<0.001	*
Multiple Sclerosis	106 (0.1)	573 (0.2)	0.460	
Parkinson's Disease	96 (0.1)	527 (0.1)	0.399	
Psychiatric Disorders	4,386 (5.9)	14,222 (3.8)	<0.001	*
Sleep Disorders	1,453 (2.0)	6,386 (1.7)	<0.001	*
Vision Conditions	402 (0.5)	2,222 (0.6)	0.063	

Health Condition	*Crash (74,167) n, (%)*	*No Crash (370,835) n, (%)*	*P value*	
Hypothyroidism	1,739 (2.3)	7,302 (2.0)	<0.001	*
Cancer	762 (1.0)	6,852 (1.8)	<0.001	*
Alcohol Abuse (Confounder)	5,807 (7.8)	9,177 (2.5)	<0.001	*
Substance Abuse (Confounder)	3,143 (4.2)	7,736 (2.1)	<0.001	*

[@] Student's t-test. * Pearson Chi-Square test.

Health insurance status, alcohol abuse, substance abuse, total encounters, inpatient days, and confirmed lookback were identified as potential confounders according to our pre-defined criteria. Subsequent Spearman's rank correlation testing identified a strong positive correlation between total encounters and confirmed lookback; $r_s = 0.88$, $p < .0001$. Since confirmed lookback was a stronger confounder of the exposure-outcome relationship than total encounters, it was retained in the adjusted model instead of total encounters.

Most (78%) of the study population had no prevalent morbidity, 16% had a single condition, and 6.0% were multimorbid (Table 4.3). The lower than expected frequency of multimorbid adults in the sample is possibly explained by the number of health conditions ascertained, undocumented health care encounters, and the disproportionate number of younger adults involved in MVAs.

Table 4.3. Associations between Morbidity and MVA N = 445,002, Cases: 74,167, Controls: 370,835

Category	*MVA, n (%)*	*No MVA, n (%)*	*Crude OR (95% CI)*	*Adjusted OR[@] A (95% CI)*	*Adjusted OR[&] B (95% CI)*
No morbidity	56,941 (76.8)	290,359 (78.3)	1.00	1.00	1.00
1 condition	11,330 (15.3)	59,584 (16.1)	0.99 (0.97 - 1.01)	0.86 (0.84 - 0.88)*	0.98 (0.96 - 1.01)
2 conditions	3,674 (5.0)	14,117 (3.8)	1.38 (1.33 - 1.44)*	1.11 (1.06 - 1.16)*	1.44 (1.37 - 1.51)*
3 conditions	1,361 (1.8)	4,597 (1.2)	1.61 (1.51 - 1.71)*	1.21 (1.13 - 1.30)*	1.76 (1.63 - 1.90)*
4 conditions	525 (0.7)	1594 (0.4)	1.81 (1.64 - 2.01)*	1.34 (1.20 - 1.49)*	2.16 (1.92 - 2.43)*
5 conditions	213 (0.3)	453 (0.1)	2.62 (2.22 - 3.09)*	1.88 (1.58 - 2.25)*	3.29 (2.72 - 3.98)*
6 or more conditions	123 (0.2)	131 (0.0)	5.34 (4.17 - 6.85)*	3.53 (2.69 - 4.64)*	6.19 (4.65 - 8.24)*

* P <.001.
Note. [@]Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.
[&]Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, confirmed lookback in days, and the interaction term of sex and multimorbidity status.

Cases (8.0%) were more frequently multimorbid than controls (5.6%), $\chi 2$ (1, N = 445,002) = 585.9, p<.0001. A monotonic exposure–response association relationship was found between multimorbidity status and MVA risk, with MVA risk increasing markedly with the number of concurrent health conditions. Compared to the no morbidity group, individuals with 2 [AOR = 1.11 (95% CI 1.06-1.16)], 4 [AOR = 1.34 (95% CI 1.20-1.49)], and 6 or more concurrent health conditions [AOR = 3.53 (95% CI 2.69-4.64)] were increasingly more likely to be involved in a MVA. This trend was replicated and odds ratios increased following the inclusion of the sex*multimorbidity interaction term in a complementary adjusted model (Table 4.3).

Women (6.2%) were more often multimorbid than men (5.9%), $\chi 2$ (1, N = 445,002) = 26.1, p<.0001 (Table 4.4). Sex was an effect modifier of the relationship between multimorbidity and MVA involvement in the bivariate [OR = 0.81 (95% CI 0.79-0.83), p <.0001] and the adjusted [OR = 0.79 (95% CI 0.77-0.81), p <.0001] models. For the 262,926 men included in our study, the adjusted odds of multimorbidity by MVA status only became relevant with the presence of 5 or more concurrent health conditions. For the 182,076 women included, the adjusted odds of multimorbidity by MVA status behaved similarly to the non-stratified sample, with a significant positive relationship increasing with the number of concurrent health conditions. Overall, the monotonic exposure–response association between increasing morbidity and MVAs was more consistent across morbidity categories in women than in men.

Table 4.4. Associations between Morbidity Status and MVA Involvement by Sex
N = 445,002, Cases: 74,167, Controls: 370,835

Category	*MVA* *n (%)*	*No MVA* *n (%)*	*Crude OR* *(95% CI)*	*Adjusted OR[&]* *(95% CI)*
Men, N =262,926		**Multimorbidity = 5.9%[@]**		
No morbidity	34,513 (78.8)	170,251 (77.7)	1.00	1.00
1 condition	6,326 (14.4)	36,407 (16.6)	0.86 (0.83 - 0.88)*	0.76 (0.73 - 0.78)*
2 conditions	1,933 (4.4)	8,525 (3.9)	1.13 (1.07 - 1.19)*	0.91 (0.86 - 0.96)*
3 conditions	667 (1.5)	2,715 (1.2)	1.23 (1.13 - 1.34)*	0.93 (0.85 - 1.02)
4 conditions	255 (0.6)	905 (0.4)	1.42 (1.23 - 1.64)*	1.05 (0.90 - 1.22)
5 conditions	94 (0.2)	248 (0.1)	1.93 (1.52 - 2.46)*	1.37 (1.06 - 1.77)*
6 or more conditions	33 (0.1)	54 (0.0)	3.13 (2.03 - 4.83)*	1.89 (1.19 - 3.01)*
Women, N =182,076		**Multimorbidity = 6.2%[@]**		
No morbidity	22,428 (73.9)	120,108 (79.2)	1.00	1.00
1 condition	5,004 (16.5)	23,177 (15.3)	1.20 (1.16 - 1.24)*	1.02 (0.98 - 1.06)
2 conditions	1,741 (5.7)	5,592 (3.7)	1.81 (1.70 - 1.91)*	1.40 (1.32 - 1.49)*
3 conditions	694 (2.3)	1,882 (1.2)	2.22 (2.03 - 2.43)*	1.63 (1.48 - 1.80)*
4 conditions	270 (0.9)	689 (0.5)	2.41 (2.08 - 2.78)*	1.72 (1.47 - 2.02)*
5 conditions	119 (0.4)	205 (0.1)	3.57 (2.84 - 4.49)*	2.57 (2.00 - 3.31)*
6 or more conditions	90 (0.3)	77 (0.1)	7.60 (5.58 - 10.36)*	5.13 (3.61 - 7.28)*

* P <.001.
Note. [&]Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.
[@] Percent differences in multimorbidity frequency between the sexes are significant, $\chi 2$ (1, N = 445,002) = 26.1, p<.0001.

As expected, multimorbidity increased with age, $\chi 2$ (3, N = 445,002) = 29,907.5, p<.0001 (Table 4.5). Multimorbid individuals accounted for 1.5%, 3.3%, 10.3%, and 24.7% of the 16-24, 25-44, 45-64, and 65 years and older age categories, respectively. Age was an effect modifier of the association between multimorbidity and MVAs in the bivariate model [OR = 0.998 (95% CI 0.997-0.999), p <.0001] but not in the adjusted [OR = 1.000 (95% CI 0.999-1.000), p=0.673] model. Considering the large study sample, the age*multimorbidity interaction term had no practical relevance. The adjusted odds ratios increased from 0.85 to 4.01 across the morbidity categories in the 25 to 44 years of age group, and from 0.87 to 3.49 in those aged 45 to 64 years. With the exception of the 16 to 24 years age group, which showed a minor trend disruption, adjusted odds ratios across all age groups displayed a positive monotonic exposure-outcome relationship.

Table 4.5. Associations between Morbidity Status and MVA Involvement by Age Group, N = 445,002. Cases: 74,167, Controls: 370,835.

Category	*MVA n (%)*	*No MVA n (%)*	*Crude OR (95% CI)*	*Adjusted OR[@] (95% CI)*
Ages 16 to 24 years, N =130,746 (29.4%)			**Multimorbidity = 1.5%**, &**	
No morbidity	19,038 (87.4)	95,671 (87.8)	1.00	1.00
1 condition	2,301 (10.6)	11,819 (10.8)	0.98 (0.93 - 1.03)	0.83 (0.79 - 0.87)***
2 conditions	355 (1.6)	1,227 (1.1)	1.47 (1.30 - 1.65)***	1.05 (0.92 - 1.19)
3 conditions	60 (0.3)	174 (0.2)	1.78 (1.32 - 2.39)***	1.20 (0.88 - 1.64)
4 conditions	21 (0.1)	51 (0.0)	2.19 (1.31 - 3.66)**	1.61 (0.93 - 2.79)
5 conditions	10 (0.0)	10 (0.0)	5.24 (2.18 - 12.61)***	3.13 (1.19 - 8.24)*
6 or more conditions	6 (0.0)	3 (0.0)	11.03 (2.75 - 44.20)***	10.70 (2.44 - 46.96)**

Category	*MVA n (%)*	*No MVA n (%)*	*Crude OR (95% CI)*	*Adjusted OR[@] (95% CI)*
Ages 16 to 24 years, N =130,746 (29.4%)			**Multimorbidity = 1.5%**, &**	
Ages 25 to 44 years, N = 172,788 (38.8%)			**Multimorbidity = 3.3%**	
No morbidity	23,504 (81.6)	120,017 (83.4)	1.00	1.00
1 condition	3,908 (13.6)	19,580 (13.6)	1.02 (0.99 - 1.06)	0.85 (0.81 - 0.88)***
2 conditions	942 (3.3)	3,302 (2.3)	1.47 (1.37 - 1.59)***	1.05 (0.97 - 1.14)
3 conditions	286 (1.0)	806 (0.6)	1.86 (1.62 - 2.13)***	1.16 (1.00 - 1.35)*
4 conditions	94 (0.3)	213 (0.1)	2.34 (1.83 - 2.98)***	1.56 (1.20 - 2.03)***
5 conditions	38 (0.1)	48 (0.0)	4.35 (2.82 - 6.70)***	2.88 (1.81 - 4.57)***
6 or more conditions	26 (0.1)	24 (0.0)	6.06 (3.47 - 10.58)***	4.01 (2.19 - 7.34)***
Ages 45 to 64 years, N = 110,214 (24.8%)			**Multimorbidity = 10.7%**	
No morbidity	12,178 (66.3)	62,565 (68.1)	1.00	1.00
1 condition	3,726 (20.3)	20,383 (22.2)	0.94 (0.91 - 0.98)**	0.87 (0.83 - 0.91)***
2 conditions	1,504 (8.2)	5,933 (6.5)	1.32 (1.24 - 1.40)***	1.14 (1.07 - 1.22)***
3 conditions	601 (3.3)	2,026 (2.2)	1.56 (1.42 - 1.71)***	1.26 (1.14 - 1.40)***
4 conditions	228 (1.2)	682 (0.7)	1.76 (1.51 - 2.05)***	1.39 (1.18 - 1.64)***
5 conditions	86 (0.5)	207 (0.2)	2.19 (1.70 - 2.82)***	1.61 (1.24 - 2.11)***
6 or more conditions	46 (0.3)	49 (0.1)	5.20 (3.45 - 7.82)***	3.49 (2.25 - 5.42)***
Ages 65 years and older, N = 31,254 (7.0%)			**Multimorbidity = 24.3%**	
No morbidity	2,221 (42.6)	12,106 (46.5)	1.00	1.00
1 condition	1,395 (26.8)	7,802 (30.0)	0.98 (0.91 - 1.06)	0.96 (0.89 - 1.04)
2 conditions	873 (16.8)	3,655 (14.0)	1.33 (1.22 - 1.45)***	1.22 (1.10 - 1.34)***
3 conditions	414 (7.9)	1,591 (6.1)	1.46 (1.30 - 1.65)***	1.28 (1.12 - 1.47)***
4 conditions	182 (3.5)	648 (2.5)	1.59 (1.34 - 1.89)***	1.24 (1.02 - 1.51)*
5 conditions	79 (1.5)	188 (0.7)	2.42 (1.85 - 3.18)***	2.13 (1.56 - 2.90)***
6 or more conditions	45 (0.9)	55 (0.2)	4.69 (3.15 - 6.99)***	3.09 (1.95 - 4.89)***

* P <.05; ** P <.01; *** P <.001.

Note. [@] Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.

& Percent differences in multimorbidity frequency between the age groups are significant, $\chi 2$ (3, N = 445,002) = 29,907.5, p<.0001.

Our sensitivity analyses limited to individuals seen only in outpatient settings included 860 MVA cases matched to 4,300 controls (Appendix B). The exposure-response trends identified in the complete sample were replicated in the outpatient subgroup with minor disruptions, likely attributable to a lower overall prevalence of highly multimorbid individuals; there were no individuals (neither cases nor controls) with 6 or more comorbid conditions.

Discussion

Main findings

The present study investigated the relationship between multimorbidity and MVAs, with exploration of sex and age as potential effect modifiers of this relationship. To our knowledge, this is the first study to demonstrate a positive monotonic exposure–response association between increasing morbidity and MVAs in adults of all ages extensively distributed across the U.S. The exposure-outcome relationship differed between men and women before and after adjusting for relevant covariates. The relationship between multimorbidity on MVAs was less pronounced in men, as evidence by lower overall odds across multimorbidity categories and the greater number of concurrent health conditions needed before the exposure-outcome relationship statistically surpassed the reference category.

Investigating habitual driving behaviours, using a database based on an annual survey drivers compiled by the Dutch research institute Traffic Test, Lourens, Vissers, and Jessurun (1999) did not find a difference in crash involvement by sex after controlling for annual kilometers driven. The sex differences observed in our study may reflect uncontrolled sources of confounding with a differential effect by sex. Survey data from a sample of Texas university students showed that men generally felt safer than women in several driving situations that may be associated with

increased risk of MVAs. Specifically, men felt safer than women driving at night, in unfamiliar places, in foul weather, after drinking, while tired, in an unfamiliar car, and at higher speeds (Bergdahl, 2005, 2007). These differences in attitudes by sex are likely to translate into differences in driving behaviors. In a study on crash culpability based on all driver-related hospitalizations in the state of Maryland between 1994 and 1996, Dischinger et al. (2000) found that men (70.6%) were more likely to be designated as being responsible for a crash than women (63.3%), $p<0.001$. Similarly, historical U.S. traffic statistics show that alcohol use, defined as blood alcohol concentrations exceeding 0.01 g/dL or 0.08 g/dL, is consistently present in a higher proportion of fatal crashes involving male drivers than female drivers (NHTSA, 2016). These factors, which are more likely to affect crash involvement in men than in women, limit the potential explained variance in MVAs in men possibly attributable to multimorbidity, particularly in younger drivers where multimorbidity is at its lowest.

While the direction of the exposure-response relationship was similar across age categories, the odds of an MVA did not increase in the same manner with increasing morbidity. In the youngest age category [16 to 24 years], the positive association between the exposure and the outcome only reached significance with 5 or more concurrent health conditions. In the second youngest age category [25 to 44], significance was achieved with 3 or more concurrent health conditions, and in the two oldest group, it was reached significance with 2 or more concurrent conditions. The observed differences in odds ratios between the sex and age categories, as well as between levels of multimorbidity, are likely due to several uncontrolled factors. For instance, the distinct etiology of the pre-selected health conditions pooled in our composite indicator of multimorbidity are likely to result in combinations of prevalent health conditions that differ in frequency between males and females and across age groups. For instance, Parkinson's disease is

more likely to be diagnosed in men and in the elderly (Pringsheim, Jette, Frolkis, & Steeves, 2014). Comorbid Parkinson's disease and dementias, which are also associated with old age (Mayeux & Stern, 2012), are more likely to be prevalent in the oldest age category as opposed to the youngest age groups. In turn, the consequences of comorbid dementia and Parkinson's disease on driving abilities could be linked to possible functional and cognitive impairments and behaviors such as self-imposed driving restrictions that differ from consequences associated with other combinations of comorbid conditions more frequently diagnosed in young adults.

Study Strengths

Use of Cerner Health Facts allowed for the retrospective analysis of over 11 million individuals from several U.S. States. The large sample size and the distribution of observations across the four U.S. census regions should allow for some ability to generalize our findings to the general population living in urban settings. By matching cases to controls on treating health care facility and index year, we aimed to minimize the potential effects of unknown confounders, such as coding practices and procedural preferences, between facilities and across time. As a result, matched cases and controls share the same care setting characteristics, including U.S. census region [Northeast, Midwest, South, West], hospital teaching status, and population density [rural, urban]. Our findings show that 99.2% of the sample received care at facilities in urban settings. Since some rural hospitals may not be equipped to deal with traumatic injuries (such as those that may result from serious motor vehicle crashes), a portion of individuals living in rural settings should be included in our sample due to emergency transfers. However, it is unclear if our findings are reflective of the rural environment as a whole.

Studies investigating the risk of traffic accidents due to health-related factors are often based on older adults and elderly populations (Marshall & Man-Son-Hing, 2011). In a study by Papa et al. (2014) for instance, the relationship between comorbidities and crash involvement considered younger drivers as those between the ages of 40 and 70 years. By including all adults 16 years of age and older, this study acknowledged that while multimorbidy is significantly more prevalent in the elderly, younger adults also demonstrate multimorbidity, albeit to a lesser degree. Moreover, the last decades have seen multimorbidity rates increase across all age groups (Koné Pefoyo et al., 2015; Uijen & van de Lisdonk, 2008) and if this trend continues, potential increases in the absolute number of MVAs could be of concern. A Scottish population-based study on the prevalence of multimorbidity by Barnett et al. (2012) found that 11.3% (95% CI 11.2 – 11.4) of adults aged 25 to 44 years were multimorbid. The inclusion of younger aged participants in studies investigating the relationship between health status and MVA may be particularly relevant when the sample is based on the general population and includes persons from all socioeconomic strata. In the last study, onset of multimorbidity was found to occur 10 to 15 years earlier in the poorest stratum as compared to the most affluent stratum. Inclusion of younger drivers in studies of the relationship between health status and MVA risk is also relevant since they have the highest rate of fatal, injury, and property damage crashes among licensed drivers (NHTSA, 2016) and per unit of travel (Alvarez & Fierro, 2008; Langford, Methorst, & Hakamies-Blomqvist, 2006).

Exposure measurement in this study was based on a standardized coding structure—ICD-9-CM diagnostic codes—as opposed to self-reported medical histories, which are prone to recall and response bias (Jenkins et al., 2002). To reduce the likelihood of exposure misclassification and detect health conditions not recorded during the index admission, patient records were assessed during the two years that preceded the index (Preen et al., 2006; Zhang et al., 1999). Selecting a

sufficient look back period helps limit bias resulting from the discharge abstract coding process. When patients are treated for severe acute health conditions, secondary conditions are less likely to be recorded and coded in the discharge abstract and vice-versa (Elixhauser et al., 1998; Hughes et al., 1996).

Alcohol and drug abuse were purposefully treated as potential confounders of the exposure-outcome relationship as opposed to health conditions in the multimorbidity assessment. Preliminary results—not reported—in which alcohol and drug abuse indicators were included in the multimorbidity count showed increased odds of MVA in every multimorbidity category, with better differentiation between confidence intervals in all analyses. For present purposes, the decision was made to ensure our findings did not simply reproduce the well-established link between alcohol/drug abuse and adverse driving events.

Limitations

This exploratory study is subject to several limitations. To critically assess potential sources of error, bias, and confounding, we relied on the assessment framework for evaluating studies on the relationship between driver health and MVA risk proposed by Elvik (2011). The most important limitation of this study is the absence of control for driving exposure, including driving habits, driver's license and restriction statuses, average annual driving distance, and driving setting (Vaa, 2005). In HF, electronic records are anonymized to comply with the U.S. Health Insurance Portability and Accountability Act (HIPPA). Consequently, there was no possibility of linking patient records to external data sources containing data on traffic accidents, such as the data repositories compiled by the U.S. National Highway Traffic Safety Administration (NHTSA). The presence of selection bias can therefore be assumed, since all cases were implicated

in driver-related crashes, while an unknown proportion of controls do not drive and are therefore not at risk of an MVA. To partially address this issue, we assumed that members of the sample covered under a private health insurance plan would be more likely to be employed and consequently have a greater likelihood of owning or having access to a vehicle and drive, compared to the uninsured and those covered by Medicaid. Consequently, we expected to find a greater proportion of MVAs in the privately insured group than in the other categories. This hypothesis was confirmed in the present analysis. It is expected that the inclusion of health insurance status in our adjusted models should help control for some of the missing driving exposure information. Since study MVAs were ascertained from electronic health records, our findings are likely reflective of the subset of crashes having considerable health consequences and exclude crashes where property damage was the most serious reported outcome. To put our findings in perspective, the U.S. Department of Transportation estimated that in 2014, MVAs resulting in injuries and fatalities made up 27.7 % of the 6,064,000 police-reported crashes in the country, while crashes limited to property damage made up remaining proportion.

Our inability to adjust for the annual mileage driven by study participants could render our findings prone to the so-called low-mileage effect. Several studies have demonstrated that irrespective of age, there is an association between annual driving distance and accident rates, with those driving greater annual distances having reduced MVA risk, per distance unit, than those who drive less annually (Adam, 2015; Alvarez & Fierro, 2008; Hakamies-Blomqvist, Raitanen, & O'Neill, 2002; Langford et al., 2006). In a replication study based on a sample of Dutch drivers, Langford et al. (2006) demonstrated the particularly strong effect of this bias by showing that drivers with less than 3,000 kilometers of annual mileage had six times the MVA rate than those who drove more than 14,000 kilometers annually.

It is reasonable to assume that persons with a greater number of concurrent health conditions drive shorter annual distances than those with fewer health conditions. Related evidence summarized in a systematic review by Marshall and Man-Son-Hing (2011) suggests that as the number of concurrent health conditions increases, the likelihood of driving cessation and avoidance also increases. Conclusions drawn by Marshall and Man-Son-Hing, however, were based on studies with mean sample ages of 70 years and above. Compensating for the presence of multiple health conditions through driving avoidance and cessation may be less of an option for non-elderly adults who may need to drive to maintain employment or for other purposes. In a study of 327 Italian drivers controlled for driving exposure, Papa et al. (2014) reported a proportional decrease in drivers with increasing multimorbidity based on tertiles of the Cumulative Illness Rating Scale (CIRS) score. Findings on driving cessation were significant in drivers over the age of 70 years, but not in those aged 40 to 70 years. The same study supported our findings of an increase in MVA risk with increasing multimorbidity in drivers 40 to 70 years of age, but not in those aged 70 years or more. Papa et al. (2014) study also addressed a caveat of most studies on driver health and crash risk, including ours, by not only accounting for the total number of health conditions, but also for the overall severity of the multimorbidity status of drivers.

Another limitation of our study is the use of dichotomous indicators of alcohol and drug abuse based on clinical diagnoses. Misclassification of substance abuse is likely given the sensitivity of detecting such conditions with the same ICD codes used in this study ranged between 48% to 55% when compared to chart reviews in a previous validation study by Quan et al. (2008). Clinical diagnoses of substance abuse are also not likely help control for accidents resulting from the consumption of these substances prior to driving. Similarly, our study results were not controlled for any pharmacologic treatments that may have been prescribed for the prevalent health

conditions identified. Such treatments could mitigate or enhance MVA risk independently of the condition they are prescribed to treat.

In contrast to multimorbid individuals, having a single health condition appeared to confer a small protective effect both in men and in those younger than 65 years of age, as well as in the full dataset. These conflicting observations suggest the presence of uncontrolled confounding or outcome misclassification. As discussed previously, direct information on driving habits would be useful in further exploring residual confounding. It was not possible to adjust for outcome misclassification bias in the absence of information on accident misclassification rates in the present dataset (Magder & Hughes, 1997).

Conclusion

This case-control study reports on a potential exposure-response relationship between multimorbidity and MVAs in drivers of all ages distributed across the United States. Sex was an effect modifier of this relationship and women demonstrated greater relative increases in MVA risk compared to men. Age did not modify the exposure-outcome relationship, yet the direction of the observed exposure-response relationship was consistent in all age groups. Given the current demographic change in population aging and increasing rates of multimorbidity in the general population, these findings may signal an emerging public health concern. Complementary studies that account for the driving habits and annual mileage driven by multimorbid drivers of all-ages are needed to replicate the findings of this study and advance evidence-based policy-making surrounding motor-vehicle licensing.

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Appendix A

Outcome	ICD-9 CM Codes
Driver-related Motor-Vehicle Accident	E8100, E8102, E8110, E8112, E8122, E8130, E8132, E8140, E8142, E8150, E8152, E8160, E8162, E8170, E8172, E8180, E8182, E8140, E8142, E8150, E8152, E8160, E8162, E8170, E8172, E8180, E8182, E8190, E8192, E81120
Health Condition Group	**ICD-9CM Codes**
Cancer	
Lymphoma	"200","201","202","2030","2386"
Solid Tumors	"140","141","142","143","144","145","146", "147","148","149","150","151","152","153", "154","155","156","157","158","159","160", "161","162","163","164","165","166","167", "168","169","170","171","172","174","175", "176","177","178","179","180","181","182", "183","184","185","186","187","188","189", "190" "191","192","193","194","195"
Cancer with Metastasis	"196","197","198","199"
Cardiovascular Disorders	
Syncope	"7802"
Arrhythmias	"4260","42613","4267","4269","42610","42612","4270","4271","4272","4273","4274","4276","4278","4279","7850","99601","99604","V450","V533"
Myocardial Infarction	"410","410","410","41001","41002","4101", "4101","41011","41012","4102","4102","41021","41022","4103","4103","41031","41032","4104","4104","41041","41042","4105","4105","41051","41052","4106","4106","41061","41062","4107","4107","41071","41072","4108","4108","41081","41082","4109","4109","41091","41092","412"

Cerebrovascular Disease	"36234","430","431","432","432","4321","4329","433","433","433","43301","4331","4331","43311","4332","4332","43321","4333","4333","43331","4338","4338","43381","4339","4339","43391","434","434","434","43401","4341","4341","43411","4349","4349","43491","435","435","4351","4352","4353","4358","4359","436","437","437","4371","4372","4373","4374","4375","4376","4377","4378","4379","438","438","4381","4381","43811","43812","43813","43814","43819","4382","4382","43821","43822","4383","4383","43831","43832","4384","4384","43841","43842","4385","4385","43851","43852","43853","4386","4387","4388","43881","43882","43883","43884","43885","43889","4389"
Pulmonary Circulation Disorders	"4150","4151","416","4170","4178","4179"
Congestive Heart Failure	"39891","40201","40211","40291","40401","40403","40411","40413","40491","40493","4254","4255","4257","4258","4259","428"
Peripheral Vascular Disease	"0930","4373","440","441","4431","4432","4438","4439","4471","5571","5579","V434"
Hypertension	"402","403","404","405"
Diabetes	
Uncomplicated	"2500","2501","2502","2503"
Complicated	"2504","2505","2506","2507","2508","2509"
Chronic Pulmonary Disease	"4168","4169","490","491","492","493","494","495","496","500","501","502","503","504","505","5064","5081","5088"
Dementia	"3310","3311","3312","3317","2900","2901","29010","29011","29012","29013","29020","29021","2903","29040","29041","29042","29043","2940","2941","2948","797"
Epilepsy	"345"
Hypothyroidism	"2409","243","244","2461","2468"
Multiple Sclerosis	"340"
Parkinson's Disease	"3320","3321","3330","3331"
Psychiatric Disorders-Excluding Substance Abuse	
Depression	"2962","2963","2965","3004","309","311"

Psychosis, Including Schizophrenia	"2938","295","29604","29614","29644","29654","297","298"
Rheumatic Disease	"4465", "710", 7101","7102","7103","7104","714","7141","7142","7148", "725"
Sleep Disorders	"29182","29285","30740","30741","30742","30745","30746","30747","30748","30749","32711","32712","32720","32721","32723","32724","32726","32727","32729","32730","32731","32732","32733","32734","32735","32736","32737","32739","32742","32743","32752","32753","32759","3278","7805","78050","78051","78053","78055","78056","78057","78058","78059","V694","347","34701","34710","34711"
Sleep Apnoea	"7805"
Shift Work Disorder	"32736"
Obstructive Sleep Apnea	"32723"
Narcolepsy	"347","34701","34710","34711"
Vision Conditions	
Cataracts	"366"
Glaucoma	"365"
Retinopathy	"361","362"
Alcohol Abuse	"2652","291","2911","2912","2913","2915","2918","2919","3030","3039","3050","3575","4255","5353","5710","5711","5712","5713","980","V113"
Substance Abuse	"292","304","3052","3053","3054","3055","3056","3057","3058","3059","V6542"

Appendix B

Table S4.1. Sensitivity Analysis, Associations between Morbidity and MVA, N = 5,160, Cases: 860, Controls: 4,300

Category	*MVA, n (%)*	*No MVA, n (%)*	*Crude OR (95% CI)*	*Adjusted OR[@] A (95% CI)*
No morbidity	602 (70.0)	3,404 (79.2)	1.00	1.00
1 condition	177 (20.6)	731 (17.0)	1.41 (1.17 - 1.71)*	1.16 (0.95 - 1.42)
2 conditions	54 (6.3)	129 (3.0)	2.46 (1.77 - 3.44)*	1.69 (1.17 - 2.44)*
3 conditions	23 (2.7)	30 (0.7)	4.56 (2.62 - 7.93)*	2.46 (1.32 - 4.57)*
4 conditions	2 (0.2)	5 (0.1)	2.56 (0.49 - 13.35)	1.59 (0.27 - 9.51)
5 or more conditions	2 (0.2)	1 (0.0)	10.81 (0.98 - 119.5)	5.96 (0.40 - 87.86)

* P <.001.

Note. [@]Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.

Table S4.2. Sensitivity Analysis, Associations between Morbidity Status and MVA Involvement by Sex, N = 5,160, Cases: 860, Controls: 4,300

Category	*MVA n (%)*	*No MVA n (%)*	*Crude OR (95% CI)*	*Adjusted OR[&] (95% CI)*
Men, N =2,880 (55.8%)		**Multimorbidity = 3.8%**		
No morbidity	368 (76.7)	1,910 (79.6)	1.00	1.00
1 condition	84 (17.5)	408 (17.0)	1.09 (0.83 - 1.42)	0.95 (0.71 - 1.27)
2 conditions	21 (4.4)	65 (2.7)	1.72 (1.03 - 2.88)*	1.10 (0.62 - 1.96)
3 conditions	7 (1.5)	14 (0.6)	2.68 (1.06 - 6.78)*	2.05 (0.71 - 5.91)
4 conditions	0 (0.0)	2 (0.1)	NA	NA
5 or more conditions	0 (0.0)	1 (0.0)	NA	NA
Women, N =2,280 (44.2%)		**Multimorbidity = 6.0%**		
No morbidity	234 (61.6)	1,494 (78.6)	1.00	1.00
1 condition	93 (24.5)	323 (17.0)	1.90 (1.45 - 2.50)*	1.44 (1.07 - 1.92)*
2 conditions	33 (8.7)	64 (3.4)	3.43 (2.19 - 5.36)*	2.44 (1.50 - 3.97)*
3 conditions	16 (4.2)	16 (0.8)	6.84 (3.37 - 13.87)*	2.97 (1.36 - 6.48)*
4 conditions	2 (0.5)	3 (0.2)	5.57 (0.90 - 34.47)	2.13 (0.30 - 15.00)
5 or more conditions	2 (0.5)	0 (0.0)	NA	NA

* P <.001.

Note. [&]Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.

Table S4.3. Sensitivity Analysis, Associations between Morbidity Status and MVA Involvement by Age Group, N = 5,160, Cases: 860, Controls: 4,300

Category	*MVA n (%)*	*No MVA n (%)*	*Crude OR (95% CI)*	*Adjusted OR[@] (95% CI)*
Ages 16 to 24 years, N =2,082 (40.4%)			**Multimorbidity = 2.5%**, &**	
No morbidity	267 (76.9)	1,470 (84.7)	1.00	1.00
1 condition	58 (16.7)	236 (13.6)	0.99 (0.94 - 1.03)	0.83 (0.79 - 0.88)
2 conditions	19 (5.5)	22 (1.3)	1.43 (1.27 - 1.60)	1.02 (0.90 - 1.16)
3 conditions	2 (0.6)	7 (0.4)	1.37 (1.04 - 1.80)	0.91 (0.68 - 1.21)
4 conditions	1 (0.3)	0 (0.0)	1.96 (1.21 - 3.17)	1.00 (0.60 - 1.68)
Ages 25 to 44 years, N = 1,794 (34.8%)			**Multimorbidity = 4.6%**	
No morbidity	213 (71.2)	1,203 (80.5)	1.00	1.00
1 condition	64 (21.4)	232 (15.5)	1.00 (0.97 - 1.04)	0.84 (0.81 - 0.87)
2 conditions	19 (6.4)	49 (3.3)	1.43 (1.33 - 1.54)	1.04 (0.96 - 1.12)
3 conditions	2 (0.7)	9 (0.6)	1.89 (1.66 - 2.16)	1.30 (1.13 - 1.50)
4 conditions	1 (0.3)	2 (0.1)	2.27 (1.80 - 2.87)	1.52 (1.18 - 1.95)
Ages 45 to 64 years, N = 1,120 (21.7%)			**Multimorbidity = 8.0%**	
No morbidity	111 (59.4)	649 (69.4)	1.00	1.00
1 condition	48 (25.7)	222 (23.7)	0.94 (0.91 - 0.98)	0.88 (0.84 - 0.92)
2 conditions	14 (7.5)	48 (5.1)	1.30 (1.22 - 1.37)	1.15 (1.08 - 1.22)
3 conditions	12 (6.4)	13 (1.4)	1.52 (1.38 - 1.66)	1.30 (1.18 - 1.44)
4 conditions	1 (0.5)	2 (0.2)	1.78 (1.53 - 2.06)	1.49 (1.27 - 1.75)
Ages 65 years and older, N = 162 (3.1%)			**Multimorbidity = 13.0%**	
No morbidity	11 (40.7)	82 (60.7)	1.00	1.00
1 condition	7 (25.9)	41 (30.4)	0.95 (0.89 - 1.02)	0.93 (0.86 - 1.00)
2 conditions	2 (7.4)	10 (7.4)	1.31 (1.20 - 1.43)	1.25 (1.14 - 1.38)
3 conditions	7 (25.9)	1 (0.7)	1.43 (1.27 - 1.61)	1.33 (1.17 - 1.51)
4 conditions	0 (0.0)	1 (0.7)	1.66 (1.40 - 1.97)	1.39 (1.15 - 1.68)

* P <.05; ** P <.01; *** P <.001.

Note. [@] Adjusted for health insurance status, alcohol abuse, substance abuse, inpatient days, and confirmed lookback in days.

& Percent differences in multimorbidity frequency between the age groups are significant, $\chi 2$ (3, N = 445,002) = 29,907.5, p<.0001.

Chapter 5 - A systematic review of the risks factors associated with the onset and natural progression of epilepsy

Stephanie Walsh[1], Jennifer Donnan[2], Yannick Fortin[3], Lindsey Sikora[4], Andrea Morrissey[1], Kayla Collins[1], Don MacDonald[1]

Authors Note

1. Newfoundland and Labrador Centre for Health Information, St. John's, NL, Canada. 2. School of Pharmacy, Memorial University of Newfoundland, Health Science Centre, St. John's, NL, Canada. 3. McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, ON, Canada. 4. Health Sciences Library, University of Ottawa, Ottawa, ON, Canada, Canada.

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Abstract

Epilepsy is a neurological condition that affects more than 50 million individuals worldwide. It presents as unpredictable, temporary and recurrent seizures often having negative physical, psychological and social consequences. To inform disease prevention and management strategies, a comprehensive systematic review of the literature on risk factors for the onset and natural progression of epilepsy was conducted. Computerized bibliographic databases were searched for systematic reviews, meta-analyses, observational studies and genetic association studies published between 1990 and 2013 describing etiological risk factors for epilepsy. The quality of systematic reviews was validated using the AMSTAR tool and articles were reviewed by two referees. A total of 16,958 articles went through stage one review of abstracts and titles. A total of 76 articles on genetic and non-genetic risk factors for the onset and progression of epilepsy met the eligibility criteria for data extraction. Dozens of risk factors were significantly associated with onset of epilepsy. Inconsistent levels of evidence for risk of onset included family history of epilepsy, history of febrile seizures, alcohol consumption, CNS and other infections, brain trauma, head injury, perinatal stroke, preterm birth and three genetic markers. Limited evidence showed that symptomatic epilepsy, focal seizures/syndromes, slow waves on EEG, higher seizure frequency, high stress or anxiety, and lack of sleep decreased the odds of seizure remission. High quality studies were rare and while a large body of work exists, relatively few systematic reviews were found.

Keywords: epilepsy; onset; etiology; progression; risk factors; systematic review

Introduction

Globally, it is estimated that 50 million individuals are affected by epilepsy and the prevalence of epilepsy requiring treatment ranged between 4 to 6 cases per 1000 (WHO, 2012). Hirtz et al. (2007) reported the median annual incidence of epilepsy in European and North American populations to range between 32 to 71 cases per 100,000. The incidence of epilepsy follows a u-shaped curve, peaking below the age of 1 and above the age of 80. Recently, it was estimated that over 2.3 million Americans had epilepsy, including 467,711 children aged 0–17 years, and the associated direct and indirect costs of the disease in the U.S. are $15.5 billion annually (Kobau et al., 2012). In the 2011 cycle of the Canadian Community Health Survey, the prevalence of epilepsy was estimated at 0.42% (Statistics Canada, 2011). This estimate very likely underestimates the true percentage of people with epilepsy given the survey excluded children under twelve years of age, a subpopulation with above average incidence of the disease. In 2000–2001, the Public Health Agency of Canada estimated the total costs associated with epilepsy in the country at approximately $797.7 million (CIHI, 2007).

Epilepsy is a disease of the brain associated with the likelihood of recurrent seizures (Fisher et al., 2014). Furthermore, a diagnosis of epilepsy must satisfy any of the following clinical conditions: (1) two or more unprovoked (or reflex) seizures separated by more than 24 h; (2) one unprovoked (or reflex) seizure with a high probability of additional seizures in the next 10 years; (3) fitting the profile for an epilepsy syndrome. Several types of epilepsy are identified and the sudden temporary abnormal disturbances of neuronal activity experienced by persons with epilepsy presents in several ways. Acute manifestations can include variations in consciousness, involuntary muscle spasms, convulsions, psychic events, and changes in sensory and autonomic functions (CEP- ILAE, 1993).

The International League Against Epilepsy (ILAE) classifies seizures according to several schemes (Berg et al., 2010). In the most recent guidelines, seizures are broadly organized as generalized, focal, and unknown. Generalized seizures involved both hemispheres of the brain, focal seizures were limited to a single hemisphere or region of the brain while unknown types were reserved for those evading classification. To align the text with the most recent ILAE guidelines, the term focal (e.g. focal seizures) replaces the term partial.

Seizures can also be classified by etiology. Genetic epilepsies result from known or presumed genetic origin. Structural and metabolic epilepsies include seizures resulting from brain lesions or conditions associated with structural or metabolic abnormalities. Seizures for which a cause cannot be presumed are classified as unknown (Berg et al., 2010). Age and geography are important dimensions with regards to the onset of epilepsies. The most common cause of epilepsy in early childhood are perinatal and congenital in nature, often genetic in origin (Shorvon, 2005). In adults, non-genetic external factors, including vascular disease such as stroke are more common risk factors. In certain areas of the world, mostly developing countries, where endemic infections tend to have a higher prevalence, infections secondary to tuberculosis (TB), cysticercosis, human immunodeficiency virus (HIV) or other viral diseases are more frequently assigned as causal agents (Shorvon, 2005). In approximately 60% of persons with epilepsy, the cause of epilepsy is unknown (NINDS, 2004).

Policies and strategies to prevent epilepsy onset and disease progression are likely to be more effective if they are derived from strong evidence of causal mechanisms linked to the etiology of specific types of epilepsy and epileptic syndromes. The evidence collected here supports the research trajectory advocated in a recent report by the Institute of Medicine to identify risk factors that could enhance primary and tertiary prevention of epilepsy (IOM, 2012). In the present study,

the numerous risk factors that contribute to the onset and natural progression of epilepsy are investigated. The first step toward this objective was to systematically review the peer-reviewed literature by focusing specifically on systematic reviews, meta-analyses and observational studies dealing with the onset and natural progression of the epilepsies.

Rationale and objectives

Rationale

As one of the most prevalent neurological condition in the world, epilepsy places a significant burden on societies and persons affected (de Boer et al., 2008; Ngugi et al., 2010). The purpose of this study is to systematically assess and synthesize the published literature on risk factors for the onset and natural progression of epilepsy. This work is intended to provide a basis for policy makers to identify appropriate risk management measures to mitigate the burden of disease in Canada. The systematic review intends to provide a comprehensive summary of the current evidence on risk factors for disease onset and progression, including biological, lifestyle, socioeconomic, environmental, and psychosocial factors. In addition to identifying potential modifiable risk factors for the onset and progression of epilepsy, this study hopes to fill etiological knowledge gaps about this neurological condition.

Objectives

The primary objectives of this study are as follows:

1. Conduct a comprehensive, systematic literature review on the onset and progression of epilepsy with respect to a wide range of risk factors, including biological, lifestyle, socioeconomic, environmental, genetic and psychosocial factors.

2. Assess and summarize the available evidence on the determinants of onset and progression of epilepsy, as well as describe the strengths and weaknesses of the current scientific literature.

Methods

Criteria for considering studies for this review

The following is a brief description of the methodology used for the selection of genetic and non-genetic association studies. A complete description of the approach and methods used in this study was published in a separate paper in this issue (Hersi et al., 2016).

Types of studies

Eligibility criteria were established a priori. To be included in the study, articles had to meet each of the inclusion criteria: evaluate at least one etiological risk factor for the onset or the natural progression of epilepsy; a systematic review, meta-analysis, case-control study, cohort study or a meta-analysis of genome-wide association studies; involve human subjects; report a measure of risk (including odds ratio, relative risk, etc.); be published in English or French.

Studies were excluded if they met any of the criteria: published prior to 1990; evaluated only the association between variables and not the causal relationship; risk factor under review was a form of intervention or treatment for the disease and potentially impacted the natural progression of disease.

Types of participants

Epilepsy can be classified into various categories trough a clinical assessment of seizures, symptoms and other observations. For the identification of relevant articles that looked at risk

factors for onset of disease, studies that defined their case population as having a diagnosis of epilepsy were included. Studies where the main outcome was febrile seizures or other provoked seizure types were excluded. Studies were also excluded if the case population comprised a combination of epilepsy patients and patients who had experienced non-epileptic seizures.

Search methods for identifications of studies

Protocol for non-genetic association studies

Computerized bibliographic databases were searched for relevant studies published between January 1990 and February 2013. The January 1990 cut-off was selected in order to retain the expansive scope of the review while ensuring a minimum level of feasibility. An earlier cut-off of January 1950 had to be abandoned because it yielded an excessively large volume of scientific literature that was not reasonably manageable given available resources. The authors recognised that this compromise might possibly privilege results that favored more recently identified risk factors at the expense of long-established factors of risk. All database searches were conducted by a health sciences librarian (LS) and carried out in three stages (Table 5.1). The search terms and strategy used to locate studies in the databases were adapted for each database (Appendix A). Searches for risk factors associated with the onset of epilepsy were carried out independently of searches for risk factors associated with the natural progression of the disease. The first stage consisted of a search to identify all existing systematic reviews or meta-analyses of risk factors associated with the onset of epilepsy. The second stage was a search to identify existing observational studies. Following completion of the review process for risk factors associated with the onset of epilepsy, it was determined that a more efficient approach for searching for risk factors associated with progression would be to combine search strategies for systematic review, meta-analyses and observational studies. This completed the third and final stage of database searches.

Table 5.1. Electronic databases used in each stage of the search strategy.

Stage	Onset vs. Progression	Study Designs	Databases/Sources	Date Range
Stage One	Onset	Systematic Review Meta-Analysis	Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Medline and Medline in Process (via OVID), EMBASE, PsycINFO	January 1990 – February 2013
Stage Two	Onset	Cohort Case Control	Medline and Medline in Process (via OVID), EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), TOXNET, HUGENET and Proquest Dissertations	January 1990 – February 2013
Stage Three	Progression	Systematic Review Meta-Analysis Cohort Case Control	Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Medline and Medline in Process (via OVID), EMBASE, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), TOXNET, HUGENET and Proquest Dissertations	January 1990 – November 2012

Protocol for genetic studies

The process of identify genetic studies for epilepsy was completed in two steps. Firstly, the Medline, Embase, PsycInfo, Cochrane Library, CINAHL and ProQuest databases were thoroughly searched to identify relevant systematic reviews and meta-analyses. This step was combined with the search strategy for identifying non-genetic studies but results were compiled separately. Secondly, the HuGENet portal (http://hugenavigator. net/HuGENavigator/home.do) was searched independently which allowed for the identification of a regularly updated online genetic database

for epilepsy known as EpiGAD: The Epilepsy Genetic Association Database (www.epigad.org). The EpiGAD database was then searched for any additional meta-analyses.

Data collection and analysis

The software application DistillerSR (Evidence Partners, 2016) was used for data management in this study. This application is specifically designed to assist with the screening and data extraction phases of systematic reviews.

Systematic reviews and meta-Analyses

Study selection

Following deduplication, references identified through the search strategies were uploaded into DistillerSR (Evidence Partners, 2016) for screening by two independent reviewers. The articles were screened using the eligibility criteria described above. Two levels of screening were used to narrow the articles down to those matching the inclusion criteria. Level one consisted of screening titles and abstracts. Papers that did not meet the inclusion criteria were eliminated. Studies that met the inclusion criteria and those with insufficient information to assess eligibility were selected for the second level of screening. In the second level of screening, full text articles were retrieved and the same inclusion and exclusion criteria were applied. In cases were multiple publications from the same study group were identified, the most complete and recent results were retained. Both levels of screening relied on a process known as the "liberal accelerated method" where the second reviewer only reviews articles excluded by the first reviewer. This practice was adopted to increase efficiency while ensuring the retention of all relevant articles. When reviewers disagreed about whether an article met the eligibility criteria, they met to discuss. Occasionally, a third reviewer was consulted in order to reach consensus.

Quality assessment

All papers that met the eligibility criteria proceeded to quality screening. Two reviewers independently validated the methodological quality each study using the AMSTAR ("assessment of multiple systematic reviews") tool (Shea et al., 2007). Studies that scored low (three or less) on the AMSTAR scale were eliminated from the review, studies that scored moderate (between four and seven) or high (greater than seven) were included.

Data extraction

Data extraction was completed within DistillerSR (Evidence Partners, 2016) using a data collection form designed a priori. Information extracted from the relevant sources included the year of study, study location, risk factor(s) under study, risk estimate and confidence intervals, whether or not publication bias was addressed, main conclusions of the article, etc. (Appendix B).

Observational studies

Where systematic reviews or meta-analysis of moderate to high quality (according to the AMSTAR tool) existed for a particular risk factor, an update to these reviews was conducted. Only studies that were published after the search was conducted for the previous systematic review were included.

Study selection

The selection process for observational studies was conducted using an identical approach as was used for systematic reviews and meta-analyses. The screening approach for observational studies also relied on the liberal accelerated method described earlier.

Data extraction

Data extraction for the observational studies used the same approach as the one used for the systematic reviews and meta-analyses reported above.

Results

Systematic reviews and meta-Analyses of risks factors for the onset of epilepsy

Search results

A total of 3870 unique articles were identified through electronic database searches (Figure 5.1). Of these, 3217 articles were excluded at stage one, leaving 653 articles for stage two screening. A further 635 articles were excluded at stage two, leaving a total of 18 reviews for quality assessment (Appendix C). Ten of the latter reviews were then excluded because they had a score of three or less using the AMSTAR tool; four reviews were set aside to be included as genetic risk factors, and the remaining four reviews went through data extraction.

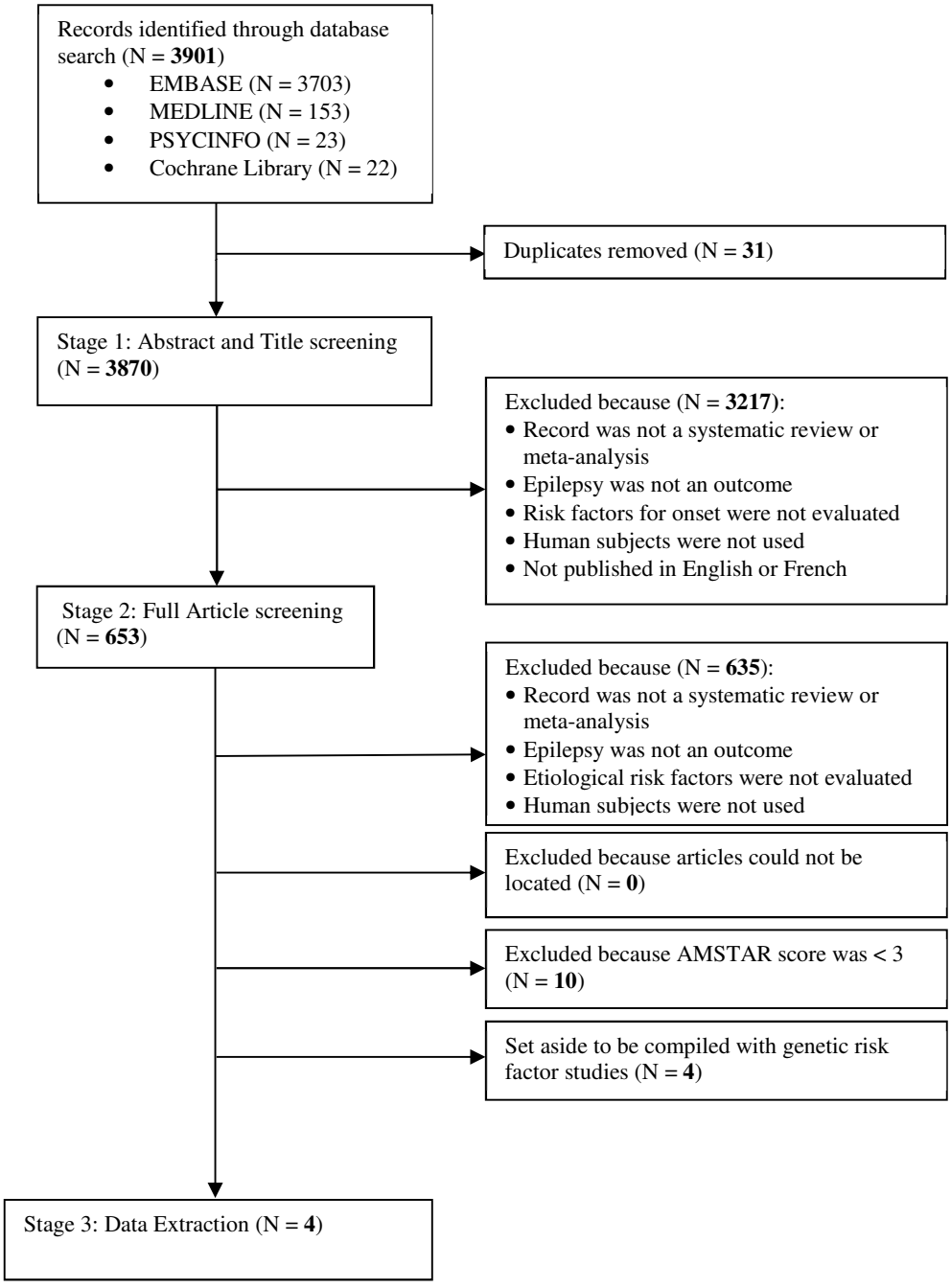

Figure 5.1. Flowchart of Literature Search: Systematic Reviews and Meta-analyses of Risk Factors for Epilepsy Onset

Description of studies

Four studies met the inclusion criteria for non-genetic systematic reviews and meta-analyses evaluating risk factors for the onset of epilepsy. They all included a meta-analysis. Two of these studies examined infectious causes, one looked at a chronic disease cause and the final study looked at a lifestyle factor: alcohol consumption (Table 5.2).

Druet-Cabanac et al. (2004) conducted a meta-analysis to identify the risk of epilepsy in patients infected with Onchocerca volvulus (a parasitic roundworm common to Africa). They reported that in many circumstances the diagnosis of the O. volvulus infection could not be confirmed as preceding the diagnosis of epilepsy. For this reason, they opted to include cross-sectional studies as well. The pooled estimate of nine studies showed that the overall relative risk for epilepsy in these patients was, RR = 1.21 (95% CI 0.99–1.47), which did not reach the significance threshold. Given the significant heterogeneity between studies and the inclusion of cross-sectional study designs, an increased risk of epilepsy in patients with O. volvulus infection was not confirmed.

Quet et al. (2010) looked at the risk of epilepsy in patients with Cysticercosis (CC) infection in Africa. Pooled odds ratios of 11 studies using a random effects model demonstrated a significant increased risk of epilepsy, OR = 3.4 (95% CI 2.7–4.3). While this meta-analysis also included studies with cross-sectional designs, and thus, verification of the precedence of the exposure to CC prior to a diagnosis of epilepsy was not possible in all cases, eight of the 11 studies included had a case-control design, which does suggest support for a significant association.

Table 5.2. Systematic Reviews and Meta-analyses of Moderate to High Quality that Assess the Association Between Risk Factors and Onset of Epilepsy

First Author & Year	Design of included studies	Years included	Risk Factor	Risk Estimate (95% Confidence Interval); heterogeneity; publication bias	Overall main conclusion of review
Druet-Cabanac, 2004(Druet-Cabanac et al. 2004, 144-149)	Case-control, cross-sectional	1966-2002	Onchocerciasis (Onchocerca volvulus infection)	RR=1.21 (0.99-1.47) (random effects) Cochrane Q test for heterogeneity: p<0.001 Publication bias: none detected	The results of this meta-analysis do not allow the conclusion of a significant association between O. volvulus infection and epilepsy. However, the results lie close to the threshold of significance, suggesting a probable but a weak risk of epilepsy with onchocerciasis infections.
Lionetti, 2010(Lionetti et al. 2010, S347)	Cross sectional, case-control, cohort, case series	1950-2009	Celiac disease in childhood	RR=2.1 (1.5-2.8) Heterogeneity: not reported Publication bias: none suspected	Children with celiac disease are 2.1 times more likely to develop epilepsy than a comparable child without celiac disease. However, chance co-occurrence is probable based on further statistical analysis (i.e., risk difference is close to zero when factoring in the inverse risk for celiac disease in children with epilepsy: RR=1.7, 95% CI 1.4-2.1).
Quet, 2010(Quet et al. 2010, 830-837)	Case-control, cross-sectional	Inception-2009	Cysticercosis (CC) infection	OR=3.4 (2.7-4.3) (random effects) Cochrane Q test for heterogeneity: p=0.43	In Africa, people with a CC infection have a significantly increased risk for developing epilepsy. A better understanding of the relationship would be beneficial for identifying

				Publication bias: not addressed	potential epilepsy prevention strategies.
Samokhvalov, 2010(Samokhvalov, Irving, and Rehm 2010, 1177-1184)	Case-control, cohort	1960-2008	Alcohol consumption (compared to no alcohol consumption)	Overall: RR=2.19 (1.83-2.63) Dose dependent relationships 4 drinks per day: RR=1.81 (1.59-2.07) 6 drinks per day: RR=2.44 (2.00-2.97) 8 drinks per day: RR=3.27 (2.52-4.26) Heterogeneity: none detected Publication bias: none detected	Results suggest that excessive alcohol consumption significantly increases a person's risk of developing epilepsy. There also appears to be a dose-response relationship whereby the greater the alcohol consumption the greater the risk for developing epilepsy.

N.B. Outcome for each study was onset for epilepsy unless otherwise stated.

Lionetti et al. (2010) examined the link between childhood celiac disease and epilepsy, both as a cause and as an outcome. Pooled risk estimates of five studies showed that children with celiac disease were about two times as likely to develop epilepsy, RR = 2.1 (95% CI: 1.5–2.8). However, when considered together with the risk estimate for developing celiac disease among those with epilepsy (RR = 1.7, 95% CI: 1.4–2.1), the calculated risk difference was close to zero. Consequently, the authors stated that the evidence suggested a chance association between the two conditions.

The final study by Samokhvalov et al. (2010) sought to identify the risk of epilepsy in individuals who consume alcohol compared to those who do not consume alcohol. Pooled estimates of nine studies showed that consumers of alcohol had a greater than two- fold increased risk of epilepsy (RR = 2.19; 95% CI 1.83–2.63). Four of the included studies had sufficient data to calculate pooled risk estimates at various daily doses of alcohol. The dose-response curve showed that the relationship between daily alcohol consumption and epilepsy was relatively flat up to about 24 g of alcohol per day, after this point the relative risk of epilepsy/ unprovoked seizures increased steeply with higher levels of alcohol consumption.

Observational studies of risks factors for the onset of epilepsy

Results of the search

A total of 7672 unique articles were identified using the electronic databases search strategies (Figure 5.2). Of these, 7190 articles were excluded at stage one. Of the remaining 482 articles, 418 were excluded at stage two based on the exclusion criteria, 5 were excluded because they could not be retrieved and 59 were selected for data extraction.

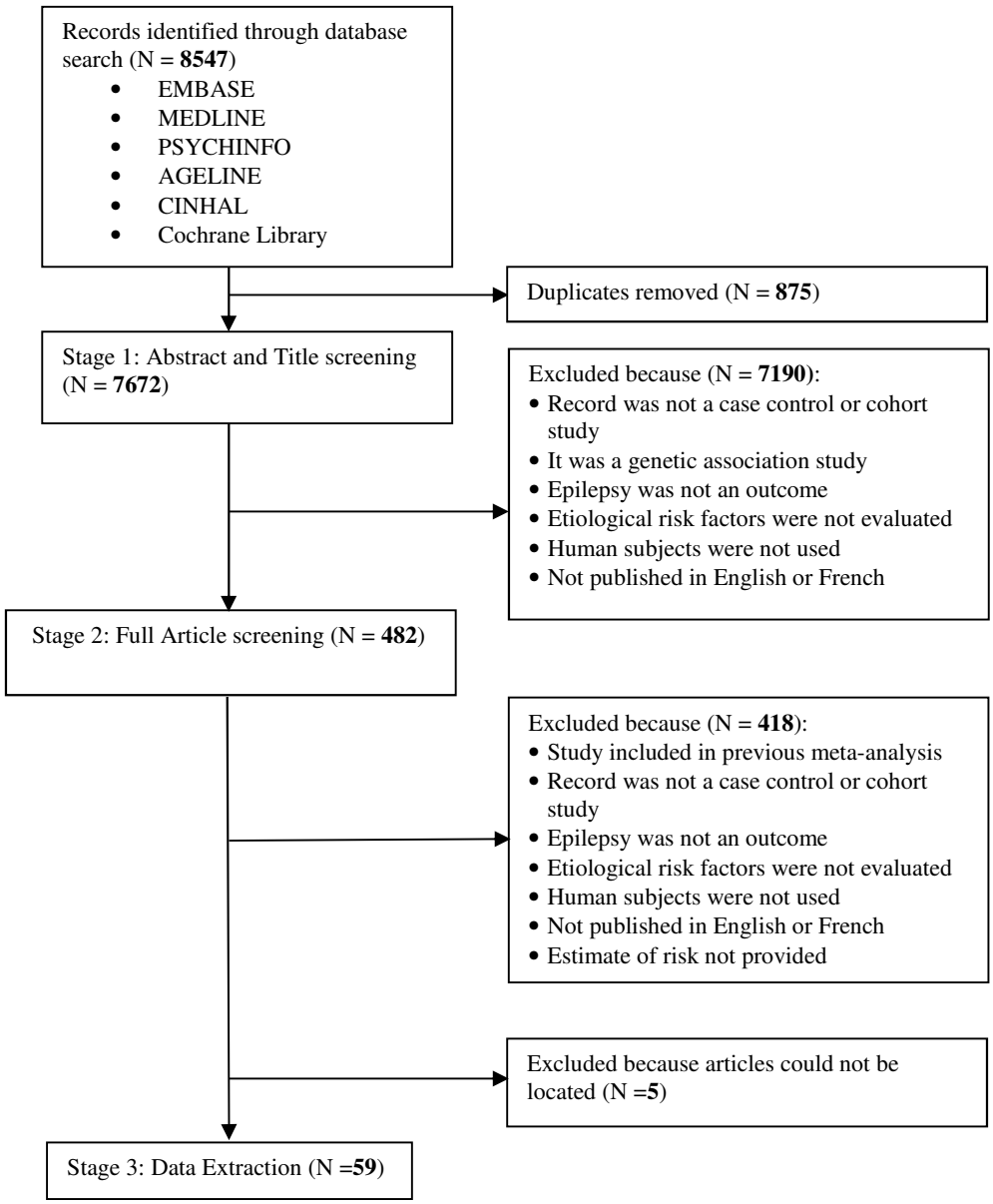

Figure 5.2. Flowchart of Literature Search of Risk Factors for Onset of Epilepsy: Observational Studies

Description of the studies

A total of 59 observational studies that examined risk factors for epilepsy onset met our inclusion criteria. Organizing the studies into logical groupings was a challenge because many of the studies investigated several risk factors of various types. Twenty-seven of the studies had a primary focus on perinatal risk factors (Appendix D); five were classified as dealing primarily with infectious biological risk factors (Appendix E), three studies focused only on febrile seizures (Appendix F), six studies were primarily focused on epilepsy following trauma (Appendix G), eleven studies dealt with other miscellaneous biological risk factors (Appendix H), two looked at psychosocial risk factors (Appendix I), and five focused mainly on lifestyle, environmental, and/or other uncategorized risk factors (Appendix J). Dozens of risk factors were considered within and across studies. Appendix D through J detail all the risk factors studied. Describing each risk factor that appeared in all 59 studies is beyond the scope of this paper. Instead, risk factors that occurred multiple times and/or for which at least limited evidence exists for their association with epilepsy onset are highlighted below. Studies reporting adjusted risk estimates and indicators of significance were privileged in our reporting. These included: (1) family history of epilepsy or seizures; (2) history of febrile seizures; (3) history of CNS infection; (4) history of brain trauma, head injury and stroke; (5) gestational age; (6) neonatal seizures (non-febrile); (7) restricted fetal growth; (8) eclampsia/ preeclampsia; (9) increased maternal age; and 10) maternal infection during pregnancy. Other potential factors that were controversial or showed mixed results were pooled.

Family history of epilepsy or seizures was shown to be a significant risk factor in all of the 16 studies that included it (Asadi- Pooya and Hojabri, 2005; Burton et al., 2012; Cansu et al., 2007; Chin et al., 2012; Daoud et al., 2003; Deepa, 2011; Dworetzky et al., 2010; Kannoth et al., 2009; Masri et al., 2008; Matuja et al., 2001; Monetti et al., 1995; Murphy et al., 2004; Ngoungou et al., 2006; Nicoletti et al., 2007, 2008; Tran et al., 2007). The risk estimates ranged from, OR = 2.36

(95% CI 1.72–3.22), for a population-based cohort study of 21,441 individuals to, OR = 12.8 (95% CI 1.4–119.5), for a small sample including 31 cases and 124 controls living in rural Lao PDR. One large cohort study of 107,408 individuals (563 epilepsy cases) reported the risk of childhood epilepsy as, OR = 3.8 (95% CI 2.1–6.5), for paternal history of epilepsy and, OR = 3.5 (95% CI 2.1–5.8), for maternal history of epilepsy (Chin et al., 2012).

History of febrile seizures was identified as a significant risk factor in nine of the ten studies that included it (Burton et al., 2012; Cansuet al., 2007; Daoud et al., 2003; Deepa, 2011; Kannoth et al., 2009; MacDonald et al., 1999; Matuja et al., 2001; Monetti et al., 1995; Ngoungou et al., 2006; Sapir et al., 2000; Vestergaard et al., 2007). The risk estimates ranged from a non-significant OR of 2.4 (95% CI 0.8–7.0) for one small case control study of childhood epilepsy in rural Tanzania (112 cases, 113 controls) to an OR of 13.5 (95% CI 3.28–42.32) for a population-based study that included 55 cases and 165 controls living in Copparo, Italy. One large, population-based cohort study of 1.54 million individuals born in Denmark (14,332 epilepsy cases) reported an OR of 5.43 (95% CI 5.19–5.69). In addition to studies that looked at increased risk of epilepsy with a history of febrile seizure, one cohort study investigated risk factors for onset of epilepsy only among children who had experienced febrile seizures (MacDonald et al., 1999). However, none of the factors studied were shown to significantly increase risk: these factors included age at first febrile seizure, sex, neurological abnormality prior to first febrile seizure, and first complex seizure.

History of CNS infection (e.g., meningitis, cerebral malaria, other unspecified) was shown to be a significant risk factor in seven of the eight studies that included it (Bearden et al., 2013; Birbeck et al., 2010; Cansu et al., 2007; Daoud et al., 2003; Dworetzky et al., 2012; Li et al., 1997; Matuja et al., 2001; Ngoungou et al., 2006; Whitehead et al., 2006). Two of these studies

significantly linked cerebral malaria to epilepsy onset, more particularly in those who experienced coma with convulsions or convulsions alone (OR = 3.9, 95% CI 1.7–8.9) (Ngoungou et al., 2006), or in children who experienced acute seizures (OR = 6.37, 95% CI 1.02–141.2) (Birbeck et al., 2010). One study reported that the elderly are at increased risk of developing epilepsy if they had meningitis (OR = 4.6, 95% CI 1.1–19.7) (Li et al., 1997). The highest risk estimate for epilepsy following CNS infection, OR = 12.6 ($p < .001$), occurred for a subpopulation of children with HIV/AIDS in Botswana. The single non-significant finding between CNS infections and epilepsy, OR = 1.3 (95% CI 0.5– 3.2), was reported in a case-control study (200 cases, 200 controls) limited to patients of a single hospital in Irbid, Jordan, conducted over a 7-month period (Daoud et al., 2003). When considering the risk of epilepsy for CNS infections as a group, a large population-based cohort study of 116,363 adult women reported a RR of 5.43 (95% CI 2.00–14.75) (Dworetzky et al., 2010).

History of brain trauma or head injury was identified as a significant risk factor in seven of the nine studies that included it (Burton et al., 2012; Cansu et al., 2007; Christensen et al., 2009; Daoud et al., 2003; Ferguson et al., 2010; Li et al., 1997; Matuja et al., 2001; Pugh et al., 2009; Tran et al., 2007) In one of the non- significant studies, there were only four individuals with a history of head trauma (Matuja et al., 2001) and risk estimates were not reported. Similarly, in the study by Burton et al. (2012), there were only five cases of head traumas and the results were non-significant. The highest risk estimate following head trauma, OR = 9.17 (95% CI 4.501–2420.74), was reported in a case-control study (805 cases and 846 controls) of childhood epilepsy in Turkey (Cansu et al., 2007). Logistic regression analysis by the last authors also showed that abnormal signs during neurological examination were indicative of high risk of epilepsy, OR = 30.26 (95% CI 13.905–65.834). A cohort study of over 1 million older veterans reported head injury as a

significant risk factor for epilepsy onset in this population, OR = 2.11 (95% CI 1.41–3.14) (Pugh et al., 2009). Perhaps the strongest evidence came from a large population-based cohort study of 1,605,216 individuals (17,470 epilepsy cases), which looked at risk of epilepsy following mild brain injury, severe brain injury, and skull fracture in children and young adults (Christensen et al., 2009). In the latter, risk of epilepsy was significant regardless of whether the injury was mild, RR = 2.22 (95% CI 2.07–2.38), severe, RR = 7.40 (95% CI 6.16–8.89), or involved a skull fracture, RR = 2.17 (95% CI 1.73– 2.71). In a U.S. cohort study of 1961 individuals who suffered a traumatic brain injury, severe traumatic events increased risk of epilepsy, RR = 2.54 (95% CI 1.46–4.42), when compared to mild events (Ferguson et al., 2010). The same study found that posttraumatic seizure prior to hospital discharge, 5.82 (95% CI 3.41–9.92), and higher number of comorbidities (3 or more), RR = 2.91 (95% CI 11.46–5.81), increased risk of epilepsy.

Studies investigating the association between stroke and epilepsy onset had mixed results (Bladin et al., 2000; Fitzgerald et al., 2007). In a prospective cohort study, Bladin et al. (2000) followed 1897 stroke victims with no prior history of epilepsy for 9 months. Ischemic stroke and haemorrhagic stroke were associated with increased risk of first time seizures but not epilepsy. Ischemic stroke was a risk factor for epilepsy only in cases of late onset initial seizure (>2 weeks following stroke), HR = 12.37 (95% CI 4.74–32.32). In a small cohort study of 45 children with delayed presentation of perinatal stroke, initial presentation with seizure, RR = 3.2 (95% CI 2.0–4.9) and infantile spasms, RR = 3.2 (95% CI 2.0–4.9) were risk factors for epilepsy (Fitzgerald et al., 2007).

Gestational age was shown to be significantly associated with epilepsy onset in six of the eight studies that included it (Asadi- Pooya and Hojabri, 2005; Chin et al., 2012; Crump et al., 2011; Ehrenstein et al., 2007; Kannoth et al., 2009; Murphy et al., 2004; Sun et al., 2008b; Zelnik

et al., 2010). Preterm birth was the most frequently reported risk factor for epilepsy (Chin et al., 2012; Crump et al., 2011; Kannoth et al., 2009; Murphy et al., 2004; Sunet al, 2008b). However, there was contradictory evidence that a term birth also increased risk (Zelnik et al., 2010). Post term births were not significantly associated with higher risk even if estimates appeared to increase with gestational age (Ehrenstein et al., 2007; Sun et al., 2008b). Two large cohort studies showed that as the gestational age decreases, the risk of epilepsy increases (Chin et al., 2012; Crump et al., 2011). In a population-based study of more than 630,000 adults, Crump and colleagues (2011) compared term births, those at 37–42 weeks, to those between 35 and 36 weeks, OR = 1.76 (95% CI 1.3–2.38); those between 32 and 34 weeks, OR = 1.98 (95% CI 1.26–3.13); and those between 23 and 31 weeks, OR = 4.98 (2.87–8.62). A second cohort study of nearly 1.5 million individuals showed similar results, for those born severely preterm (22 to 32 weeks of gestation), lifetime risk of epilepsy varied by age. The risk of developing epilepsy during the first year of life was reported as, IRR = 5.41 (95% CI 4.44–6.59); while, the risk of developing epilepsy between the age of 15 and 24 years was, IRR = 2.05 (95% CI 1.32–3.19) (Sun et al., 2008b). There was one non-significant study pertaining to premature birth, a small case-control study (142 cases, 138 controls) that looked at history of prematurity as a risk factor for childhood epilepsy, OR = 1.56 (95% CI 0.5–4.9) (Asadi-Pooya and Hojabri, 2005). In one small cohort study of children with cerebral palsy (197 patients), when compared to preterm birth, normal term birth was associated with increased risk of epilepsy, OR = 2.85 (95% CI 1.36–5.98) (Zelnik et al., 2010, 67–72).

Neonatal seizures were associated with increased risk of epilepsy. One large population-based cohort study of 124,207 individuals showed that neonatal seizures greatly increase the risk of childhood epilepsy, RR = 11.4 (95% CI 7.3–18.0) (Whitehead et al., 2006). A smaller, case-control study (362 cases and 362 controls) found a significantly increased risk for adults in an

Indian population, OR = 7.82 (95% CI 1.73–35.36) (Kannoth et al., 2009). Within various pediatric clinical subpopulations, children who experienced neonatal seizures or infantile spasms were reported to be at an increased risk for developing epilepsy, including: children with cerebral palsy (Zelnik et al., 2010), perinatal stroke (Fitzgerald et al., 2007), neonatal encephalopathy (Glass et al., 2011), and periventricular leukomalacia (Humphreys et al., 2007). In addition, in one small cohort study of 158 infants who experienced neonatal seizures, those who had an abnormal neurological examination upon discharge had an increased risk of developing epilepsy versus those whose exam was normal (unadjusted), OR = 10.35 (2.33– 45.89) (Garcias Da Silva et al., 2004). There was some evidence that children born small for gestational age were at increased risk for epilepsy. In one large cohort study of 619,001 individuals, restricted fetal growth, as measured by proportion of optimal birth weight of less than 75%, was shown to increase the risk of epilepsy diagnosed between the ages of 1–5 years, HR = 2.22 (95% CI 1.65–2.99), but not for diagnosis between the ages of 6–10 years, HR = 1.18 (95% CI 0.73– 1.91) (Cooper et al., 2012). A second large cohort study of nearly 1.5 million individuals further demonstrated that, for risk up to age 5 years, the IRRs for epilepsy tended to increase with increasing deviations from expected birth weight (estimated based on the weight of an older sibling) (Sun et al., 2008b). For example, for infants born at term with birth weights less than 60% of expected birth weight, the risk was estimated at, IRR = 6.08 (95% CI 2.89– 12.79). Even for those born slightly below the expected birth weight, at 80–89%, there were increased risks, IRR = 1.27 (95% CI 1.11–1.45). Likewise, another cohort study of 124,207 individuals reported that infants born small for gestational age (less than the 10th percentile) were at a significantly increased risk for developing childhood epilepsy, RR = 1.3 (95% CI 1.1–1.7) (White-head et al., 2006).

Eclampsia and/or preeclampsia were investigated as risk factors for epilepsy onset in five studies (Deepa, 2011; Mann and McDermott, 2011; Murphy et al., 2004; Whitehead et al., 2006; Wu et al., 2008). In a large cohort study of more than 1.5 million individuals (20,260 epilepsy cases), mild preeclampsia in mothers was associated with an increased risk of epilepsy in offspring, IRR = 1.20 (95% CI 1.11–1.30); however, neither severe preeclampsia, IRR = 1.14 95% (CI 0.96–1.36) nor eclampsia, IRR = 1.35 (95% CI 0.81–2.24) were found to significantly increase risk (Wu et al., 2008). A second cohort study of 95,450 individuals reported that maternal preeclampsia significantly increased the risk of child-hood epilepsy by about 1.5 times, OR = 1.46 (95% CI 1.17–1.82) (Mann and McDermott, 2011). A small case control study (30 cases, 60 controls) reported that preeclampsia increased the risk of epilepsy in children under 5 years of age by more than 9 times, OR = 9.1 (CI N/A) (Deepa, 2011). A third cohort study of 21,441 individuals found no increase in risk of epilepsy in adulthood following maternal preeclampsia, OR = 1.14 (95% CI 0.67–1.93) (Murphy et al., 2004). In one cohort study of 124,207 individuals, maternal eclampsia significantly increased the risk of childhood epilepsy, RR = 14.2 (95% CI 3.5–57.3) (Whitehead et al., 2006).

Two studies reported increased maternal age as a significant risk factor for epilepsy in offspring: for mothers aged 30 years and older living in Kerala, India, OR = 2.45 (95% CI 1.57–3.84) (Kannoth et al., 2009); and for mothers older than 35 years living in Copparo, Italy, OR = 2.83 (95% CI 1.05–7.61) (Monetti et al., 1995).

Several studies examined maternal health, non-CNS infections during pregnancy and/or maternal use of antibiotics to treat infection during pregnancy. The results were mixed. One cohort study of 135,347 individuals reported an increased risk of childhood epilepsy in offspring of mothers who had a genitourinary infection during pregnancy; the risk for mothers who themselves had epilepsy

was notably higher, HR = 3.74 (95% CI 1.67–8.40) than for mothers without epilepsy, HR = 1.23 (95% CI 1.12–1.34), however, both were significantly increased compared to mothers without infection (McDermott et al., 2009). A second cohort study of 191,383 mothers showed that treatment with antibiotics during pregnancy and/or admission to hospital for an infection significantly increased the risk of childhood epilepsy in their offspring, OR = 1.40 (95% CI 1.22–1.61) (Norgaard et al., 2012). A similar study of 72,533 individuals found that maternal use of antibiotics, particularly penicillin, OR = 1.5 (95% CI 1.1–2.0) slightly increased an offspring's risk of childhood epilepsy while urinary-tract infection medications, OR = 1.5 (95% CI 1.0–2.2) showed non-significant increased risks (Norgaard et al., 2009). The authors noted that it was difficult to ascertain whether the observed increased risk was due to the medication use versus some undetermined consequences of the infection (Norgaard et al., 2009). Another cohort study of 90,619 mothers reported increased risk of childhood epilepsy to offspring following maternal cystitis, IRR = 1.42 (95% CI 1.15–1.74); pyelonephritis, IRR = 2.32 (95% CI 1.15–4.70); diarrhea, IRR = 1.23 (95% CI 1.03–1.47); maternal cough with epilepsy onset prior to year 1 in offspring, IRR = 1.55 (95% CI 1.11–2.17) and vaginal yeast infection in cases of children born preterm, IRR = 2.56 (1.43–4.61) (Sun et al., 2008a). The same study reported no increased risk due to genital herpes, venereal warts, or herpes labialis. In a different cohort study of 124,207 mothers, infections (unspecified) during pregnancy showed an non-significant increased risk of childhood epilepsy in offspring, RR = 1.4 (95% CI 1.0–1.6) (Whitehead et al., 2006). For adult onset epilepsy, two small case-control studies reported significant increased risks associated with specific types of infection. First, Toxocara canis was associated with epilepsy onset in a Burundi population, OR = 2.13 (95% CI 1.18–3.83) (Nicoletti et al., 2007) and in an Italian population, OR = 3.90 (95% CI 1.91–7.98) (Nicoletti et al., 2008). Second, cycticercosis infection was a significant risk factor in the Burundi

study, OR = 3.71 (95% CI 1.90–7.24) (Nicoletti et al., 2007), a finding supporting conclusions reached in a previously described systematic review on this type of infection (Quet et al., 2010). A small case control study (38 cases, 38 controls) reported no increased risk for adult epilepsy onset following Onchocerciasis volvulus infection, OR = 1.68 (95% CI 0.60–4.57) (Kaiser et al., 2011), supporting the findings of a systematic review on this type of infection presented earlier (Druet-Cabanac et al., 2004).

Areas that require further evidence regarding the onset of epilepsy include breastfeeding and birth delivery method. One cohort study of 69,750 offspring in Denmark reported significant protective effects of breastfeeding both within and beyond the first year of life; the longer the period of breastfeeding, the greater the reduction in risk of childhood epilepsy, with risks as low as IRR = 0.35 (95% CI 0.17–0.71) for epilepsy onset within the first year of life, and as low as IRR = 0.41 (95% CI 0.24–0.71) for risk of epilepsy onset after the first year of life (Sun et al., 2011). Conversely, a large cohort study of 107,408 offspring in Norway reported no significant protective effect of breastfeeding (statistical values not provided) (Chin et al., 2012). One small case-control study (142 cases, 138 controls) also reported no significant benefit to breastfeeding for decreasing risk of childhood epilepsy OR = 0.5 (95% CI 0.19–1.3) (Asadi-Pooya and Hojabri, 2005). Likewise, the relationship between delivery method and risk of epilepsy remains controversial: one small case-control study (142 cases, 138 controls) reported an increased risk for offspring of mothers with a previous vaginal delivery, OR = 1.84 (95% CI 1.07–3.17), while a protective effect for caesarian section was observed, OR = 0.54 (0.31–0.94) (Asadi-Pooya and Hojabri, 2005). Two small case control studies each reported no significant association between epilepsy onset in offspring and delivery method (Glass et al., 2011; Masri et al., 2008). In contrast, one small case control study (30 cases, 60 controls) reported increased risk of epilepsy in offspring

with maternal history of abnormal delivery (unspecified), OR = 11 (95% CI not reported), as well as with prolonged labour, OR = 10.5 (95% CI's not provided) (Deepa, 2011). Another case control study (362 cases, 362 controls) similarly reported an increased risk of epilepsy following complicated delivery, defined as greater than 12 h of labour or assisted by forceps or vacuum extraction, OR = 6.80 (95% CI 1.66–4.53) (Kannoth et al., 2009).

Limited evidence suggested that smoking may increase the risk of epilepsy onset in both adults and unborn children. In a cohort study of 124,207 individuals, maternal smoking during pregnancy was reported to slightly increase the risk of childhood epilepsy in offspring, OR = 1.2 (95% CI 1.1–1.5) (Whitehead et al., 2006). Conversely, another cohort study of 107,408 offspring in Norway reported no increased risk with maternal smoking during pregnancy (statistical values not provided) (Chin et al., 2012). A cohort study of 116,363 individuals on epilepsy onset in adult women found a significantly increased risk for those who smoked cigarettes, RR = 1.46 (95% CI 1.01–2.12) (Dworetzky et al., 2010).

One small case control study reported that a history of passive smoke exposure for mothers did not increase risk of epilepsy in offspring, OR = 1.44 (95% CI 0.89–2.32) (Asadi-Pooya and Hojabri, 2005).

A host of other risk factors were considered but the results were mixed, inconclusive, or current evidence was inadequate. Factors that fell into this category included: sickle cell disease (Ngoungou et al., 2006), migraines with aura (Ludvigsson et al., 2006), menstrual irregularity (Dworetzky et al., 2012), major affective disorders paired with substance abuse (Nilsson et al., 2003), low Apgar scores (Chin et al., 2012; Vestergaard et al., 2007; Zelnik et al., 2010), low parental education (Chin et al., 2012), parental consanguinity (Masri et al., 2008), social class/deprivation (Murphy et al., 2004), CNS disease and metabolic disease (Whitehead et al.,

2006), and stress due to the loss of child (Christensen et al., 2007). These and other risk factors with minimal evidence of risk can be reviewed in Appendix D–J.

Risks Factors for the Progression of Epilepsy

Results of the Search

A total of 5,397 unique references were found using the electronic database search strategies. Of these, 5,127 articles were excluded at the first stage of screening. A further 261 articles were excluded at stage two because they did not meet the study criteria, 3 articles were excluded because they could not be retrieved and 6 papers remained for data extraction (Figure 5.3).

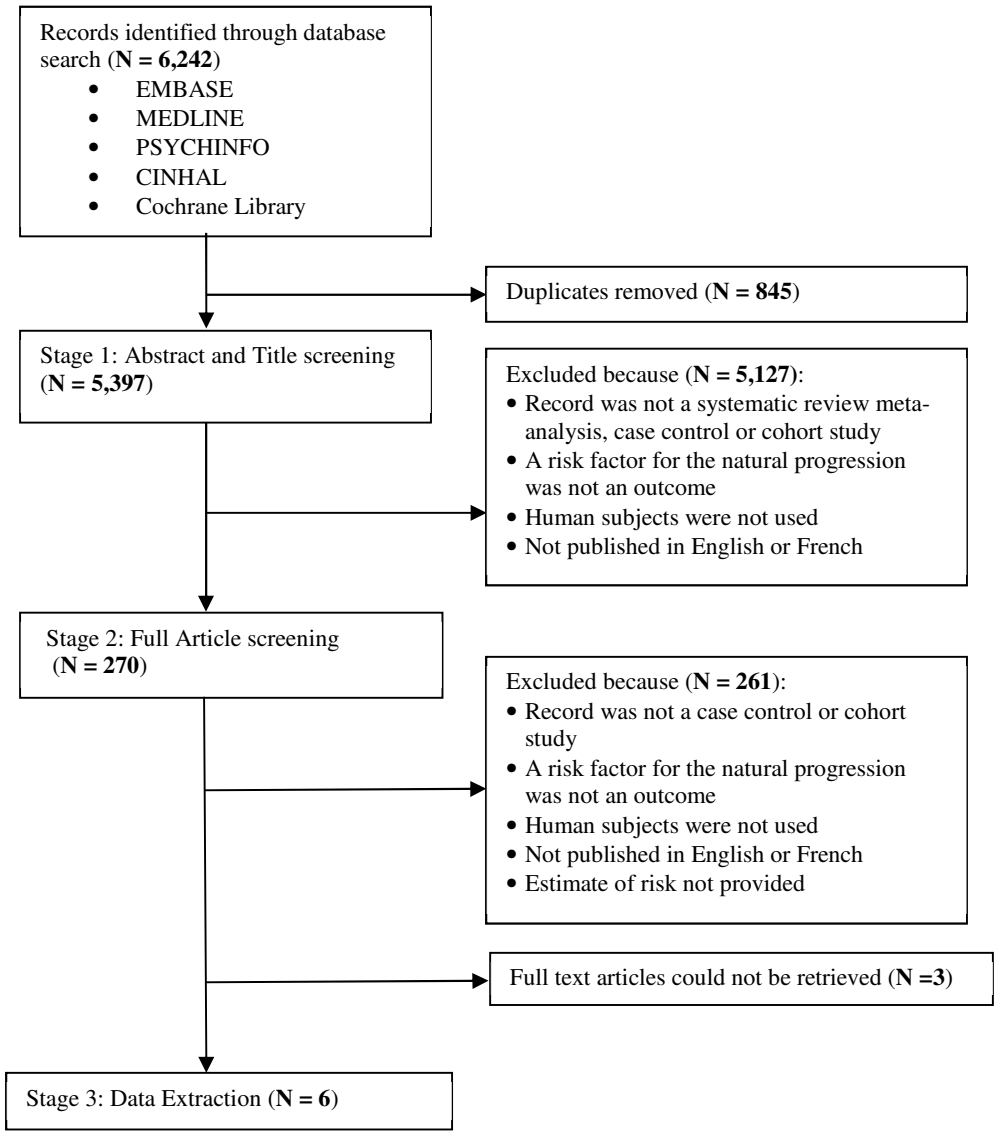

Figure 5.3. Flowchart of Literature Search of Risk Factors for Natural Progression of Epilepsy

Description of Observational Studies Examining the Natural Progression of Epilepsy

One important aspect of epilepsy prognosis is whether or not terminal remission of seizures is achieved. Several studies looked at factors that affect the likelihood of the continuation of seizure events after diagnosis (Supplementary Material XI). In one community-based cohort study in the city of Junin in Argentina, 96 epilepsy patients were followed for eight years, and 32 cases of recurrent seizures were recorded (Kochen and Melcon, 2005). Within this population, patients with symptomatic epilepsy were more likely to have ongoing seizures than those with genetic or unknown epilepsy, OR = 2.7 (95% CI 1.1–6.7) (Kochen and Melcon, 2005). The risk of ongoing seizures was near seven times greater for patients with focal seizures than for those with generalized seizures, OR = 6.9 (95% CI 2.5–18.9). Similarly, the risk of ongoing seizures was 6.6 times greater for those with focal syndromes than for those with generalized syndromes, OR = 6.6 (95% CI 2.3–18.8) (Kochen and Melcon, 2005). In another community-based cohort study of newly diagnosed children in Ibadan, Nigeria, significant predictors of poor seizure control and lack of seizure remission included: 1) slow waves on an EEG, OR = 0.115 (95% CI -0.034-0.387); 2) greater seizure frequency (≥1/month), OR = 0.156 (95% CI 0.046-0.532) (Lagunju and Asinobi, 2011). The presence of associated neurocognitive impairments, or, having one's first seizures within the first year of life, did not significantly affect the probability of remission (Lagunju and Asinobi, 2011). A third cohort study reported that adults with epilepsy are more likely to experience a seizure recurrence if they have a higher self-reported level of stress or anxiety (moderate stress: OR = 1.3 (95% CI 1.0-1.7), high stress: OR = 1.6 (95% CI 1.2-2.1), moderate anxiety: OR = 1.5 (95% CI 1.2-1.9), high anxiety: OR = 2.0 (95% CI 1.4-2.6); or if they lacked sleep over the preceding one or two nights (hours of sleep one night prior: OR = 0.91 (95% CI

0.86-0.96, hours of sleep two nights prior: OR = 0.89 (95% CI 0.81-0.97) (Haut et al., 2007). The effect of sleep was calculated as the relative odds of a seizure for each additional hour of sleep.

In addition to seizure remission status, prognosis was also examined in terms of mortality. In one community-based cohort study, 103 individuals with epilepsy were identified and 71 cases had sufficient data available for ten years of follow-up (Nicoletti et al., 2009). None of the factors examined significantly affected seizure remission status at two or five years, including sex, age at onset, neurocysticercosis (NCC), underlying causes, type of seizure, treatment for at least one year, or treatment for at least two months. However, age at onset was a significant predictor of mortality for those 20-59 years (unadjusted), OR = 4.65 (95% CI 1.03-21.0) and those 60 years and older (unadjusted) OR = 22.3 (95% CI 2.29-217.4) when compared to those aged 19 years or younger (Nicoletti, Sofia, 2009). Unfortunately, adjusted estimates were not reported. In comparison to the general population, the mortality rate was also significantly higher among patients with remote symptomatic epilepsy, SMR = 3.0 (95% CI 1.2–6.3), but not for those with epilepsy of unknown cause, SMR = 0.74 (95% CI 0.2–1.8) (Nicoletti, Sofia, 2009).

Status epilepticus (SE) is a severe, often life-threatening form of seizure in which individuals experience either a continuous, unremitting seizure or recurrent seizures without regaining consciousness between seizures over a certain period of time. Berg et al. (2004) defined status epilepticus as: "1) continuous seizure activity or 2) intermittent seizure activity without definite return to baseline between seizures that lasted more than a minimum period of 30 minutes." In one cohort study of 613 children with epilepsy (58 cases of status epilepticus), children were found to be at a greater risk for status epilepticus following diagnosis if they had: 1) a history of status epilepticus prior to epilepsy diagnosis, RR = 4.49 (95% CI 2.54-7.92); 2) symptomatic etiology, RR = 2.47 (95% CI 1.44-4.23); or 3) early age at onset, RR = 0.91 per

increase in year of age at onset (95% CI 0.85-0.98), indicating a decline in risk with increasing age at onset (Berg et al., 2004).

Genetic Risk Factors for the Onset and/or Natural Progression of Epilepsy

A total of 19 articles were identified through electronic database searches (Figure 5.4). Search for relevant systematic reviews and meta-analyses of genetic risk factors using Medline, Embase, PsycInfo, Cochrane Library and CINAHL yielded four systematic reviews/meta-analyses. A search of HuGE Navigator (http://hugenavigator.net/HuGENavigator/home.do) yielded 19 potentially relevant articles. A search of The Epilepsy Genetic Association Database (EpiGAD) (www.epigad.org), identified 11 potential articles. From a total of 34 articles, 15 duplicates were excluded. During Level 1 screening, eight articles were excluded either because they were primary studies (1), the outcome was not related to epilepsy (1), or the outcome was associated with pharmacological interventions rather than natural progression of the disease (6). An additional 4 articles were excluded following a full text review because they were either not a meta-analysis (2), or they did not provide summary measures of risk (2). Seven articles were retained for data extraction (Appendix L).

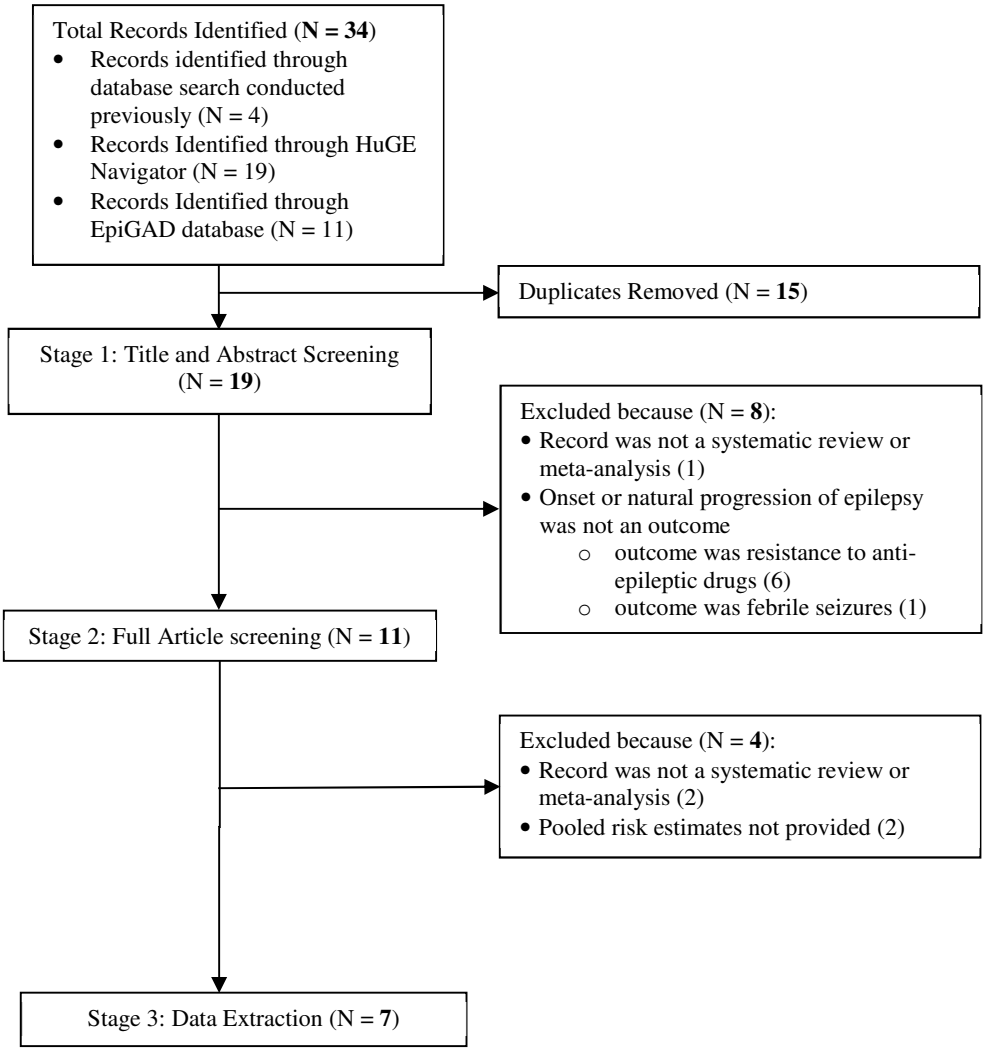

Figure 5.4. Flowchart of Literature Search of Genetic Risk Factors for Onset and/or Natural Progression of Epilepsy

Description of Genetic Studies Examining the Risk of Epilepsy Onset or Progression

Seven reviews examined genetic risk factors for the onset or natural progression of epilepsy. Three reviews identified significant genetic risk factors for epilepsy onset (Kauffman et al., 2008a; Kauffman et al., 2008b; Xi et al., 2011). In one review, individuals with a familial predisposition of epileptic disorder carrying L alleles of PDYN gene promoter were shown to have a 40% greater risk of developing temporal lobe epilepsy (TLE) than those homozygous for the H alleles, OR = 1.40 (95% CI 1.12-1.74) (Kauffman et al., 2008a). A second review reported that individuals with single nucleotide polymorphisms in Interleukin 1B were found to have a nearly 50% increased risk of developing TLE with hippocampal sclerosis, OR = 1.48 (95% CI 1.09-2.00) (Kauffman et al., 2008b). Finally, a third review identified the Gamma-Aminobutyric acid B receptor 1 (GABBR1) gene polymorphism G1465A as a risk factor for TLE, OR = 5.38 (95% CI 1.726-16.776), although the mechanism informing the association has not been established (Xi et al., 2011).

Three additional reviews examined genetic risk factors for epilepsy but no significant associations were found. One review failed to find any evidence to suggest that the SLC6A4 promoter and intron 2 variant number repeat polymorphisms (VNTR) SLC6A4 gene polymorphism were associated with an increased risk for TLE (5HTTLPR polymorphism: OR = 0.90, 95% CI 0.77-1.06; 5HTTVNTR polymorphism: OR = 1.10, 95% CI 0.78-1.57) (Córdoba et al., 2012). In a second review, no association was found between ABCBI C3435T polymorphisms and the risk of epilepsy, OR = 1.07 (95% CI 0.76-1.51) (Nurmohamed et al., 2010). In the third review, the SYN2 rs3773364 A>G polymorphism was not significantly associated with an increased risk of epilepsy, OR = 0.97 (95% CI 0.7-1.34) (Haerian et al., 2011).

A final genetic study reported that carriers of ApoE ε4 experience the onset of epilepsy significantly earlier than non-carriers, by 5.15 years on average, (95% CI 2.08-6.22) (Kauffman et

al., 2010). While this study does not report a measure of risk of onset of epilepsy, individuals who possess this variant are at risk of developing epilepsy earlier in the life course, which could suggest a genetic influence on the natural progression of disease.

Discussion

This is the first systematic review that has attempted a comprehensive identification of all risk factors associated with the onset and natural progression of epilepsy. The review highlighted several risk factors that likely play a role in the onset of epilepsy. Most of the evidence collected came from observational studies and there was a surprisingly low number of systematic reviews and meta-analyses; a total of 8 for genetic and non-genetic factors was captured by the search strategy. Only a limited amount of evidence on the risk factors associated with the natural progression of epilepsy was found through the searches. This review confirmed more established risk factors, brought to light critical gaps in the current knowledge base and offered leads for future research.

Onset

Of the four non-genetic systematic reviews and meta-analyses investigated, only one showed a significant risk of epilepsy onset. The paper by Samokhvalov et al. (2010) not only reported a threshold effect between alcohol consumption and epilepsy onset, a dose effect also suggested that with increased daily doses of alcohol, there was increased risk of disease onset passed a daily minimum of alcohol consumption.

The 59 case-control and cohort observational studies retained included dozens of risk factors that were pooled together by convenience for reporting purposes. Given that an important category of seizure classification by the ILAE (Berg et al., 2010) is for seizures of genetic etiology, it was no

surprise that family history of epilepsy, including paternal history and maternal history, was a significant risk factor of onset in all the studies that included it. Having a history of febrile seizures, a classic risk factor for epilepsy onset, was confirmed.

Risk of epilepsy onset from CNS infections were confirmed for cerebral malaria, meningitis, HIV/AIDS and for a pooled group of CNS infections. These results lend credibility to a possible pathogenesis mechanism linking CNS infections to the formation of brain lesions leading to acquired symptomatic epilepsy. The only non-significant results pertaining to an association between CNS infections and epilepsy onset was a case-control study with a small sample size, completed with data from a single hospital, and where CNS infections were pooled making it more prone to bias and confounding. Head trauma, another frequently reported risk factor for epilepsy, was confirmed in all studies that included it except for two studies that had too few cases to derive any meaningful multivariate analysis results. Together, studies on head trauma appeared to suggest increased risk of epilepsy onset with increased level of trauma severity.

The low number of studies on, or including, stroke as a potential risk factor for onset of epilepsy was surprising. Similarly, aside from increased risk reported for perinatal stroke, findings appeared to defy conventional knowledge that stroke is a risk factor for epilepsy. However, a significantly high hazard ratio, HR = 12.37 (95% CI 4.74-32.32), showing increased risk of epilepsy onset when the first seizures post ischemic stroke is more than 2 weeks after the traumatic event may warrant additional investigation in cases of delayed seizures following other types of exposure.

Studies on gestational age suggested a greater risk of onset of epilepsy in preterm births, a risk that increased even more with fewer weeks of completed pregnancy. Reported findings of a potential association between epilepsy onset and term or post term delivery were not convincing.

Experiencing neonatal seizures, as well as being born with a lower than expected birth weight increased risk of epilepsy onset. But while neonatal seizures were associated with risk of childhood and adult onset, risk associated with low birth weight disappeared in later childhood (6 to 10 years).

Limited evidence suggests that perinatal risk factors for epilepsy in offspring may include factors related to the mother, pregnancy, and birth. Risk of epilepsy onset associated with pre-eclampsia or eclampsia were contradictory and will need further investigation. Increased risk associated with higher maternal age were reported by two studies but the age categories and study populations were notably different. On a similar topic, findings highlighted the need to further investigate factors related to maternal health during pregnancy, with particular attention on research designs that disaggregate different non-CNS infections and their related treatments on risk of the onset of epilepsy. More research is also needed to determine whether birth delivery method, breastfeeding, smoking in adults or smoking during pregnancy affects risk.

Low Apgar scores appeared to suggest increased risk of epilepsy onset but the thresholds and populations used were heterogeneous between studies and prevented adequate comparisons.

Three genetic markers were identified as significantly increasing the risk of epilepsy onset, while a fourth was shown to shorten time to onset. Still, the paucity of research suggests that a significant gap exists in our knowledge of the genetic basis of epilepsy and that this area warrants further examination.

Progression

There were no systematic reviews or meta-analyses and only six observational studies evaluated risk factors pertaining to the natural progression of epilepsy. Lack of evidence on the natural progression of epilepsy may be the result of the clinical inclination to treat seizures with

anticonvulsant in developed countries, or possibly over treat (Holmes, 2002), thereby limiting the number of cases available for tracking the natural progression of disease. This would perhaps explain why half of the progression studies included in the review where conducted in developing countries where treatment opportunities may be limited. Our exclusion of search terms in languages other than French and English may have prevented the selection of studies completed on populations in which cases of natural progression of epilepsy are more readily available for study.

Limited evidence from a few small cohort studies suggests that there are several risk factors that significantly reduce the likelihood of terminal remission. Together, the studies found that symptomatic epilepsy (versus idiopathic or unknown), focal seizures or syndromes (versus generalized), slow waves on an EEG, higher seizure frequency, high stress or anxiety, and lack of sleep significantly decreased the odds of seizure remission. In one study, ages at onset of epilepsy was reported as a significant predictor of mortality but since the odds ratio were not adjusted and age itself is a predictor of mortality, the results had limited validity. Overall, symptomatic etiology had worst long term outcomes compared to genetic or unknown epilepsies and is associated with a higher standardized mortality rate and greater risk of status epilepticus in children.

Limitations

Several gaps in the current knowledge base of available literature were identified. Many studies that examined biological risk factors (e.g., specific diseases or infections) had very small sample sizes. In such cases, failure to reach significant results could be due to insufficient statistical power.

In some of the studies included in the review, exposure was determined based on self-reported disease status (e.g. for infections) rather than by clinical diagnoses; these findings may

be less reliable, given that, for example, pregnant women are being asked to retrospectively recall the occurrence and timing of illnesses over periods of nine months or more, during a potentially stressful and highly demanding time in their lives. In this area, studies exempt of recall bias are needed to validate existing findings.

One limitation of this study is that the search strategy was intentionally very broad, as we were attempting to identify any and all possible risk factors for epilepsy onset and progression. Because search terms specifically target more common or well-known risk factors were not included, relevant articles may have possibly been missed. In order to ensure the manageability and resource demands of a study with a very broad search strategy, articles published before 1990 were excluded. This decision likely contributed to the exclusion of seminal articles describing now widely recognised risk factors published in the decades preceding the cut-off.

Many of the risk factors identified were specific to a certain geographical region, often with a unique set of demographic characteristics (e.g. communities in developing countries) or clinical subpopulations that were from a single facility. Results from such studies may be less generalizable. Also, the perinatal causes of epilepsy likely vary greatly from the causes of adult onset or from epilepsy acquired following head trauma, brain injury or infection. For this reason, comparing results across different population demographics may not be feasible nor judicious. The same conclusion is likely to apply to studies that focused on certain subpopulations, such as those with a history of prenatal seizures, or patients with specific types of CNS infection. Thus, it is not possible to generalize risk factors across studies for the different types of epilepsy and/or populations under study.

Another potential limitation related to the inclusion criteria for this study relates to the language restrictions used. Due to limited resources and the costly nature of translating papers into

English, only articles published in English and French were eligible for inclusion. Although potentially relevant articles may have been excluded because of this criterion, it is difficult to evaluate the overall impact of this decision. Firstly, language restrictions were not implemented at the database search stage. Thus, all papers that met the search criteria were screened at level one by two reviewers. While not specifically documented nor quantified, our reviewers agreed upon recall that the number of articles that met all inclusion criteria except for language was minimal. Secondly, the exclusion of search terms in languages other than English and French, e.g. Spanish, may have excluded studies from developing countries describing risk factors for epilepsy that are geographically relevant in these populations.

Finally, the broad approach used in the search strategy, which did not include the specific inclusion of terms relating to known risk factors, may have been responsible for the fact that findings on the onset of epilepsy from genetic disorders such as single-gene pure epilepsies, chromosomal aberrations or single gene diseases that manifest themselves with epileptic seizures, neurodegenerative conditions, cerebral tumors and abscesses, hippocampal sclerosis, some neurocutaneous syndromes, developmental anomalies, cerebrovascular diseases, metabolic causes, and intoxications (Shorvon, 2005) were not mentioned in the papers that were screened and reviewed.

Conclusions

Potential risk factors for epilepsy onset are numerous and vary on multiple dimensions. While a large body of work exists, heterogeneity in study designs and populations create a lack of generalizability, and very few factors have been adequately scrutinized through the systematic review process. As well, much more work is needed to determine the possible risk factors for the

natural progression of epilepsy, in both children and adults. The limited available evidence suggests that many perinatal risk factors are non-modifiable. However, further research is needed to determine whether certain types of interventions may be warranted when a combination of conditions for increased risk are met. Certain instances of childhood or adult onset epilepsy may be linked to modifiable risk factors, including alcohol consumption, acquired brain injuries, CNS infections, and thus be the target of prevention strategies.

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Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Update

A supplementary search of the MEDLINE database identified 113 citations reporting on the onset of epilepsy and 17 on the natural progression of epilepsy between February 2013 and December 2015. After full screening of these articles according to the original inclusion criteria, the following 10 articles reporting on the factors associated with the onset of epilepsy were retained. No new studies on the natural progression of epilepsy were retained. The majority of these studies focussed on genetic polymorphisms that may be associated with epilepsy.

Bruno, E., Bartoloni, A., Zammarchi, L., Strohmeyer, M., Bartalesi, F., Bustos, J.A., et al. 2013. Epilepsy and neurocysticercosis in Latin America: a systematic review and meta-analysis. PLoS Negl Trop Dis. 7:e2480.

Christensen, S.S., Eslick, G.D. 2015.Cerebral malaria as a risk factor for the development of epilepsy and other long-term neurological conditions: a meta-analysis. Trans R Soc Trop Med Hyg. 109:233-8.

Haerian, B.S., Baum, L. 2013. GABRG2 rs211037 polymorphism and epilepsy: a systematic review and meta-analysis. Seizure. 22:53-8.

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Appendix A

Search Strategies

ToxNET and Cochrane Library

Combinations of keywords were used to search ToxNET and the Cochrane Library from the search strategies utilized in MEDLINE and Embase. Search terms included “risk factors”, “etiology”, and “epilepsy”.

Search strategies for systematic reviews and meta-analysis of risk factors associated with the onset of epilepsy.

Medline
1. meta-analysis/
2. (meta anal* or metaanal*).ti,ab,sh.
3. 1 or 2
4. ((methodol* or systematic* or quantativ*) adj (review* or overview* or survey*)).ti,ab,sh.
5. 4 and review.pt,sh.
6. 3 or 5
7. exp risk/
8. etiology.fs.
9. genetics.fs.
10. prevention & control.fs.
11. 7 or 8 or 9 or 10
12. exp Epilepsy/
13. Seizures/
14. ((seizure* adj disorder*) or convuls*).mp.
15. 12 or 13 or 14
16. 6 and 11 and 15
17. limit 16 to yr="1950 - 2010"

Embase
1. "systematic review"/
2. exp review/
3. (literature adj3 review$).ti,ab.
4. (systematic$ adj2 (review$ or overview)).ti,ab.
5. exp meta analysis/
6. (meta?anal$ or meta anal$ or meta-anal$ or metaanal$ or metanal$).ti,ab.
7. 1 or 2 or 3 or 4 or 5 or 6
8. exp risk/
9. et.fs.
10. exp genetics/
11. pc.fs.
12. 8 or 9 or 10 or 11
13. epilepsy/

14. 7 and 12 and 13
15. limit 14 to (yr="1950 - 2010")

PsycINFO

1. systematic review*.mp.
2. meta analy*.mp.
3. meta-analy*.mp.
4. meta analysis/
5. (systematic adj3 literature).mp.
6. metaanaly*.mp.
7. ("systematic review" or "meta analysis").md
8. "literature review"/
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. risk factors/
11. at risk populations/
12. etiology/
13. exp genetics/
14. prevention/
15. 10 or 11 or 12 or 13 or 14
16. exp seizures/
17. exp epilepsy/
18. convulsion.mp.
19. 16 or 17 or 18
20. 9 and 15 and 19
21. limit 20 to (yr="1950 - 2010")

Search strategies for observational studies of risk factors associated with the onset of epilepsy

Medline

1. exp risk/
2. etiology.fs.
3. genetics.fs.
4. prevention & control.fs.
5. 1 or 2 or 3 or 4
6. exp Epilepsy/
7. Seizures/
8. ((seizure* adj disorder*) or convuls*).mp.
9. 6 or 7 or 8
10. Epidemiologic Studies/
11. exp Case-Control Studies/
12. exp Cohort Studies/
13. case control.tw.
14. Cohort analy$.tw.
15. (cohort adj (study or studies)).tw.
16. (Follow up adj (study or studies)).tw.
17. (observational adj (study or studies)).tw.
18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. 5 and 9 and 18

Embase

1. exp risk/
2. et.fs.
3. exp genetics/
4. pc.fs.
5. 1 or 2 or 3 or 4
6. epilepsy/
7. clinical study/
8. case control study/
9. family study/
10. prospective study/
11. controlled clinical trial/ or randomized controlled trial/
12. 10 not 11
13. cohort analysis/
14. (cohort adj (study or studies)).tw.
15. (Follow up adj (study or studies)).tw.
16. (observational adj (study or studies)).tw.
17. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18. 5 and 6 and 17

CINAHL

S1 (MH "Epilepsy+")
S2 (MH "Seizures")
S3 (convulsion*)
S4 S1 OR S2 or S3
S5 (MH "Prospective Studies")
S6 (MH exp "Case Control Studies")
S7 (MH "Correlational Studies")
S8 (MH "Nonconcurrent Prospective Studies")
S9 (MH "Cross Sectional Studies")
S10 (cohort N1 stud*)
S11 (observational N1 stud*)
S12 S5 or S6 or S7 or S8 or S9 or S10 or S11
S13 S4 and S12

PsycINFO

1. risk factors/
2. at risk populations/
3. etiology/
4. exp genetics/
5. prevention/
6. 1 or 2 or 3 or 4 or 5
7. exp seizures/
8. exp epilepsy/
9. convulsion.mp.

10. 7 or 8 or 9
11. (double adj2 blind).mp.
12. (random* adj2 assign*).tw.
13. control.tw.
14. (observational adj (study or studies)).tw.
15. 11 or 12 or 13 or 14
16. 6 and 10 and 15

Search strategies for risk factors associated with the natural progression of epilepsy

Medline:
1.exp Epilepsy/
2. ((seizure* adj2 disorder*) or convuls*).tw.
3. 1 or 2
4. exp disease progression/
5. (rate* adj4 (progress* or deterioration or exacerbation)).tw.
6. (disease course or clinical course or natural history or natural course or longitudinal outcome).tw.
7. exp Longitudinal Studies/
8. (longitudinal stud* or follow-up stud* or prospective stud*).tw.
9. 7 or 8
10. severity.tw.
11. 9 and 10
12. 4 or 5 or 6 or 11
13. 3 and 12

Embase:
1. epilepsy/
2. disease course/
3. (rate* adj4 (progress* or deterioration or exacerbation)).tw.
4. (disease course or clinical course or natural history or natural course or longitudinal outcome).tw.
5. longitudinal study/
6. (longitudinal stud* or follow-up stud* or prospective stud*).tw.
7. 5 or 6
8. severity.tw.
9. 7 and 8
10. 2 or 3 or 4 or 5 or 6 or 9
11. 1 and 10
12. limit 11 to embase

CINAHL:

S11 S3 AND S10
S10 S4 or S5 or S6 or S7 or S8 or S9
S9 "natural course"

S8 (MH "Prospective Studies+")
S7 "Natural history"
S6 (MH "Disease Exacerbation")
S5 "disease deterioration"
S4 (MH "Disease Exacerbation")
S3 S1 or S2
S2 (MH "Seizures")
S1 (MH "Epilepsy+")

PsycINFO:
1. exp epilepsy/
2. exp seizures/
3. 1 or 2
4. disease course/
5. (rate* adj4 (progress* or deterioration or exacerbation)).tw.
6. (disease course or clinical course or natural history or natural course or longitudinal outcome).tw.
7. exp longitudinal studies/
8. (longitudinal stud* or follow-up stud* or prospective stud*).tw.
9. 7 or 8
10. severity.tw.
11. 9 and 10
12. 4 or 5 or 6 or 11
13. 3 and 12

Appendix B.

Data extraction questionnaires.

Table 5B1. Risk Factors for Onset, Systematic Reviews and Meta-Analysis: Level One Title and Abstract Screening Questionnaire

	Question	Responses
1	Is this article a systematic review and/or meta-analysis?	• Systematic Review ONLY • Meta-Analysis ONLY • BOTH • Neither • Can't Tell
2	Is this article related to epilepsy as an outcome? (Note: if the article refers to seizures or convulsions with no specific mention of epilepsy, select "Can't tell".)	• Yes • No • Can't Tell
3	Is this article related to etiological risk factors for developing epilepsy (i.e., ONSET)?	• Yes • No • Can't Tell
4	Does this study report on data for human participants?	• Yes • No • Can't Tell
5	In which language is this article written?	• English • French • Other • Can't Tell

Table 5B2. Risk Factors for Onset, Systematic Reviews and Meta-Analysis: Level Two Full Article Screening Questionnaire

	Question	Responses
1	Is this article a systematic review and/or meta-analysis?	• Systematic Review ONLY • Meta-Analysis ONLY • BOTH • Neither
2	Does this article report on epilepsy as an outcome?	• Yes • No
3	Is this article related to etiological risk factors for developing epilepsy (i.e., ONSET)?	• Yes • No

4	Does this study report on data for human participants?	• Yes • No
5	In which language is this article written?	• English • French • Other

Table 5B3. Risk Factors for Onset, Systematic Reviews and Meta-Analysis: Level Three AMSTAR Screening Tool

	Question	Response
1	Was an 'a priori' design provided? (1)The research question/aim and (2) inclusion criteria should be established before the conduct of the review.	• Yes (1 point)- Must satisfy both criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
2	Was there duplicate study selection and data extraction? (1)There should be at least two independent data extractors and a (2) consensus procedure for disagreements should be in place.	• Yes (1 point) Must satisfy both criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
3	Was a comprehensive literature search performed? (1) At least two databases must be searched; (2) The report must include years and databases used; (3) keywords and/or MESH terms must be stated; (4) search strategy must be provided where feasible; (5) All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the field, and by reviewing the references in the studies found.	• Yes (1 point)- Must satisfy all five criteria • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)
4	Was the status of publication (i.e. grey literature) used as an inclusion criteria? (1) Authors should state they searched reports regardless of publication type; (2) Authors should state whether or not they excluded any reports (from the systematic review) based on their publication status, languages, etc.	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
5	Was a list of studies (included and excluded) provided? A list of (1) included and (2)excluded studies should be provided. Note: excluded studies can be provided in an appendix or external link	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
6	Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. Ranges of characteristics (age, sex, relevant socioeconomic data, disease status, duration , severity, or other diseases should be reported)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not Applicable (0 points)

7	Was the scientific quality of the included studies assessed and documented? A priori methods of assessment should be provided Note: (for example, did they mention an instrument/tool to assess quality?)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
8	Was the scientific quality of the included studies used appropriately in formulating conclusions? Results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
9	Were the methods used to combine the findings of studies appropriate? For pooled results, a test should be done to ensure studies were comparable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable
10	Was the likelihood of publication bias assessed? Assessment of publication bias should include a combination of graphical aids (e.g. full plots, other available tests) and/or statistical tests (e.g. Egger regression test)	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
11	Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies	• Yes (1 point) • No (0 points) • Can't Answer (0 points) • Not applicable (0 points)
12	Overall AMSTAR score: low quality (0-3) moderate quality (4-7) high quality (8-11)	
13	Was this article deemed to be of low quality (i.e., scored between 0-3 points)?	• Yes • No

Table 5B4. Risk Factors for Onset, Systematic Reviews and Meta-Analysis: Level Four Data Extraction Tool

	Criteria	Response
1	Author, year of publication	Freeform Response
2	AMSTAR score	Freeform Response
3	Sex:	Freeform Response
4	Age:	Freeform Response
5	Co-morbidities:	Freeform Response
6	Disease Status:	Freeform Response
7	Race:	Freeform Response
8	Nationality (select all that apply):	Freeform Response
9	Duration:	Freeform Response
10	Severity:	Freeform Response

11	What was the stated target population of the study?	Freeform Response
12	What was the setting of the study (community, institutional care, residential setting)?	Freeform Response
13	What was the research question/aim stated in the review article?	Freeform Response
14	What study designs were included in the review?	Freeform Response
15	Inclusion Criteria:	Freeform Response
16	Exclusion Criteria:	Freeform Response
17	What years were included in the search strategy?	Freeform Response
18	Which databases were searched?	Freeform Response
19	What MeSH terms included in the search strategy?	Freeform Response
20	What were the keywords included in the search strategy?	Freeform Response
21	Did they use a quality assessment tool/instrument to assess the methodological quality of the included studies?	Freeform Response
22	If YES to 22, Please list the tool used:	Freeform Response
23	If only a systematic review was done (qualitative), Is it reasonable to report the individual risk estimates from the included studies of the SR?	Freeform Response
24	Risk Factor	Freeform Response
25	Disease Outcome (if applicable)	Freeform Response
26	Sub-group (if applicable)	Freeform Response
27	Risk estimate and confidence interval	Freeform Response
28	What were the sample sizes of included studies (n)? (Provide as a range)	Freeform Response
29	If only a systematic review was done (qualitative), what were their main conclusions?	Freeform Response
30	What were the main conclusions resulting from the meta-analysis?	Freeform Response
31	Was publication bias addressed?	Freeform Response
32	If Yes, indicate whether or not they addressed any of the following:	Freeform Response
33	Were there any limitations noted?	Freeform Response
34	If YES, note the limitations addressed:	Freeform Response
35	Overall main conclusion of review (2-3 sentences):	Freeform Response

Table 5B5. Risk Factors for Onset, Observational Studies: Level One Title and Abstract Screening Questionnaire

	Question	Responses
1	Is this article related to etiological risk factors for developing epilepsy (i.e., ONSET)?	• Yes • No • Can't Tell
2	Is this article a case-control, cohort or genetic association study?	• Case Control • Cohort

		• Both • Genetic Association Study • None of the Above • Can't Tell
3	Does the study include data on human participants?	• Yes • No • Can't Tell
4	In which language is this article written?	• English • French • Other • Can't Tell

Table 5B6. Epilepsy: Risk Factors for Onset, Observational Studies: Level Two Full Article Screening Questionnaire

	Question	Responses
1	In which language is this article written?	• English • French • Other
2	Is this article a case-control, cohort or genetic association study?	• Case Control • Cohort • Both • Genetic Association Study • None of the Above
3	Is this article related to etiological risk factors for developing epilepsy (i.e., ONSET)?	• Yes • No
4	If yes to Question 3: Which risk factors were considered?	• Alcohol consumption • Antiphospholipid syndrome • Birth trauma • CNS infections Cysticercosis • Drugs/toxins • Head injuries Head injuries • Infectious disease • Manganese (low levels) • Onchocerciasis

		• Stroke (cerebrovascular disease) • Toxoplasmosis gondii infection
5	Does the study include data on human participants?	• Yes • No
6	Was an estimate of risk provided, or can one be calculated from the data provided in the article?	• Yes • No

Table 5B7. Risk Factors for Onset, Observational Studies: Level Three Full Article Data Extraction Questionnaire (Case-Control)

	Question	Responses
1	Does this article provide an estimate of risk for epilepsy (i.e., relative risk, odds ratio, risk ratio, hazard ratio, etc.) OR can such be calculated using raw data?	• Yes • No
2	First author last name, Year of publication:	Freeform Response
3	Location of the study (City, Country):	Freeform Response
4	Race/Ethnicity:	Freeform Response
5	Period of recruitment:	• Case-control
6	Average follow-up (cohort studies):	Freeform Response
7	Sample size (For case-control studies: # cases/controls):	Freeform Response
8	Source of participants:	Freeform Response
9	Age (mean age or range):	Freeform Response
10	Inclusion/ exclusion criteria:	Freeform Response
11	Response rate (%):	Freeform Response
12	Method for exposure ascertainment (ex. serum levels, self-report):	Freeform Response
13	Outcome under study (ex. Birth Trauma, etc.):	Freeform Response
14	Outcome ascertainment/Case Definition (DSM, NINCDS-ADRDA, ICD-10, etc.):	Freeform Response
15	Study limitations:	Freeform Response
16	General conclusions:	Freeform Response
17	Risk factor under study:	Freeform Response
18	Categorization of the exposure (ex. Quartile 1 vs. Quartile 4, Exposed vs. Unexposed, 250 mg vs. 0 mg, Former vs. Current smokers, Yes vs. No):	Freeform Response
19	Confounding Adjustment (variables):	Freeform Response
20	Risk estimate(s) and 95% confidence interval and/or p-value (for each comparison):	Freeform Response

Table 5B8. Risk Factors for Onset, Observational Studies: Level Three Full Article Data Extraction Questionnaire (Cohort)

	Question	Responses
1	Does this article provide an estimate of risk for epilepsy (i.e., relative risk, odds ratio, risk ratio, hazard ratio, etc.) OR can such be calculated using raw data?	• Yes • No
2	First author last name, Year of publication:	Freeform Response
3	Location of the study (City, Country):	Freeform Response
4	Race/Ethnicity:	Freeform Response
5	Study design:	• Cohort
6	Period of recruitment:	Freeform Response
7	Average follow-up (cohort studies):	Freeform Response
8	Sample size (For cohort studies: # cases/final cohort size):	Freeform Response
9	Source of participants (community, hospital/institution, population-based):	Freeform Response
10	Age (mean age or range):	Freeform Response
11	Inclusion/Exclusion Criteria:	Freeform Response
12	Response rate (%):	Freeform Response
13	Method for exposure ascertainment (ex. serum levels, self-report):	Freeform Response
14	Outcome under study (ex. Birth Trauma, etc.):	Freeform Response
15	Study limitations:	Freeform Response
16	General Conclusions:	Freeform Response
17	Risk factor under study:	Freeform Response
18	Categorization of the exposure (ex. Quartile 1 vs. Quartile 4, Exposed vs. Unexposed, 250 mg vs. 0 mg, Former vs. Current smokers, Yes vs. No):	Freeform Response
18	Confounding Adjustment (variables):	Freeform Response
19	Risk estimate(s) and 95% confidence interval and/or p-value (for each comparison):	Freeform Response

Table 5B9. Risk Factors for Progression, Systematic Reviews, Meta-Analysis and Observational Studies: Level One Title and Abstract Screening Questionnaire

	Question	Responses
1	Is this article related to risk factors for the natural progression of epilepsy?	• Yes • No • Can't Tell
2	What study design was used?	• Systematic Review • Meta-Analysis • Case-control • Cohort • Genetic Association • None of the Above

		• Can't Tell
3	Does the study include data on human participants?	• Yes • No • Can't Tell
4	In which language is this article written?	• English • French • Other • Can't Tell

Table 5B10. Risk Factors for Progression, Systematic Reviews, Meta-Analysis and Observational Studies: Level Two Full Article Screening Questionnaire

	Question	Responses
1	Was this article unable to be retrieved?	• Yes • Not Applicable
2	Is this article related to risk factors for the natural progression of epilepsy?	• Yes • No
3	What study design was used?	• Systematic Review • Meta-Analysis • Case-control • Cohort • None of the Above
4	Does the study include data on human participants?	• Yes • No • Can't Tell
5	In which language is this article written?	• English • French • Other
6	Was an estimate of risk provided?	• Yes • No

Table 5B11. Risk Factors for Progression, Systematic Reviews and Meta-Analysis and Observational Studies: Level Four Data Extraction Tool (Case-Control)

	Criteria	Response
1	Author, year of publication	Freeform Response
2	Study Design	Freeform Response
3	Does this article provide an estimate of risk for Epilepsy (i.e., RR, OR, risk ratio, etc.)?	Freeform Response
4	Location of the study (City, Country):	Freeform Response
5	Race/Ethnicity:	Freeform Response
6	Period of recruitment:	Freeform Response
7	Sample size: For case-control studies: # cases/controls.	Freeform Response

8	Source of participants	Freeform Response
9	Age (mean or range)	Freeform Response
10	Sex	Freeform Response
11	Inclusion / Exclusion Criteria	Freeform Response
12	Response rate (%):	Freeform Response
13	Method for exposure ascertainment (ex. serum levels, self-report, phone interview, questionnaire):	Freeform Response
14	Categorization of the exposure	Freeform Response
15	Outcome under study (ex. Glioma, Meningioma, etc.):	Freeform Response
16	Outcome ascertainment/Case Definition (DSM, NINCDS-ADRDA, ICD-10, etc.):	Freeform Response
17	Risk estimate(s) and 95% confidence interval and/or p-value (for each comparison):	Freeform Response
18	Confounding Adjustment (variables):	Freeform Response
19	Limitations of the study:	Freeform Response
20	General Conclusion:	Freeform Response
21	Quality Score:	Freeform Response

Table 5B12. Risk Factors for Progression, Systematic Reviews and Meta-Analysis and Observational Studies: Level Four Data Extraction Tool (Cohort)

	Criteria	Response
1	Author, year of publication:	Freeform Response
2	Study Design:	Freeform Response
3	Does this article provide an estimate of risk for Epilepsy (i.e., RR, OR, risk ratio, etc.)?	Freeform Response
4	Location of the study (City, Country):	Freeform Response
5	Race/Ethnicity:	Freeform Response
6	Period of recruitment:	Freeform Response
7	Sample size: For cohort studies: (# cases/final cohort size)	Freeform Response
8	Source of participants:	Freeform Response
9	Mean/Median length of follow-up:	Freeform Response
10	Age (mean or range):	Freeform Response
11	Sex:	Freeform Response
12	Inclusion / Exclusion Criteria:	Freeform Response
13	Response rate (%):	Freeform Response
14	Risk factor under study:	
15	Method for exposure ascertainment (ex. serum levels, self-report, phone interview, questionnaire):	Freeform Response
16	Categorization of the exposure:	Freeform Response
17	Outcome under study (ex. Glioma, Meningioma, etc.):	Freeform Response
18	Outcome ascertainment/Case Definition (DSM, NINCDS-ADRDA, ICD-10, etc.):	Freeform Response

19	Risk estimate(s) and 95% confidence interval and/or p-value (for each comparison):	Freeform Response
20	Confounding Adjustment (variables):	Freeform Response
21	Limitations of the study:	Freeform Response
22	General Conclusion:	Freeform Response
23	Quality Score:	

Appendix C

Table 5C1. Quality Assessment Screening using the AMSTAR tool: Systematic Reviews and Meta-Analyses

	*Nurmoh-amed, 2010 (Nurmohamed et al., 2010, 1882-1885)	*Kauffman, 2010 (Kauffman et al., 2010, 234-239)	Samokh-valov, 2010(Samokhvalov, Irving, and Rehm 2010, 1177-1184)	Quet, 2010(Quet et al., 2010, 830-837)	*Kauffman, 2008(Kauffman, Consalvo, and Kochen 2008, 135-140)	*Kauffman, 2008(Kauffman et al., 2008, 83-88)	Lionetti, 2010(Lionetti et al., 2010, S347)	Druet-Cabanac, 2004(Druet-Cabanac et al., 2004, 144-149)
Was an 'a priori' design provided?	Can't Answer	Can't Answer	Yes	Yes	Yes	Can't Answer	Yes	Yes
Was there duplicate study selection and data extraction?	Yes	Yes	No	No	Yes	Yes	Yes	Yes
Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Was the status of publication (i.e. grey literature) used as an inclusion criterion?	No	Yes	Yes	Yes	No	Yes	No	Yes
Was a list of studies (included and excluded) provided?	No	No	No	No	No	No	No	No
Were the characteristics of the included studies provided?	No	No	Yes	Yes	No	Yes	Yes	Yes
Was the scientific quality of the included studies	No	Yes	Yes	Yes	No	Yes	Yes	Yes

assessed and documented?								
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Can't Answer	Can't Answer	Yes	Yes	No	Yes	Can't Answer	Yes
Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Can't Answer	Yes
Was the likelihood of publication bias assessed?	Yes	Yes	Yes	No	Yes	No	No	Yes
Was the conflict of interest included?	Yes	No	No	No	No	Yes	No	No
Overall AMSTAR quality score: low (0-3), moderate (4-7) high (8-11)	5	6	8	7	4	8	4	9

Appendix D

Table 5D1. Description of Studies that Examine Biological (Perinatal) Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CIs)	Conclusion
Asadi-Pooya et al., 2005	Case-control Cases: 142; controls: 138	Childhood epilepsy	History of prematurity, history of admission in neonatal ICU, history of neonatal complications, history of vaginal delivery, caesarean section, history of formula consumption, history of breastfeeding, history of passive smoke exposure, history of neonatal jaundice, family history of epilepsy	Where defined: Exposed: family history: first degree, second degree, other relative Unexposed: Family history: none	Unadjusted: History of prematurity: OR=1.56(0.5-4.9); history of admission in neonatal ICU: OR=0.72(0.16-3.3); history of neonatal complications: OR=1.89(0.73-4.9); history of vaginal delivery: OR=1.84 (1.07-3.17); caesarean section: OR=0.54 (0.31-0.94); history of formula consumption: OR=0.82 (0.46-1.44); history of breastfeeding: OR=0.5 (0.19-1.3); history of passive smoke exposure: OR=1.44 (0.89-2.32); history of neonatal jaundice: OR=1.42 (0.7-1.84); family history of epilepsy (overall): OR=3.34 (1.95-5.73); family history of epilepsy (first degree): OR=3.5 (1.39-4.0); family history of epilepsy (second degree): OR= 4.2 (1.31-13.5); family history of epilepsy (other relation): OR= 3.1 (1.59-5.91)	This study demonstrated that a positive family history of epilepsy (regardless of the degree of relation) and vaginal delivery were risk factors for developing epilepsy in childhood.

Cansu et al., 2007	Case-control Cases: 805; controls: 846	Childhood epilepsy in Turkey	Sex, abnormal neurological signs, febrile seizures, head trauma, CNS infection, epilepsy in family, pre- and perinatal risks (hypertension, infection during pregnancy, Apgar ≤6 at any time, neonatal jaundice) and/or newborn jaundice	Exposed: Sex: Male; abnormal neurological signs: present; febrile seizures: present, head trauma: present; CNS infection: present; epilepsy in family: present; pre- and perinatal risk and/or newborn jaundice: present Unexposed: Sex: female; other risks: absent	Adjusted: Sex (male): OR=1.26 (0.996-1.593); abnormal neurological signs: OR=30.26 (13.905-65.834); febrile seizures: OR=8.52 (5.247-13.842); head trauma: OR=9.17 (4.501-2420.74); CNS infection: OR=2.6 (1.020-6.677); epilepsy in family: OR=4.75 (3.267-6.906); pre- and perinatal risk and/or newborn jaundice: OR=4.21 (2.708-6.534) Note: not all results were published	Children in this study were more likely to develop epilepsy if they had abnormal neurological signs, a history of febrile seizures, experienced head trauma or CNS infections, a family history of epilepsy or they had a pre- and perinatal risk and/or newborn jaundice.
Chin et al., 2012	Cohort Case: 563; final cohort size: 107,408	Childhood epilepsy	Antenatal risk factors: maternal smoking during pregnancy; premature birth, Apgar score, maternal history of epilepsy, paternal history of epilepsy, paternal education, parental age, low intake of omega-3 or omega-6 fatty acid, breastfeeding	Where defined: Exposed: Premature birth: 32-36 wks; 23-31 wks; Apgar ≤3; paternal education: > 16 years Unexposed: not defined	Adjusted: maternal smoking during pregnancy OR=1.5 (1.1-2.0); premature birth (32-36 wks) OR=1.6 (1.2-2.2); premature birth (23-31 wks): OR=3.0 (1.9- 4.8); Apgar score(<=3): OR=2.4 (1.3-4.5); maternal history of epilepsy OR=3.5(2.1-5.8); paternal history of epilepsy: OR=3.8 (2.1-6.5); paternal education (> 16 years): OR=0.6 (0.4-0.8) Non significant risk estimates not published	After adjusting for socioeconomic variables, children were at a greater risk of developing epilepsy if their mother smoked during pregnancy, if they experienced a premature birth less than 37 weeks, if their Apgar score at birth was less than or equal to three or if either parent had a history of epilepsy.

						Paternal education of greater than 16 years was found to have a protective effect on epilepsy risk.
Cooper et al., 2012	Cohort Cases: epilepsy diagnosis between ages 1-5 (N =1,282) and between ages 6-10 (N =766); final cohort size: 619,001	Epilepsy in children aged 1-5 and 6-10 years.	Restricted fetal growth measured using proportion of optimal birth weight (POBW)	Exposed: POBW <0.75 Unexposed: not defined	Adjusted: For epilepsy diagnosis between 1 and 5 years HR=2.22 (1.65-2.99); for epilepsy diagnosis between 6 and 10 years HR= 1.18 (0.73-1.91)	Restricted fetal growth, as measured using POBW, is an independent risk factor for epilepsy in children between the ages of one and five after adjusting for gestational age, birth weight and other prenatal risk factors.
Crump et al., 2011	Cohort Cases: 27,953; final cohort size: 630,090	Epilepsy in adults aged 25-37 years	Preterm birth	Exposed: preterm birth (23–31 wks; 32-34 wks; 35-36 wks) Unexposed: full term birth (37-42 weeks)	Adjusted: 1) preterm birth (23–31 wks) OR=4.98 (2.87-8.62); preterm birth (32-34 wks) OR=1.98 (1.26-3.13); preterm birth (35-36 wks) OR= 1.76 (1.30-2.38)	This study demonstrates that preterm birth at any point prior to 37 weeks is a risk factor for epilepsy in adults between the ages of 25 and 37 years.
Deepa et al., 2011	Case-control	Childhood epilepsy	1) Maternal factors, including: history	Not specified.	1) Maternal factors, including: history of abnormal delivery,	Various maternal and child-related

	Cases: 30, controls: 60	(children under five years)	of abnormal delivery, prolonged labour, preeclampsia, family history of seizure disorders; 2) child-related factors, including: birth asphyxia, mental retardation, cerebral palsy, childhood accident, history of febrile convulsion; 3) additional factors: brain haemorrhage, agenesis of corpus callosum, premature rupture of membrane, and polyhydramnios		OR = 11; prolonged labour, OR = 10.5; preeclampsia, OR = 9.1; family history of seizure disorders, OR = 7.3; 2) child-related factors, including: birth asphyxia, OR = 38.0; mental retardation, OR = 21.0; cerebral palsy, OR = 12.7; childhood accident, OR = 11.8; history of febrile convulsion; OR = 9.1; 3) brain haemorrhage, agenesis of corpus callosum, premature rupture of membrane, and polyhydramnios were stated as being risk factors; however, no risk estimates were provided. *Note: No confidence intervals or p-values were provided; thus, statistical significance cannot be ascertained	factors may increase the risk of epilepsy in children under five years of age. However, the absence of statistically relevant values prevents objective interpretation of the data provided.
Garcias Da Silva et al., 2004	Cohort Cases: not stated; final cohort size: 158 patients with neonatal seizures	Postnatal epilepsy	Abnormal neurologic examination; abnormal polysomnography	Exposed: abnormal Unexposed: normal	Unadjusted: abnormal neurologic examination OR=10.35 (2.33-45.89); abnormal polysomnography OR=3.35 (0.82-13.56)	In patients who experience neonatal seizures, an abnormal neurological examination on discharge significantly increases the risk of postnatal epilepsy. An abnormal

						polysomnographic recording appears to be associated with postnatal epilepsy; however, the risk estimate did not reach statistical significance.
Ehrenstein et al., 2006	Cohort Cases: 2,805 (varies by subgroup); total cohort size: 277,435	Childhood epilepsy (first 12 years of life)	Gestational age, mode of delivery	Gestational age categories (weeks completed): 39-41 (referent), 42, ≥43; risk calculated for first year of life and for first 12 years of life; mode of delivery categorized as: unassisted vaginal (referent), vacuum/forceps assisted, caesarean section	First 12 years of life: 1) Gestational age 42 weeks: Crude IRR: 1.1 (1.0-1.3); 2) ≥43 weeks: IRR = 1.3 (1.0-1.7). First year of life: 1) Gestational age 42 weeks: Crude IRR: 1.2 (1.0-1.5); 2) ≥43 weeks: IRR = 1.9 (1.1-3.2). Risk in first year of life, stratified by mode of delivery: unassisted vaginal, 39-41 weeks (referent); 42 weeks: adjusted IRR = 1.3 (1.0-1.7); ≥43 weeks: adjusted IRR = 1.3 (0.6-2.6); Vacuum/forceps: 39-41 weeks: adjusted IRR = 1.1 (0.8-1.5); 42 weeks: adjusted IRR = 1.3 (0.7-2.4); ≥43 weeks: adjusted IRR = 2.9 (0.7-7.7); caesarean section at 39-41 weeks: adjusted IRR = 1.3 (1.0-1.8); at 42 weeks, adjusted IRR = 1.4 (0.7-2.6); at ≥43 weeks: adjusted IRR = 4.9 (1.7-10.7)	Postterm delivery is a significant risk factor for childhood epilepsy. Risk associated with postterm birth is increased further by instrument-assisted delivery and by caesarean section delivery, but the reason for this increased risk is unclear.

Eriksso et al., 2012	Cohort Cases: not stated; final cohort size 11,873	Childhood epilepsy	Antenatal corticosteroids, stratified by sex	Exposed: antenatal corticosteroids Unexposed: no antenatal corticosteroids	Unadjusted: antenatal corticosteroids (male): OR=0.94 (0.45-1.95); antenatal corticosteroids (female): OR=0.77 (0.29-2.05)	Antenatal corticosteroid use was not found to be a risk factor for the development of epilepsy.
Glass et al., 2011	Cohort Cases: 13; final cohort size: 129 patients with neonatal encephalopathy	Epilepsy in children with neonatal encephalopathy	Sex, delivery method, 5-minute Apgar score, degree of encephalopathy, therapeutic hypothermia, neonatal seizures, MRI injury	Where define: Exposed: Sex: male; delivery method: caesarean section; 5-minute Apgar score: 4-5, 0-3; degree of encephalopathy: severe; therapeutic encephalopathy: treated; neonatal seizures: EEG confirmed seizures, status epilepticus; MRI injury: severe/near total Unexposed: Sex: female; delivery method: vaginal delivery; 5 minute Apgar score: ≥6; degree of encephalopathy: moderate; therapeutic encephalopathy: not treated; neonatal seizures: clinical only;	Significant findings only: Unadjusted: degree of encephalopathy (severe): HR=10.7 (1.4-82.7), neonatal seizures (status epilepticus): HR=35.8 (6.5-196.5); MRI injury (severe/near total): HR=5.5 (1.8-16.8) For all other risk estimates see a the results table in the original article.	Children with neonatal encephalopathy are more likely to develop epilepsy if they have a severe encephalopathy, if they experienced neonatal status epilepticus, or if their MRI injury report was severe or near total.

				MRI injury: mild/moderate		
Humphreys et al., 2007	Cohort Cases: 40; final cohort size: 154 children with periventricular leukomalacia	Epilepsy in children	Periventricular leukomalacia grade, motor disability, cortical visual impairment, ambulation, cognitive ability, preterm delivery and neonatal seizures	See the results in the original article.	Significant findings only: Adjusted: neonatal seizures OR=5.1 (1.4-17.7) For all other risk estimates the results in the original article.	Neonatal seizures in children with periventricular leukomalacia is an independent risk factor for the onset of epilepsy.
Kannoth et al., 2009	Case-Control Cases: 362; controls: 362	Epilepsy in Kerala, India	Family history of epilepsy, maternal age ≥30, previous still birth, complicated delivery, prematurity, perinatal distress, neonatal seizures, febrile seizures, mental retardation, incomplete immunization.	Where defined: Exposed: Family history of epilepsy: first or second degree relatives; complicated delivery: >12 hours of labour or assisted by forceps or vacuum extraction; prematurity: gestational age < 37 weeks; febrile seizures: between 3 months and 6 years of age	Adjusted: Family history of epilepsy: OR=7.79 (3.23-18.82); maternal age ≥30: OR=2.45 (1.57-3.84); still birth: OR=2.06 (1.10-3.87); complicated delivery: OR=6.80 (2.12-21.77); prematurity: OR=2.74 (1.66-4.53); perinatal distress: OR=2.43 (1.46-4.02); neonatal seizures: OR=7.82 (1.73-35.36); febrile seizures: OR=7.74 (4.29-13.96); mental retardation: OR=3.58 (1.31-9.77); incomplete immunization: OR=1.71(1.17-2.51) Note: only significant findings reported	This study showed that for the Kerala population, significant risk factors for epilepsy are a family history of epilepsy, maternal age ≥30, previous still birth, complicated delivery, prematurity, perinatal distress, neonatal seizures, febrile seizures, mental retardation and incomplete immunization.
Mann et al., 2011	Cohort	Childhood epilepsy	Maternal preeclampsia	Exposed: maternal preeclampsia	Adjusted: OR = 1.46 (1.17-1.82)	Preeclampsia leads to a 1.5 fold

	Cases: 1,106; final cohort size: 95,450			Unexposed: no maternal preeclampsia		increased risk of childhood epilepsy.
Masri et al., 2008	Case-Control Cases: 55; controls: 111	Epilepsy in infants	Abnormal antenatal history, abnormal birth history, delivery type, birth weight, family history factors (epilepsy, febrile convulsion, global delay, neonatal or early sibling death, parental consanguinity)	Where defined: Exposed: abnormal birth history: prematurity; delivery type: caesarean delivery; birth weight: >4 or < 2.5 kg	Unadjusted: Abnormal antenatal history: OR=1.867 (0.876-3.979); abnormal birth history: OR=1.997 (0.690-4.588); delivery type: OR=1.270 (0.569-2.833); birth weight: OR=2.333 (0.998-5.456); family history of epilepsy: OR=3.126 (1.272-7.686); family history of febrile convulsion: OR=0.455 (0.161-1.286); family history of global delay: OR=5.282 (2.094-13.324); family history of neonatal or early sibling death: OR=1.211 (0.531-2.762); parental consanguinity: OR=3.397 (1.732-6.663)	This study demonstrated that infants are at a higher risk for developing epilepsy if they have a family history of epilepsy, a family history of global delay or parental consanguinity was present.
McDermott et al., 2009	Cohort Cases: 2,185; final cohort size: 135,347 of mother and child pairs	Epilepsy in children	Genitourinary (GU) infection during pregnancy in mothers with and without epilepsy	Exposed: maternal epilepsy with a GU infection Unexposed: maternal epilepsy without GU infection Exposed: GU infection (no maternal epilepsy)	Adjusted: GU infection in mothers with epilepsy: HR = 3.74 (1.67-8.40) GU infection in mothers without epilepsy: HR=1.23 (1.12-1.34)	Children born to mothers with epilepsy who experience a GU infection during pregnancy are at a significantly increased risk of developing epilepsy. For children born to

				Unexposed: no GU infection (no maternal epilepsy)		mothers without epilepsy but who experience a GU infection during pregnancy there is a weaker, yet still significantly increased risk.
Monetti et al., 1995	Case-Control Cases: 55 patients with idiopathic generalized seizures; controls: 165	Idiopathic generalized epilepsy	A total of 27 prenatal, perinatal, and other risk factors were examined. For a complete list refer to the original paper.	For categorization of exposure please refer to the original article.	Significant findings only: Unadjusted: previous parity of 2: OR=3.16(1.45-6.9); previous parity ≥3: OR=7.11(2.1-25.39); maternal age >35: OR=2.83 (1.05-7.61); continue manual labour: OR=2.47 (1.31-4.61); previous febrile convulsions OR=13.5 (3.28-42.32); family history of febrile seizures: OR=7.8 (1.74-30.46); family history of seizures: OR=5.9 (1.84-19.45) For all other risk estimates see the results table in the original article.	Study findings indicated that the following prenatal factors are associated with an increased risk of epilepsy: advanced maternal age, manual labour during pregnancy, previous parity of two or more. Other independent risk factors included history of febrile seizures and family history of seizures.
Murphy et al., 2004	Cohort Cases: not stated; final cohort size 21,441	Epilepsy in adulthood	Forceps delivery; preeclampsia, preterm birth, birth weight, multiple pregnancy, breech presentation, vaginal breech	See the original article for the results tables.	Significant findings only: Adjusted: Family history of epilepsy OR= 2.36 (1.72-3.22); Social class OR=1.14 for each decrease in Carstairs score (1.04-1.24); Male gender	The primary risk factor under review in this study, forceps delivery, did not result in an increased risk of epilepsy in

			delivery, maternal pyrexia, neonatal infection, sex, family history and social class.		OR=1.36 (1.03-1.79); Preterm birth (<37 weeks' gestation) OR=1.95 (1.19-3.19) For all other risk estimates the results tables in original article.	adulthood when compared with all other modes delivery. Significant risk factors included a family history of epilepsy, social deprivation, male gender and preterm birth.
Norgaard et al., 2009	Cohort Cases: 276, total cohort size: 72,533	Childhood epilepsy	Maternal use of antibiotics, including penicillin, urinary tract infection (UTI) antibiotic treatments, and macrolides	Exposed (separately for penicillin, UTI antibiotics, macrolides) and not exposed	1) Penicillin: adjusted rate ratios (aRR) = 1.5 (1.1-2.0); 2) UTI specific antibiotics, aRR = 1.5 (1.0-2.2); macrolides aRR = 1.1 (0.6-2.2)	Maternal use of antibiotics appears to increase the risk of epilepsy in offspring. The authors suggest that the increased risk may be due to undetermined consequences of infection rather than the specific type of infection *per se*.
Norgaard et al., 2012	Cohort Cases: 948; final cohort size 191,383	Childhood epilepsy	Maternal infection Stratification based on antibiotic, trimester, hospital diagnosis and number of antibiotic	Exposed: antibiotic prescription or hospital admission with diagnosis of infection Unexposed: no infection during pregnancy	Adjusted: OR=1.40 (1.22-1.61) See the original article for results tables on the stratification of risk factors.	Children of mothers who experienced an infection during pregnancy are at an increased risk of developing childhood epilepsy.

			prescriptions was also conducted.			
Sun et al., 2008	Cohort Cases: 646; final cohort size 90,619	Childhood epilepsy	Maternal cystitis, pyelonephritis, diarrhea, maternal cough (>1 week), vaginal yeast infection, genital herpes, venereal warts, herpes labialis Further stratification based on duration of diarrhea and age of epilepsy onset with respect to maternal cough.	Exposed or unexposed	Adjusted: Cystitis: IRR=1.42 (1.15-1.74); pyelonephritis IRR=2.32 (1.15-4.70); diarrhea: IRR=1.23 (1.03-1.47); maternal cough (epilepsy onset <1year): IRR= 1.55 (1.11-2.17); maternal cough (epilepsy onset 1-8 years): IRR= 0.91 (0.69-1.21); vaginal yeast infection (children born preterm): IRR= 2.56 (1.43-4.61); vaginal yeast infection (children born at term): IRR= 0.97 (0.78-1.20); genital herpes: IRR=1.29 (0.73-2.29); venereal warts: IRR=0.83 (0.34-2.00); herpes labialis: IRR=0.96 (0.76-1.24)	Some infections during pregnancy can cause an increased risk of epilepsy in offspring. Infections that were shown to significantly increase the risk include cystitis, pyelonephritis, diarrhea, maternal cough and vaginal yeast infections.
Sun et al., 2008b	Cohort Cases: 14,334 (varies by subgroup); total cohort size: 1,418,871	Epilepsy in first year of life, and up to 24 years	Short/long gestational age, high/low birth weight, intrauterine growth restriction (measured by a) sex-, birth-order-, and gestational-age-specific z-scores of birth weight; and b) deviation from expected birth weight estimated	1) Short gestational age: exposed (22-32 weeks) and not exposed (39-41 weeks) - compared for risk at different ages (e.g., a) first year of life; b) age 15 to 24 years); 2) long gestational age: exposed (42 weeks or more) and not exposed (39-41 weeks), compared for risk for	1) Short gestational age: a) IRR = 5.41 (4.44-6.59); b) IRR = 2.05 (1.32-3.19); 2) long gestational age: IRRs ranged from 1.00 to 1.25 and all CIs crossed 1.00 except for the fifth-to-sixth year, IRR = 1.25 (1.00-1.56); 3) IRR = 5.09 (4.34-5.96) in the first year of life and IRR = 1.73 (1.24-2.41) between ages 15-24 years; 4) NS (data not shown); 5) a) the incidence of epilepsy increased with decreasing z-score (see	The authors conclude that short gestational age, low birth weight, and intrauterine growth restriction are all associated with an increased risk of epilepsy. Within these factors, risk appears to vary by age (years).

			based on the birth weight of an older sibling	ages up to 8 years; 3) low birth weight: exposed (<2,000 g) and not exposed (3,000-3,999 g); 4) high birth weight: exposed (>4,000g) and not exposed (3,000-3,999g); 5) intrauterine growth restriction (for risk up to age 5 years only): a) z-scores categorized as: <5%, 5-9%, 10-14%, and 15+%; b) exposed (observed birth weight less than 90% of expected) and not exposed (observed birth weight between 90-109% of expected).	original article) and b) the IRRs of epilepsy tended to increase for those with increasing deviations from expected birth weight; statistically significant increase for term births only (see original article).	
Sun et al., 2010	Cohort Cases: 591; Final cohort size 65,754	Childhood epilepsy	Maternal intake of n-3 long-chain polyunsaturated fatty acids (LCPUFA) during pregnancy Stratification based on age of epilepsy onset also conducted.	Exposed: Maternal intake of LCPUFA: quintile groups (Q1, Q2, Q4, Q5) according to low to high level of intake Unexposed: Maternal LCPUFA: Q3	Adjusted: LCPUFA (Q1): IRR=1.28 (0.98-1.67); LCPUFA (Q2): IRR=1.05 (0.79-1.38); LCPUFA (Q4): IRR=1.06 (0.81-1.41); LCPUFA (Q5): IRR=1.33 (1.02-1.74); For results of stratified analysis see a reproduction of the results table in the see original article.	Children of mothers who consume a high level of LCPUFA during pregnancy have an increased risk of developing epilepsy in childhood.

	Cohort Cases: 705; final cohort size: 86,810 live born singletons	Childhood epilepsy	Fever or sauna bathing during pregnancy	Exposed or unexposed. Stratification of risk factors was conducted for fever based on the number of episodes, the level of temperature and the duration. Sauna bathing was stratified based on number of weeks exposed. See original article for complete details	Adjusted: Fever: IRR=1.01 (0.85-1.19); sauna bathing: IRR=0.73 (0.57-0.92)	This study was unable to find a significant association between maternal fever or sauna bathing and an increased risk of epilepsy in offspring.
Sun et al., 2011	Cohort Cases: 638; final cohort size: 69,750	Childhood epilepsy in first year of life and after the first year of life	Breastfeeding, exclusive breastfeeding	Exposed: breastfeeding: 1-2 months, 3-5 months, 6- 8 months, 9-12 months, ≥13 months; exclusive breastfeeding: 1 month, 2 months, 3 months, ≥4 months Unexposed: breastfeeding: <1 month; exclusive breastfeeding: <1 month	Adjusted: For epilepsy onset in the first year of life: breastfeeding: 1-2 months: IRR=0.44 (0.23-0.84); 3-5 months: IRR=0.39 (0.21-0.72); 6- 8 months: IRR=0.35 (0.17-0.71); 9-12 months: IRR=0.42 (0.12-1.50); For epilepsy onset after the first year of life: Breastfeeding: 1-2 months: IRR=1.00 (0.66-4.51); 3-5 months: IRR=0.74 (0.50-1.09); 6- 8 months: IRR=0.61 (0.42-0.88); 9-12 months: IRR=0.50 (0.32-0.77); ≥13 months: IRR=0.41 (0.24-0.71)	The study demonstrated that breastfeeding was associated with a decreased risk of epilepsy. The relationship was shown to be dose dependant with a greater reduction in the risk the longer breastfeeding continues.

					For risk estimates for exclusive breastfeeding see original article	
Whitehead et al., 2006	Cohort Cases: 648; final cohort size 124,207	Childhood epilepsy	A total of 43 prenatal, labour and delivery and neonatal risk factors were examined See the original article for results tables.	See original article for a reproduction of original results tables	Significant findings only: Adjusted: placenta abruption RR=2.3 (1.5-3.6); major anomalies RR=2.2 (1.6-3.0); CNS anomalies RR=5.7 (3.3-9.8); eclampsia RR=14.2 (3.5-57.3); infection in present pregnancy RR=1.4 (1.0-1.6); marital status (unmarried) RR=1.2 (1.0-1.7); previous low birth weight infant RR=1.5 (1.0-2.1); small for gestational age (<10th percentile) RR=1.3 (1.1-1.7); not breastfeeding RR=1.2 (1.0-1.4); CNS diseases RR=1.7 (1.1-2.6); metabolic disorders RR=1.9 (1.3-2.7); neonatal seizures RR=11.4 (7.3-18.0)	There were 12 risk factors identified, including eight prenatal and four neonatal, that showed a significant increased risk for the onset of childhood epilepsy. These included placenta abruption, major anomalies, CNS anomalies, eclampsia, infection in present pregnancy, marital status (unmarried), previous low birth weight infant, small for gestational age (<10th percentile), not breastfeeding, CNS diseases, metabolic disorders and neonatal seizures.
Wu et al., 2008	Cohort	Epilepsy	Preeclampsia (mild, severe,	Exposed or unexposed	Adjusted: mild preeclampsia IRR= 1.20 (1.11-1.30); severe	Results indicate that mild

	Cases: 20,260; final cohort size 1,537,280		unspecified); eclampsia Stratification based on gestational age and size for gestational age was also conducted		preeclampsia IRR=1.14 (0.96-1.36); unspecified preeclampsia IRR=0.95 (0.72-1.26); eclampsia IRR=1.35 (0.81-2.24) See original article for a reproduction of original results tables for the stratification of risk factors	preeclampsia is associated with an increased risk of developing epilepsy. Severe and unspecified preeclampsia and eclampsia did not demonstrate an increased risk, though sample sizes were small.
Zelnik et al., 2010	Cohort Cases: not stated; final cohort size: 197 patients with cerebral palsy (CP)	Childhood epilepsy	Type of cerebral palsy Neonatal seizures Maturity at birth Apgar score	Exposed: Quadriplegia Unexposed: other types of CP Exposed: present Unexposed: not present Exposed: Term Unexposed: prematurity Exposed: low Apgar Unexposed: high/moderate Apgar	Adjusted: quadriplegia OR=4.03 (1.91-8.45) Adjusted: neonatal seizures OR=12.55 (4.2-37.51) Term birth OR= 2.85 (1.36-5.98). Unadjusted: low Apgar score OR=4.41 (1.48-13.16)	In children with cerebral palsy, those with quadriplegia, neonatal seizures, term births and low Apgar scores have an increased risk of developing epilepsy.

Appendix E

Table 5E1. Description of Studies that Examine Biological (Infectious) Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates	Conclusion
Bearden et al., 2012	Nested case-control Not stated	Epilepsy in children with HIV/AIDS	World Health Organization (WHO) stage 4, history of HIV encephalopathy, history of CNS infection	Not defined	Unadjusted: WHO stage 4: OR=3.1 (p=0.02), history of HIV encephalopathy: OR=11.6 (p<0.02); history of CNS infection: OR=12.6 (p<0.001)	This study showed that children with HIV/AIDS have an increased risk of developing epilepsy if they had advanced stage HIV/AIDS, had a history of HIV encephalopathy, or had a history of CNS infection.
Birbeck et al., 2010	Cohort Cases: 12, total cohort size: 396	Epilepsy in children who are survivors of retinopathy-positive cerebral malaria	Retinopathy-positive cerebral malaria, with and without acute seizures	Exposed (malaria) and not exposed (no malaria)	OR = undefined, p = 0.0001 (not able to calculate OR because no subjects in the comparison group developed epilepsy). For malaria survivors with acute seizures, OR = 6.37 (95% CI: 1.02-141.2).	Retinopathy-positive malaria appears to be a risk factor for epilepsy in children, particularly those with acute seizures.
Kaiser et al., 2011	Case-Control Cases: 38;	Epilepsy	Onchocerciasis Volvulus; palpations for Onchocerciasis Volvulus nodules	Exposed: positive for onchocerciasis Unexposed: negative for onchocerciasis	Adjusted: Onchocerciasis Volvulus: OR = 1.68 (0.60-4.57); nodule palpation: OR=2.77 (0.92-8.33)	Infection with the parasite onchocerciasis was not found to be significantly associated with the onset of epilepsy.

	controls: 38					
Nicoletti et al., 2007	Case-Control Cases: 191; controls: 191	Epilepsy in a Burundi population	Toxocara canis, cycticercosis, sex, religion, occupation, family history of epilepsy, marital status, indoor toilets	Where defined: Exposed: Toxocara canis (seropositive); cycticercosis (seropositive); sex: male, religion: non-Christian; occupation: non-farmer, not active; marital status: widowed, living alone, living with relatives Unexposed: Toxocara canis (seronegative); cycticercosis (seronegative); sex: female, religion: Christian; occupation: farmer; marital status: married	Adjusted: Toxocara canis: OR=2.13 (1.18-3.83); cycticercosis: OR=3.71 (1.90-7.24); religion: OR=5.7 (1.77-18.4); occupation (non-farmer): 0.13 (0.02-0.66); occupation (not active): 10.5 (2.14-51.8); family history of epilepsy: 3.05 (1.74-5.35).	This study found that Toxoccara canis and cycticerosis infections are risk factors for the development of epilepsy. Other independent risk factors identified included being part of a non-Christian religion and working as a farmer or having no active employment.
Nicoletti et al., 2008	Case-Control Cases: 231; control: 201	Epilepsy in an Italian population	Toxocara canis, sex, education, occupation, residence, presence of dogs in the home, history of	Where defined: Exposed: Toxocara canis: seropositive; sex: male	Adjusted: Toxocara canis: OR=3.90 (1.91-7.98); sex: OR=1.52 (1.02-2.28); age (years): OR=0.99 (0.97-1.00); history of pica: OR=0.32 (0.19-0.55); family history OR=3.05 (1.74-5.35)	This study found that infection with Toxocara canis is an independent risk factor for the development of epilepsy. Other independent risk factors identified

	helminthiasis, history of pica	Unexposed: Toxocara canis: seronegative; sex: female	Only significant risk estimates were published	included being male and having a history of pica.

Appendix F

Table 5F1. Description of Studies that Examine Biological (Febrile Seizures) Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CI)	Conclusion
MacDonald et al., 1999	Cohort Cases: 220; final cohort size 1,195 with febrile convulsions	Childhood epilepsy	Febrile convulsion Stratification based on sex, age at first febrile seizure, neurological abnormality prior to first febrile seizure, type of first febrile seizure	Exposed: Sex: female; Age at first febrile seizure: >18 months, > 3 years; first febrile seizure: complex Unexposed: Sex: male; Age at first febrile seizure: <18 months, <3 years; first febrile seizure: partial	Unadjusted: Sex (female): HR=1.49 (0.48-4.62); Age at first febrile seizure (>18 months): HR=0.82 (0.26-2.54); age at first febrile seizure (>3 years): HR=0.52 (0.07-4.01); neurological abnormality prior to first febrile seizure: HR=3.48 (0.45-27.0); first seizure (complex): HR=0.82 (0.18-3.75)	This study did not identify any significant risk factors for epilepsy in a population of children who had experienced febrile seizures.
Sapir et al., 2000	Cohort Cases: 13; final cohort size: 47 patients with complex febrile convulsions	Childhood epilepsy	Prolonged seizures, partial seizures or multiple seizures occurring in the same day relative to the each other	Exposed: Partial febrile convulsions Unexposed: multiple seizures	Unadjusted: Partial febrile convulsions OR= 3.19 (0.72-14.15) Other subgroups were too small for statistical analysis	There was insufficient evidence to suggest that any particular subgroup of complex febrile convulsion sub-types puts a child at an increased risk of epilepsy compared to the other sub-types.
Vestergaard et al., 2007	Cohort Case: 14,332 final	Long term risk of epilepsy	Febrile seizure (sub-group analysis: febrile seizures in siblings, epilepsy in parents	Exposed: experienced a febrile seizure Unexposed: no febrile seizure	Adjusted: Rate Ratio = 5.43 (5.19-5.69)	Febrile seizures significantly increased a child's long-term risk of developing epilepsy. The risk was higher for

	cohort size 1,540,725	or siblings, epilepsy after febrile seizure in the same sibling, cerebral palsy, Apgar score at 5 minutes, birth weight and gestational age)	For results of subgroup analysis see the results tables the original article.	the entire follow-up period but was particularly high for the period shortly after the febrile seizure.

Appendix G

Table 5G1. Description of Studies that Examine Biological (Trauma) Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CI)	Conclusion
Bladin et al., 2000	Cohort Cases: 168, total cohort size: 1,897 patients with stroke	Seizures (including recurrent seizures, i.e., epilepsy) after stroke, in adults	Ischemic stroke: age, late-onset seizures, cortical location, moderate disability, severe disability, hemorrhagic infarction, high-risk embolic stroke, infarct size; hemorrhagic stroke: cisternal blood, ventricular blood, hemorrhage size, age, late-onset seizures, cortical location, moderate disability, severe disability	See original article.	For recurrent seizures (epilepsy): Late onset of first seizure after ischemic stroke, HR = 12.37 (4.74-32.32), after haemorrhagic stroke, HR = 3.38 (0.58-19.54). All other comparisons NS. See Tables 2 and 3 of paper in see original article.	Late onset seizures following stroke increase a patient's risk of epilepsy.

Christensen et al., 2009	Cohort Cases: 17,470; final cohort size 1,605,216	Epilepsy in children and young adults	Traumatic brain injury (mild, severe brain injury, and skull fracture) Stratification based on time since injury, age at injury, length of hospital stay and family history of epilepsy	Exposed: Traumatic brain injury Unexposed: No brain injury	Adjusted: mild brain injury RR=2.22 (2.07-2.38); severe brain injury RR=7.40 (6.16-8.89); skull fracture RR=2.17 (1.73-2.71) See original article for results tables for the stratification of risk factors	Traumatic brain injury, of any severity, significantly increases a person's risk of developing epilepsy.
Ferguson et al., 2010	Cohort Cases: 115; final cohort size: 1,961 patients with traumatic brain injury (TBI)	Posttraumatic epilepsy within 3 years of a traumatic brain injury	Age, sex, severity of injury, posttraumatic seizure prior to discharge, etiology of injury, number of concomitant injuries, number of comorbid conditions, previously knocked-out, history of stroke, history of depression	See original article results tables	Significant findings only: Adjusted: Severe TBI: RR=2.54 (1.46-4.42); posttraumatic seizure prior to discharge: RR=5.82(3.41-9.92); 3 or more comorbid conditions: RR=2.91(1.46-5.81); history of depression: RR=1.85(1.16-2.94) For all other risk estimates see results table in the original article.	Traumatic brain injury is a risk factor for epilepsy.

Fitzgerald et al., 2007	Cohort Cases: 17, total cohort size: 45	Epilepsy in children following neonatal infarction	Initial presentation with 1) seizures and 2) infantile spasms, following neonatal infarction.	1) Exposed (seizure) or not exposed (no seizure); 2) exposed (infantile spasm) or not exposed (no infantile spasm)	Initial presentation with seizures, RR = 3.2 (2.0-4.9); infantile spasms, RR = 3.2 (2.0-4.9)	In children who have suffered perinatal stoke, seizures and infantile spasms are both significant risk factors for the development of epilepsy.
Lossius et al., 2005	Cohort Cases: 15, total cohort: 484 patients with ischemic stroke	Epilepsy following ischemic stroke in adults 60 years and older	Severity of ischemic stroke in the elderly	Exposed: Scandinavian Stroke Scale (SSS) - a measure of neurological impairment - score <30) and not exposed (SSS score ≥30)	SSS score <30, OR = 4.9 (p = 0.004)	SSS scores less than 30 significantly predict post-stroke epilepsy in the elderly.
Menzler et al., 2010	Cohort Cases: 6, total cohort size: 109 patients with cavernomas (surgically confirmed)	Epilepsy following supratentorial cavernomas (a common type of vascular malformation of the brain)	Clinical risk factors, including: age, sex, side, cortical involvement, mesiotemporal archicortical versus neocortical involvement, lobar location of neocortical cavernomas, the	Age (actual values), sex (male/female), side (left/right), cortical involvement (yes/no), neocortical or mesiotemporal archicortical, lobar location of neocortical cavernomas (temporal and frontal/temporal and parieto-occipital/frontal and	Univariate analysis: No cortical involvement: OR = 0.019 (0.00015-0.15); neocortical or mesiotemporal archicortical involvement: OR = 4.3 (0.90-42); for neocortical only: temporal and frontal: OR = 4.9 (0.17-1.4), temporal and parieto-occipital: OR = 0.26 (0.059-1.0), frontal and parieto-occipital: OR = 0.53 (0.13-2.0); side: OR = 0.45 (0.20-1.0); for hemosiderin: presence: OR = 0.85 (0.24-2.9), diameter: OR = 1.1 (0.96-1.2); size: OR = 1.04 (0.99-1.09); for edema: presence: OR = 0.44 (0.17-	Cortical involvement is a significant risk factor for epilepsy in patients with cavernomas. Other factors that increase the risk of epilepsy with cavernas include: involvement of mesiotemporal archicortex, larger size cavernoma,

	presence of a hemosiderin rim and of edema, and the maximal diameters of cavernoma, hemosiderin rim, and edema (if present), number of cavernomas	parieto-occipital), hemosiderin rim (present/absent), edema (present/absent), maximal diameters of cavernomas, hemosiderin rim, and edema (actual values), number of cavernomas (one/multiple)	1.1), size: OR = 1.0 (0.98-1.1), age (OR not reported, p=.46), sex (OR not reported, p = .69). Multivariate analysis: no cortical involvement: OR = 0.024 (0.00-0.20); mesiotemporal archicortical cavernomas: OR = 6.7 (1.3-68); size: OR = 1.07 (1.01-1.13); edema: OR = 0.24 (0.057-0.85); side: OR = 0.26 (0.09-0.69).	absence of edema, and left hemisphere involvement.

Appendix H

Table 5H1. Description of Studies that Examine Other Biological Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CI)	Conclusion
Ali et al., 2010	Cohort Cases: 12; final cohort size: 543 patients with sickle cell disease (SCD)	Epilepsy in patients with sickle cell disease	Hematology findings, sex, dactylitis at age ≤ 1 year, acute, splenic sequestration	Not defined	Significant findings only Unadjusted: Hematology findings: higher mean corpuscular volume: OR=0.93 (0.85-1.00); female sex: OR=0.2 (0.05-0.97); dactylitis at age ≤ 1 year: OR=17.4 (4.82-62.85) For all other risk estimates original article.	Patients with sickle cell disease have a higher incidence of epilepsy than the general population, significant risk factors for sickle cell patients identified in this study include a lower mean corpuscular volume, being male and having a diagnosis of dactylitis at or before one year of age.
Daoud et al., 2003	Case-Control Cases: 200; controls: 200	Childhood epilepsy in Jordan	History of febrile convulsions, history of head injury, history in CNS infection, abnormal perinatal history, parental consanguinity, family history of epilepsy	Where defined: Exposed: parental consanguinity: first cousin marriage, other relation; family history of epilepsy: first degree relative, second degree relative, other relations	Unadjusted: History of febrile convulsions: OR=5.1 (2.7-9.8); history of head injury: OR=4.6 (1.2-16.2); history in CNS infection: OR=1.3 (0.5-3.2); abnormal perinatal history: OR=3.2 (1.7-6.1); parental consanguinity (first cousin marriage): OR=1.3 (0.9-2.1); parental consanguinity (other relation): OR=1.7 (0.9-3.2); family history of epilepsy (first degree relative): OR=9.8 (3.3-38.9);	This study showed that children in Jordan are more likely to develop epilepsy if they had a history of febrile convulsions, a history of head injury, an abnormal perinatal history or a positive family history of epilepsy.

				Unexposed: parental consanguinity: no relation; family history of epilepsy: no family history	family history of epilepsy (second degree relative): OR=7.2 (1.5-67.4); family history of epilepsy (other relative): OR=7.8 (1.7-72.8)	
Dworetzky et al., 2012	Cohort Cases: 151; final cohort size 114,847	Epilepsy in adults	Age at menarche, menstrual regularity at age 18, menstrual cycle length at age 18, menstrual regularity during follow up, menstrual cycle length during follow-up, oral contraceptives	Exposed: Age at menarche: < 12 years, ≥14 years; menstrual regularity at age 18: irregular; menstrual cycle length at age 18: ≤25 days, 32-39 days, ≥40 days; menstrual regularity during follow up: irregular: menstrual cycle length during follow-up: : ≤25 days, 32-39 days, ≥40 days; oral contraceptives: never, current Unexposed: Age at menarche: 12-13 years; menstrual	Significant findings only: Menstrual regularity at age 18: RR=1.67(1.12-2.51) For all other risk estimates see results table the original article.	The only reproductive risk factor identified in this study as being significantly associated with the onset of epilepsy is having an irregular menstrual cycle at age 18.

				regularity at age 18: regular; menstrual cycle length at age 18: 26-31 days; menstrual regularity during follow up: regular: menstrual cycle length during follow-up: 26-31 days; oral contraceptives: past		
Garza-Chapa et al., 1994	Cohort Cases: 1950, total cohort size: 6,586	Epilepsy in adults	Birth order and sibship size (in probands and those with unaffected siblings)	Birth order and sibship size each categorized as 1,2,3,4, or ≥ 5.	For birth order stratified by sibship size, OR's ranged from 0.8 to 1.4; all CIs crossed one, NS. See Table 2 of the original paper. For birth order ≥ 2 in probands versus unaffected siblings, the only significant comparison was for "other remote symptomatic etiology", OR = 1.5 (1.08-2.04). See Table 3 of the original paper.	There was a lack of association between birth order and risk of epilepsy in this study. However, the relationship may be confounded by sibship size. The authors conclude that it is not possible to determine whether sibship size affects risk of epilepsy versus whether those with epilepsy tend more often to be only children.
Li et al., 1997	Case-Control	Epilepsy in the elderly	Vascular determinants (stroke, total cholesterol, left ventricular	Not defined	Unadjusted: stroke: OR=3.3 (1.3-8.5); total cholesterol: OR=1.1 (0.9-1.3); left ventricular hypertrophy: OR=1.5 (0.5-4.4);	The study showed that elderly patients are more at an increased risk for developing epilepsy if they had experienced a

	Cases: 65; controls: 4,944		hypertrophy, myocardial infarction, peripheral arterial disease, any vascular determinant), head trauma, meningitis		myocardial infarction: OR=1.4 (0.5-3.5); peripheral arterial disease: OR=1.6 (0.8-3.0); any vascular determinant: OR=1.8 (1.0-3.2); head trauma: OR=2.7 (1.6-4.7); meningitis: OR=4.6 (1.1-19.7).	stroke, head trauma or meningitis.
Ludvigsson et al., 2012	Case-Control Cases: 28,885; controls: 143,166	Epilepsy	Celiac disease	Exposed: celiac disease Unexposed: no celiac disease Stratification was also done based on follow-up time in patients with epilepsy	Unadjusted: celiac disease: HR=1.42 (1.24-1.62); follow-up less than 1 year: HR=1.37 (0.88-2.11); follow-up 1-4.99 years: HR=1.55 (1.23-1.96); follow-up ≥5 years: HR=1.35 (1.13-1.62)	This study showed that celiac disease is an independent risk factor for epilepsy. This is especially true for patients who have been followed for more than 1 year.
Ludvigsson et al., 2006	Case-Control Cases: 140; controls: 280	Epilepsy in children	Migraine without aura Migraine with aura	1) Exposed: Migraine without aura Unexposed: No migraine 2) Exposed: Migraine with aura Unexposed: No migraine	1) Unadjusted: OR=1.4 (0.5-4.0) 2) Unadjusted: OR= 8.1 (2.7-24.3)	Children who experience migraines with an aura are at a significant increased risk for developing epilepsy while children with migraines without an aura are at no increased risk.

Matuja et al., 2001	Case-Control Cases: 174; controls: 174	Epilepsy in a rural area of Tanzania	Family history, febrile convulsions, neonatal intrapartum complications, CNS infections, cerebral vascular disease, head injuries, brain neoplasm	Exposed: family history: one or more first degree relatives with epilepsy; past febrile convulsion: one or more febrile seizures before the age of 6 or unexposed; intrapartum complications: prolonged labour or Apgar score < 7; CNS infection: neurological complications with fever or confirmed infection.	Unadjusted: family history of epilepsy: OR=3.52 (2.14-5.74); history of febrile convulsion: OR=2.4 (1.5-3.84); neonatal intrapartum complications: OR= 7.3 (2.15-25.2); CNS infections: OR=2.4 (CI not provided, p<0.0006); cerebral vascular disease: Not significant; head injuries: not significant; brain neoplasm (no cases)	This study showed that people living in rural Tanzania are at an increased risk for epilepsy if they have a positive family history of epilepsy, a history of febrile convulsions, a history of intrapartum complications or experienced a CNS infection.
Ngoungou et al., 2006	Case-Control Cases: 296; controls: 296	Epilepsy in individuals 6 months to 25 years	Cerebral malaria (CM) with coma alone, with coma and convulsions, with convulsions alone; sex, family history of epilepsy, history of febrile convulsions, severe, measles, meningitis, sickle cell disease.	Where defined: Exposed: Sex; male	Adjusted: CM (coma with convulsions): OR=3.9 (1.7-8.9); history of febrile convulsions (without CM): OR=9.2 (4.0-21.1); family history of epilepsy: OR=6.0 (2.6-14.1); sickle cell disease: OR=0.2 (0.1-0.6) Only risk estimates for significant findings were published.	Patients with CM who experience coma with convulsions are at an increased risk for developing epilepsy. Other independent risk factors identified include a history of febrile convulsion, a family history of epilepsy. Sickle cell disease was found to have a protective effect.

Pugh et al., 2009	Cohort Cases: 1,843; final cohort size 1,025,219 of older veterans	New onset epilepsy in older veterans	Age, sex, race, stroke and dementia, risk factors for stroke and dementia (cardiovascular disease, hypertension, peripheral vascular disease, diabetes mellitus, obesity, hypercholesterolemia, alcohol abuse, use of lipid lowering drugs)	See the original paper for the results tables.	Significant findings only: Unadjusted: age ≥ 85 (compared to 65-74): OR=0.66 (0.50-0.87); black race (versus white): OR=1.75 (1.54-1.98); dementia: OR=2.31 (1.91-2.79); stroke: OR=3.43 (3.05-3.86); stroke and dementia: OR=4.04 (3.36-4.87); brain tumor: OR=2.14 (1.46-3.13); head injury: OR=2.11 (1.41-3.14); other CNS conditions: OR= 1.57 (1.32-1.88); cardiovascular disease: OR=1.11 (1.00-1.23); obesity: OR=0.74 (0.62-0.87); alcohol abuse: OR=1.26 (1.04-1.51); use of statins: OR=0.65 (0.56-0.75). For all other risk estimates see the results table in the original article.	Several risk factors for the onset of epilepsy in older veterans were identified in this study. Risk factors that increased the risk of epilepsy included black race, dementia, stroke, stroke and dementia combined, brain tumor, head injury, other CNS conditions, cardiovascular disease and alcohol abuse. Factors that had protective effects against the development of epilepsy included age ≥ 85, obesity and use of statins.
Shoenfeld et al., 2004	Cohort Cases: 46; final cohort size: 538 with antiphosphol	Epilepsy in patients with antiphospholipid syndrome	CNS thromboembolic event, systemic lupus erythematosus (SLE), valvular vegetation	Not defined	Only significant findings were published Unadjusted: CNS thromboembolic event: OR=4.05 (2.05-8.0); SLE: OR=1.4 (1.2-4.7); valvular	Patients with antiphospholipid syndrome have an increased risk of developing epilepsy if they also have concomitant vascular

	ipid syndrome (APL)		vegetations: OR= 2.87 (1.0-8.27).	diseases including a CNS thromboembolic event, SLE, or valvular vegetations.

Appendix I

Table 5I1. Description of Studies that Examine Psychosocial Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CI)	Conclusion
Christensen et al., 2007	Cohort Cases: 382; final cohort size 314,807	Epilepsy in adulthood	Stress due to loss of a child (≤18) Stratification based on sex, time since death, age, education, residence, number of children, number of adults	Exposed: parents who lost a child ≤18 years of age Unexposed: parents who did not lose a child	Adjusted: RR = Stress in parent 1.50 (1.21-1.86) For stratified risk estimates see the results table in the original article.	Parents who suffer the loss of a child less than 18 years of age are at an increase risk for developing epilepsy.
Nilsson et al., 2003	Cohort Cases: 685 (approximate: derived from proportions stated), total cohort size: 164,277	Epilepsy in patients with a major affective disorder (MAD) aged 15 and older	MAD (includes depression, mania), with and without comorbid substance abuse	Exposed (depression, mania, and combined as MAD) and not exposed (two comparison groups: 1) osteoarthritis, 2) diabetes); includes comparisons for those with and without substance abuse	Depression versus osteoarthritis, adjusted Hazard Ratio (aHR) = 0.92 (95% CI: 0.69-1.23); depression versus diabetes, aHR = 1.02 (95% CI: 0.78-1.35); mania versus osteoarthritis, HR = 0.81 (95% CI: 0.45-1.45); mania versus diabetes, aHR = 1.08 (95% CI: 0.61-1.89); affective episode (depression and mania combined) versus osteoarthritis, aHR = 0.94 (95% CI: 0.72-	In patients with a major depressive disorder, comorbid substance abuse significantly increases the risk of epilepsy.

			1.24); affective episode versus diabetes, aHR = 1.03 (95% CI: 0.80-1.34). For depression with substance abuse versus osteoarthritis: HR = 9.01 (95% CI: 6.71-12.09); versus diabetes: HR = 5.80 (95% CI: 4.36-7.73). For mania with substance abuse versus osteoarthritis: HR = 9.89 (95% CI: 7.00-13.97); versus diabetes: HR = 5.28 (95% CI: 3.73-7.48). For affective episode with substance abuse versus osteoarthritis: HR = 8.72 (95% CI: 6.53-11.63); versus diabetes: HR = 5.78 (95% CI: 4.37-7.64)

Appendix J

Table 5J1. Description of Studies that Examine Lifestyle, Environmental and Other Risk Factors for the Onset of Epilepsy

Author, Year	Study design	Outcome	Risk factors examined	Categorization of exposure	Risk estimates (95% CI)	Conclusion
Burton et al., 2012	Case-Control Cases: 112; controls: 113	Childhood epilepsy in rural Tanzania	Ethnic group, parents' residence at home, adverse perinatal event, head injury, family history of non-febrile seizures, history of febrile seizures, poor scholastic attainment	Provided definitions: Exposed: ethnic group: not Chagga; parents residential status: one or no parents residing at home Unexposed: Parents reside at home	Significant results only: Adjusted: One parent resident at home: OR=2.8 (1.1-6.5), no parents resident at home: OR=6.2 (1.5-25.5); adverse perinatal events: OR=14.9 (1.4-151.3); head injury: OR=7.6 (0.6-97.3); family history of non-febrile seizures: OR= 5.7 (1.0-27.5); history of febrile seizures: OR=2.4 (0.8-7.0); poor scholastic attainment: OR=8.6 (3.9-18.4). See Table 4 in the original paper for complete results	This study showed that children living in rural Tanzania are at a higher risk of developing epilepsy if they have one or no parents living at home, an adverse perinatal outcome, a family history of non-febrile seizures, or poor scholastic attainment.

Dworetzky et al., 2010	Cohort Cases: 151; final cohort size: 116,363 women	Epilepsy in adult women	Cigarette smoking, caffeine intake, alcohol consumption, age, stroke, diabetes mellitus, hypertension, high cholesterol, brain tumor, brain infection, family history of seizure/epilepsy	Where defined: Exposed: age: 35-39, 40-44, 45-49, 50-56; cigarette smoking: past, current; caffeine intake (mg/day): 200-399, ≥400; alcohol consumption (g/day): 0.1-15.0, 15.1-30.0 Unexposed: age: 25-34; cigarette smoking: never; caffeine intake (mg/day): <200; alcohol consumption (g/day): 0.0	Significant findings only: Adjusted: age (40-44): RR=0.53 (0.31-0.91); age (45-49): RR=0.46 (0.24-0.86); age (50-56): RR=0.27 (0.12-0.59); stroke: RR=28.44 (17.57-46.02); brain tumor: RR=15.93 (6.93-36.62); brain infection: RR=5.43 (2.00-14.75); family history of seizure/epilepsy: RR=8.85 (5.88-13.30); past cigarette smoking RR=1.46 (1.01-2.12) For all other risk estimates see the original article.	This study demonstrated that women who were past smokers were at an increased risk for developing epilepsy. Other independent risk factors were age between 25 and 34 years, a history of stroke, brain tumor or brain infection and family history or seizure or epilepsy.
Tran et al., 2007	Case-Control Cases: 31; controls: 124	Epilepsy in Rural Lao PDR	Family history of epilepsy, history of head trauma, peripheral blood eosinophils, pork consumption, undercooked pork consumption, use of	Exposed or unexposed	Unadjusted: Family history of epilepsy: OR=12.8 (1.4-119.5); history of head trauma: OR=4.7 (1.0-21.4), peripheral blood eosinophils	This study showed that people living in rural Lao PDR are at a higher risk for developing epilepsy if they

			human feces fertilizers, latrine availability, outdoor defecation, domestic outdoor pig raising		OR=0.6 (0.2-1.7), pork consumption: OR=0.1 (0.0-0.6), undercooked pork consumption: OR=0.7 (0.3-1.7); use of human feces fertilizers: OR=4.9 (1.1-22.1), latrine availability: OR=0.4 (0.1-1.4), outdoor defecation: OR=3.9 (0.4-34.7), domestic outdoor pig raising: OR=1.2 (0.4-3.5)	had a positive family history of epilepsy, a history of head trauma or use of human feces as fertilizers. They were relatively protected from developing epilepsy if they consumed pork.
Vessey et al., 2002	Cohort Cases: 82, (includes 7 women with diagnosis of convulsions not otherwise specified); total cohort size: 17,032 white, married women aged 25-39 years	Epilepsy in adult women	Use of oral contraception, stratified by social class and body mass index (BMI)	1) Social class categorized as I-II (high, referent), III (medium), and IV-VI (low); 2) BMI categorized as <20 kg/m2 (referent), 20-21.9, 22-23.9, 24-25.9, 26-27.9, 28+; 3) oral contraception categorized as months of use in 12-month intervals: exposed (up to 12 months, 13-24, 25-48, 49-72, 73-96, 97-120, 121+ months) and not exposed (non-	1) Social Class: III (medium), Relative risk (RR) = 1.69 (1.00-2.96); IV-VI (low), RR = 2.76 (1.33-5.57); 2) BMI (kg/m2): 20-21.9, RR = 1.86 (0.79-5.07), 22-23.9, RR = 1.77 (0.73-4.91), 24-25.9, RR = 1.57 (0.54-4.86), 26-27.9, RR = 3.07 (0.97-9.95), 28+, RR = 3.52 (1.11-11.39);	Evidence suggests a lack of association between oral contraceptive use and epilepsy in adult women; however, sample size for each subcategory was small (largest N = 38). Hospital referrals for epilepsy were found to be more common in women of low

				user). Also, interval since last use (same categories as previous)	3) total duration of oral contraceptive use: RR's range from 0.41 to 1.86, all 95% CI's include one, NS; interval since last use: RR's range from 0.48 to 1.60, all 95% CI's include one, NS	social class than in other women, and a positive association between BMI and epilepsy referral was also reported.
Vaid et al., 2012	Case-Control Cases: 112; controls: 149	Epilepsy in adulthood in rural Ethiopia	Occupation (farmer/labourer, housewife, student, government/business, unemployed/not known); Education (illiteracy or read/write only, elementary, secondary/higher education); father died child < 10 years, mother died child < 10 years	Where defined: Exposed: Occupation: farmer/labourer, housewife, student, unemployed/not known; Education: illiteracy or read/write only, elementary Unexposed: Occupation: government/business; Education: secondary/higher	Significant findings only: Unadjusted: Occupation (farmer/labourer): OR=2.6 (1.2-5.6); Education (illiterate or read/write only): OR=3.0 (1.7-5.6); Education (elementary): OR=2.7 (1.3-5.5); Father died child < 10 years: OR=2.2 (1.0-4.6) For all other risk estimates see the results table in original article.	This study showed that adults living in rural Ethiopia are at an increased risk for epilepsy if they had less than or equal to an elementary education, if they worked as a farmer or labourer or if their father died before they were 10 years of age.

Appendix K

Table 5K1. Description of Studies that Examine Risk Factors for the Natural Progression of Epilepsy

Study	Study design /Study size	Outcome Included	Risk factor	Categorization of exposure	Risk estimate (95% Confidence Intervals)	General conclusion/comments
Berg et al., 2004	*Cohort* Cases: 58; cohort size: 613	Status epilepticus in children after epilepsy diagnosis	History of status epilepticus prior to epilepsy, younger age at onset, symptomatic etiology	Not defined	Adjusted: history of status epilepticus: RR= 4.49 (2.54 -7.92); symptomatic etiology: RR= 2.47 (1.44-4.23); age at onset: OR=0.91 (0.85 - 0.98)	Children with epilepsy are more likely to experience status epilepticus if they have a history of status epilepticus prior to diagnosis or they were younger when they received their epilepsy diagnosis and if they had epilepsy of symptomatic etiology.
Grabowska-Grzyb et al., 2006	*Cohort* Cases: 100; final cohort size: 203	Depression in adult (18-50 years) patients with epilepsy	Sex, etiology of epilepsy, occurrence of complex partial seizures, occurrence of generalized tonic-clonic seizures, status epilepticus or cluster seizures in the past, neuroimaging abnormalities,	Not defined	Significant findings: Unadjusted: lack of occupational activity: OR=2.89 ($p<0.004$); past hospitalizations for epilepsy: OR=2.3 ($p<0.05$), absence of generalized tonic-clonic seizures: OR=1.9 ($p<0.05$); past use	This study demonstrated that adult patients with epilepsy are at a higher risk of developing depression if they were less active professionally or educationally, had past hospitalizations for epilepsy, experienced partial seizures only,

			family history of depression and epilepsy, past hospitalizations, past or present mono- or polytherapy, present and past antiepileptic medications and occupational activity.		of clonazepam: OR=2.3 (p<0.02) Authors did not report confidence intervals.	or had a past use of clonazepam.
Kochen et al., 2005	*Cohort* Cases: 32; cohort size: 96.	Ongoing seizures	Seizure type Epilepsy syndromes Age Symptomatic epilepsy	Exposed: partial seizures Unexposed: generalized or absence seizures Exposed: partial syndromes Unexposed: generalized or absence syndromes Not defined Exposed: symptomatic epilepsy Unexposed: idiopathic or	Unadjusted: Partial seizures: OR = 6.9 (2.5-18.9); partial syndrome: OR=6.6 (2.3-18.8); age, NS: values not published; symptomatic epilepsy: OR=2.7 (1.1-6.7)	Patients with epilepsy were more likely to experience ongoing seizures if they were diagnosed with partial seizure or with a partial epilepsy syndrome or if they experienced symptomatic epilepsy.

				cryptogenic epilepsy		
Lagunju et al., 2011	*Cohort* Cases: not stated; cohort size: 116.	Seizure remission in children with newly diagnosed epilepsy	Presence of associated neurocognitive impairments; primary generalized seizure, slow waves of EEG, frequent seizures (≤1/month), first epileptic seizure in first year of life	Not defined	Adjusted: Presence of associated neurocognitive impairments: OR= 0.476 (0.130-1.745); primary generalized seizure: OR= 2.330 (0.667-8.139); slow waves on EEG: OR= 0.115 (-0.034-0.387); frequent seizures (≥1/month): OR= 0.156 (0.046-0.532); first epileptic seizure in first year of life: OR= 1.048 (0.306-3.558)	The study demonstrated that children with epilepsy who had slow waves on an EEG or their seizure frequency was greater than one per month were less likely to achieve seizure control or remission, after adjusting for co-morbidities, seizure type and frequency.
Haut et al., 2007	Cohort Cases: varied by outcome; total cohort: 71 patients with epilepsy	Seizure recurrence in adults	Stress (scale of 1 to 10), anxiety (scale of 1 to 10), hours of sleep one night prior to seizure, hours of sleep two nights prior to seizure, menses, missed medication, increase in daily	Defined categories: Exposed: stress score 3-4 (moderate), ≥ 5 (high) Unexposed: stress score 1-2	Significant findings only Unadjusted: moderate stress: OR=1.3 (1.0-1.7); high stress: OR=1.6 (1.2-2.1); moderate anxiety: OR=1.5 (1.2-1.9);	Adults with epilepsy are more likely to experience a seizure if they have a higher self-reported level of stress or anxiety, or they have had a lack of sleep over the preceding two nights.

			alcohol consumption.	Exposed: anxiety score 3-4 (moderate), ≥ 5 (high) Unexposed: anxiety score 1-2	high anxiety: OR=2.0 (1.4-2.6); hours of sleep one night prior: OR=0.91(0.86-0.96); hours of sleep two nights prior: OR=0.89 (0.81-0.97) See all other risk estimates in the original article.	
Nicoletti et al., 2009	*Cohort* Cases: remission at 2 years: 41; remission at 5 years: 31 cohort size: 71 untreated epilepsy population in rural Bolivia *Mortality* cases: 10	Epilepsy remission (2 and 5 years without seizures) Mortality	Sex, age at onset, neurocysticercosis (NCC), underlying causes, type of seizure, treatment for at least one year, treatment for at least 2 months	Exposed: Sex: men; age at onset: 20-59 years, 60+ years; neurocysticercosis (NCC): NCC present; underlying causes: known cause; type of seizure: generalized; <1 year treatment; <2 months treatment Unexposed: Sex: women; age at onset: 0-19 years; NCC: absent; underlying	Significant findings: Mortality: Age at onset (20-59 years) unadjusted OR=4.65 (1.03-21.0); age at onset (60+) unadjusted OR=22.3 (2.29-217.4); remote symptomatic epilepsy (SMR = 3.0, 95% CI 1.2–6.3), idiopathic epilepsy (with unknown cause) (SMR = 0.74; 95%CI 0.2–1.8)	An older age of epilepsy onset resulted in a higher risk of mortality compared to childhood onset. Mortality was higher for those with remote symptomatic epilepsy. No other risk factors under investigation showed a significant increased risk of remission or mortality.

cohort size: 103	causes: idiopathic; type of seizure: partial; ≥ 1 year treatment; ≥ 2 months treatment	For results tables please see the original article.

Appendix L

Table 5L1. A Summary of the Systematic Reviews and/or Meta-Analyses Assessing the Association Between Genetic Risk Factors and Epilepsy Onset or Natural Progression

First Author & Year	Study design Included	Years included	Risk Factor	Risk Estimate (95% CI)	Overall main conclusion of review
Kauffman et al., 2008a	Case-control studies	1966-2006	Transcriptionally less active polymorphic alleles of Prodynorphin (PDYN) gene (Outcome: Temporal Lobe Epilepsy, TLE)	L allele: OR = 1.40 (1.12-1.74)	This study demonstrated that individuals with a familial predisposition of epileptic disorder carrying L alleles of PDYN gene promoter have a 40% greater risk of TLE than those homozygous for the H alleles.
Kauffman et al., 2008b	Case control studies	Inception - 2007	Single nucleotide polymorphism at the promoter region of the interleukin 1B	OR = 1.48 (1.09-2.00)	Individuals with single nucleotide polymorphisms in interleukin 1B were found to have a nearly 50% increased risk of developing temporal lobe epilepsy with hippocampal sclerosis.
Kauffman et al., 2010	All published, peer-reviewed primary studies	Inception - 2009	ApoE ε4	Mean difference (between carriers vs. non-carriers) = 5.15 years (2.08-6.22)	Carriers of ApoE ε4 experience the onset of epilepsy significantly earlier than non-carriers, by about 5 years.
Nurmohamed et al., 2010	Case-control studies	1966-2009	ABCBI gene	OR = 1.07 (0.76-1.51)	No association was found between ABCBI C3435T polymorphisms and the risk of having epilepsy. The authors conclude that

					ABCBI genotyping for epileptic patients is not warranted.
Haerian et al., 2011	Not Specified	1950-2010	SYN2 rs3773364 A>G	OR = 0.97 (0.7-1.34)	This study suggests that the SYN2 rs3773364 A>G polymorphism is not associated with an increased risk of epilepsy.
Xi et al., 2011	Case control studies	1950-2011	Gamma-Aminobutyric acid B receptor 1 (GABBR1) gene polymorphism G1465A (Outcome: Temporal Lobe Epilepsy)	OR = 5.381 (1.726-16.776)	This study suggests that the GABBR1 G1456A polymorphism is a risk factor for temporal lobe epilepsy, though the mechanism of the association has not been established.
Córdoba et al., 2012	Not Specified	1950-2011	SLC6A4 promoter and intron 2 variant number repeat polymorphisms (VNTR) (Outcome: Temporal Lobe Epilepsy)	5HTTLPR polymorphism : OR = 0.90 (0.77-1.06) 5HTTVNTR polymorphism : OR = 1.10 (0.78-1.57)	This study did not find any evidence to suggest that SLC6A4 gene polymorphism or VNTR were associated with an increased risk for temporal lobe epilepsy.

N.B. Outcome for each study was onset for epilepsy unless otherwise stated.

Chapter 6 - Association between multimorbidity and motor-vehicle accidents in persons with epilepsy

Yannick Fortin[1,2], James A.G. Crispo[1,2,3], Deborah Cohen[2,4,5], Simone Dahrouge[6,7], Douglas S McNair[8], Donald R. Mattison[1,9], Daniel Krewski[1,2,9]

Authors Note

1. McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada. 2. School of Epidemiology, Public Health and Preventive Medicine, University of Ottawa, Ottawa, Ontario, Canada. 3. Fulbright Canada Student, University of Pennsylvania, Philadelphia, Pennsylvania, USA. 4. Canadian Population Health Initiative (CPHI), Canadian Institute for Health Information (CIHI), Ottawa, Ontario, Canada. 5. Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada. 6. C.T. Lamont Primary Health Care Research Center, Bruyère Research Institute, Ottawa, Ontario, Canada. 7. Department of Family Medicine, University of Ottawa, Ottawa, Canada. 8. Cerner Corporation, Kansas City, Missouri, USA. 9. Risk Sciences International, Ottawa, Ontario, Canada.

Abstract

Purpose

Increasing morbidity has been shown to be associated with an elevated risk of experiencing a motor-vehicle accident (MVA) in populations without epilepsy. The primary objective of this study was to investigate if increasing multimorbidity is associated with increasing MVA in persons with epilepsy (PWE), who are disproportionally multimorbid. The secondary objective was to test if select comorbidities were independently associated with MVAs in PWE.

Methods

Individuals 16 years of age and older between 2001 and 2013 were identified from the Cerner Health Facts database and included in this study if they satisfied one of the following epilepsy criteria: 1) 1 emergency department visit or inpatient stay where ICD-9 code 345.x was documented; 2) ≥2 outpatient visits separated by 30 days where ICD-9 code 345.x was documented during each encounter; or 3) ≥3 outpatient encounters separated by 30 days where ICD-9 codes 780.39 or 780.3 were documented during each encounter. PWE involved in driver-related MVAs following an epilepsy diagnosis were matched to a maximum of five MVA free PWE controls by sex, age, health care facility, and encounter year [± 2 years]. Prevalent health conditions were identified over a retrospective period of one year using Elixhauser comorbidity measures. Multimorbidity status was categorized as the presence (0, 1, 2, 3, 4+) of prevalent health conditions. Crude and adjusted odds of MVA by multimorbidity status were estimated using conditional logistic regression.

Results

Of 71,371 PWE, 336 MVA cases were identified and matched to 1,541 controls. The median age of the sample was 39 years and the majority were male (51.5%). No clear trend in the odds of an MVA with increasing multi-morbidity was observed, although the odds of an MVA increased somewhat with the number of comorbid conditions. Comorbid depression was independently associated with an increase in odds of MVA in PWE, adjusted OR = 1.885 (95% CI: 1.341-2.649, p <.001).

Conclusion

In PWE, multimorbidity was not associated with increasing risk of MVA. Comorbid depression was identified as a MVA risk factor after adjustment for other comorbidities. Future studies that examine MVA risk from multimorbidity in PWE should control for driving habits in order to confirm these initial findings.

Keywords: motor-vehicle accident; crash; epilepsy; multimorbidity; comorbidities; logistic regression

Introduction

In Western countries, driving eligibility for persons with epilepsy (PWE) varies by jurisdiction, through policies designed to be equitable by balancing individual rights and public safety (Adam, 2015; Winston and Jaiser, 2012). Access to a driver's license for PWE is typically dependent on personal disclosure or statutory physician reporting of epilepsy status and seizure characteristics, and may include a minimum seizure-free period (Winston and Jaiser, 2012; Vernon et al., 2002). Although some studies report no elevated risk of MVA in PWE compared to persons without epilepsy (PWOE) (Kwon et al., 2011), the weight of evidence suggests that PWE are more likely than the latter to be involved in motor-vehicle accidents (MVA) (Vaa, 2005; Charlton et al., 2010).

Results from a systematic review and meta-analysis by Vaa (2005) found a relative risk of 1.84 (95% CI 1.68-2.02) for PWE, sudden disturbance of state of consciousness, and other seizures compared to PWOE, based on the results of eight studies. Likewise, a systematic review evaluating the risk of MVA related to a large number of health conditions by Charlton et al. (2010) concluded that increased risk of MVA in PWE ranged from slightly elevated [RR: 1.1-2.0] to highly elevated [RR: 5.0+]. In a survey of PWE licensed to drive, McLachlan et al. (2007) concluded that MVA risk was a potential concern, as 78% of participants indicated suffering from seizures with loss of consciousness, 89% had waking seizures, 59% did not have premonitory signs of coming seizures such as auras, 41% acknowledged sleepiness as a consequence of their antiepileptic medications (AEDs), and 39% admitted to occasionally missing medication doses. The same study reported that 38% of licensed PWE viewed driving as a determinant to maintaining employment. Time since diagnosis of epilepsy is likely associated with

driving status and seizure-related MVAs. In one retrospective case-control study involving PWE from three epilepsy outpatient clinics in Maryland, longer seizure free intervals (≥12 months versus < 12 months) was associated with reduced odds of MVA (8). In most US states, driving eligibility for PWE requires a seizure free period of 3 to 18 months (Epilepsy Foundation, 2017).

Over the last decade, several studies have reported a positive association between higher levels of multimorbidity and MVA risk (Marshall and Man-Son-Hing, 2011; Fortin et al., 2016; Papa et al., 2014). In a recent population-based case-control study by Fortin et al. (2016), higher levels of multimorbidity were associated with greater odds of MVA in the general public, as well as in this populations stratified by sex or by age. It is well established that PWE are disproportionally multimorbid compared to PWOE, which could contribute to higher risks of MVA (Hinnell et al., 2010; Gaitatzis et al., 2004; Rai et al., 2012; Selassie et al., 2014). A Canadian study of MVA risk by Kwon et al. (2011) showed a higher rate of comorbidities in PWE compared to PWOE using administrative claim data involving 1.4 million individuals. Of 30 health conditions measured using the Elixhauser algorithm (Quan et al., 2005), PWE had a significantly greater prevalence of diagnosed health conditions than PWOE on all of the health indicators. These findings prompted the research question: could multimorbidity be contributing to the risk of MVAs in PWE?

In epilepsy, clinical, regulatory, and employment indicators are the most frequently investigated exposure variables associated with being involved in motor-vehicle accidents. To our knowledge, no study has examined the relationship between higher multimorbidity and MVA risk in PWE, despite evidence of greater multimorbidity and MVA risk in this group. The primary objective of this study was to evaluate the contribution of

multimorbidity to the risk of MVA in PWE. A secondary objective was to investigate if individual comorbidities were independently associated with MVAs in the same population.

Methods

Design

Retrospective EHR-based matched case-control study in persons with epilepsy.

Source of Electronic Health Records

Electronic health record (EHR) data recorded between January 2001 and December 2013 in the Cerner Health Facts data warehouse (Kansas City, Missouri, USA) was used. Health Facts is a longitudinal health services database that contains demographic, clinical, and hospital pharmacy records describing inpatient, outpatient, and emergency department encounters at over 480 US healthcare facilities (B.R.I.D.G.E. to Data, 2014). Health Facts outpatient clinics include general and specialist care delivered at independent physician offices and clinics embedded within larger healthcare centers. Health Facts data contributors are categorized by teaching status, population density, bed size, and census region. Secondary use of Health Facts data for this study was approved by the Office for Research Ethics and Integrity at the University of Ottawa.

Study sample

First, PWE were identified according to the following criteria: 1) 1 emergency department visit or inpatient stay where ICD-9 code 345.x was documented; 2) ≥2 outpatient visits separated by 30 days where ICD-9 code 345.x was documented during each encounter; or

3) ≥3 outpatient encounters separated by 30 days where ICD-9 codes 780.39 or 780.3 were documented during each encounter. The epilepsy selection criteria were developed in collaboration with a health services research neurologist and is aligned with recommendations from the International League Against Epilepsy (Thurman et al., 2011). Both primary and secondary diagnostic codes were used to identify PWE. The date of the epilepsy diagnosis was assigned as the date of the earliest healthcare encounter satisfying the diagnostic criteria (Figure 6.1). PWE without subsequent health care encounters following their epilepsy diagnosis were excluded as there is no possibility of identifying the outcomes of interest in these individuals. PWE with missing sex, age, and healthcare facility were excluded, as these variables were necessary for matching. PWE with a recorded MVA during their diagnosis encounter were also excluded to further ensure a diagnosis of epilepsy preceded the outcome of interest.

Second, PWE with a primary or secondary diagnostic code for a driver-related MVA according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were identified as cases (Appendix A). To ensure the onset of epilepsy was not a consequence of the MVA and that MVAs were not the result of a first seizure, only MVAs recorded during health encounters following the epilepsy diagnosis were admissible. MVA cases were identified during inpatient stays, emergency department visits, and outpatient care. The earliest recorded MVA was assigned as the index encounter to avoid confusion between follow-up care and subsequent MVAs. Since the Health Facts database is not linked to transport databases and indicators of driver's license status are unavailable, MVA identification was limited to PWE 16 years of age and older.

Third, cases were matched to a maximum of 5 controls on sex, age, healthcare facility, and index encounter year (+/-2 years). Controls were unique and cases were available as controls prior to their MVA. Matching on age was applied to help control for years of driving experience and differential rates of MVA across age groups (NHTSA, 2016). Moreover, younger PWE adults are more likely to drive than older PWE adults (Berg et al., 2000), or to have a driver's license (Classen, Crizzle, Winter, Silver, & Eisenschenk, 2012). Matching on sex was essential because women with epilepsy are less likely to drive and hold a driver's license than males with epilepsy (Berg et al., 2000; Classen et al., 2012; Sillanpää & Shinnar, 2005). To limit the possibility of bias resulting from differential coding practices across time and between health care facilities, the treatment facility identification number and the year of the index encounter were included as matching variables.

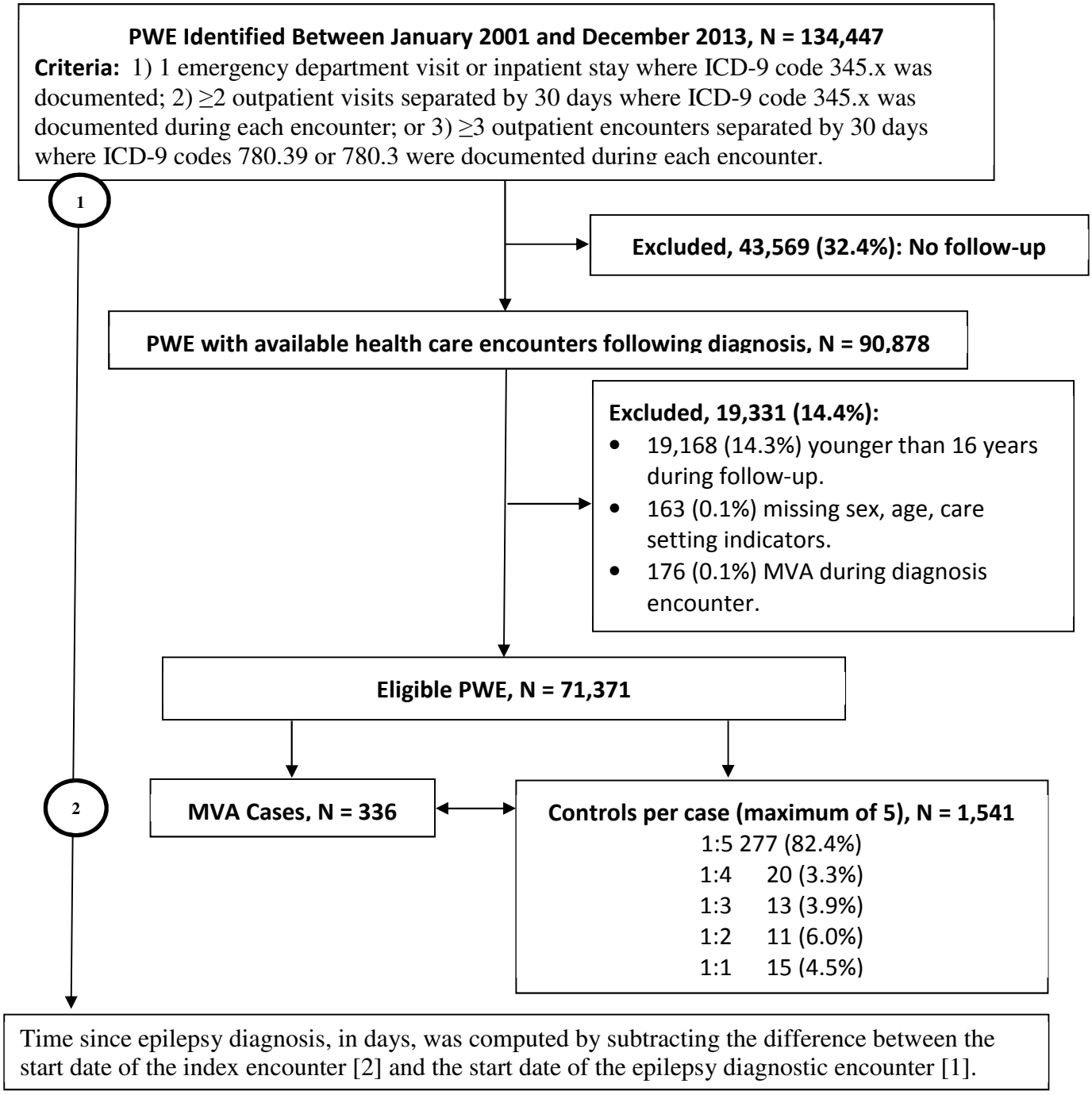

Figure 6.1. Schema describing the selection of cases and controls for matched PWE. Percentages reported in parentheses use the PWE identified between January 2001 and December 2013 as denominator, N = 134,447.

Multimorbidity Status

PWE were considered multimorbid if any one of 28 health conditions [after excluding comorbid measures of alcohol and drug abuse] in the modified Elixhauser comorbidity measures (Quan et al., 2008) were identified in their patient history. Encounters admissible for the ascertainment of health conditions included the index health care encounter and all encounters recorded in the 365 days preceding the index date (Figure 6.2). Increasing the length of time used for diagnostic screening beyond a single health encounter improves the likelihood of identifying prevalent health conditions and reduces exposure misclassification (Preen, Holman, Spilsbury, Semmens, & Brameld, 2006; Sharabiani, Aylin, & Bottle, 2012). Health conditions listed in the Elixhauser algorithm include the leading causes of disability, morbidity, mortality, and health expenditures in the U.S., such as heart disease, dementia, diabetes, pulmonary diseases, and cancer (Bauer, Briss, Goodman, & Bowman, 2014; CDC, 2009, 2013). Alcohol and drug abuse are health conditions integral to the 30 Elixhauser comorbidity measures; however, given the widely recognized positive relationship between substance abuse and MVA risk (Charlton et al., 2010; Gjerde, Normann, Christophersen, Samuelsen, & Mørland, 2011; Koepsell et al., 1994; Vaa, 2005; Vernon et al., 2002), these two condition groups were treated as control variables. An ordinal measure of multimorbidity was created by summing the prevalent health conditions identified and categorizing this total as follows: no comorbidities (reference); 1 comorbidity; 2 comorbidities; 3 comorbidities; and 4 or more comorbidities.

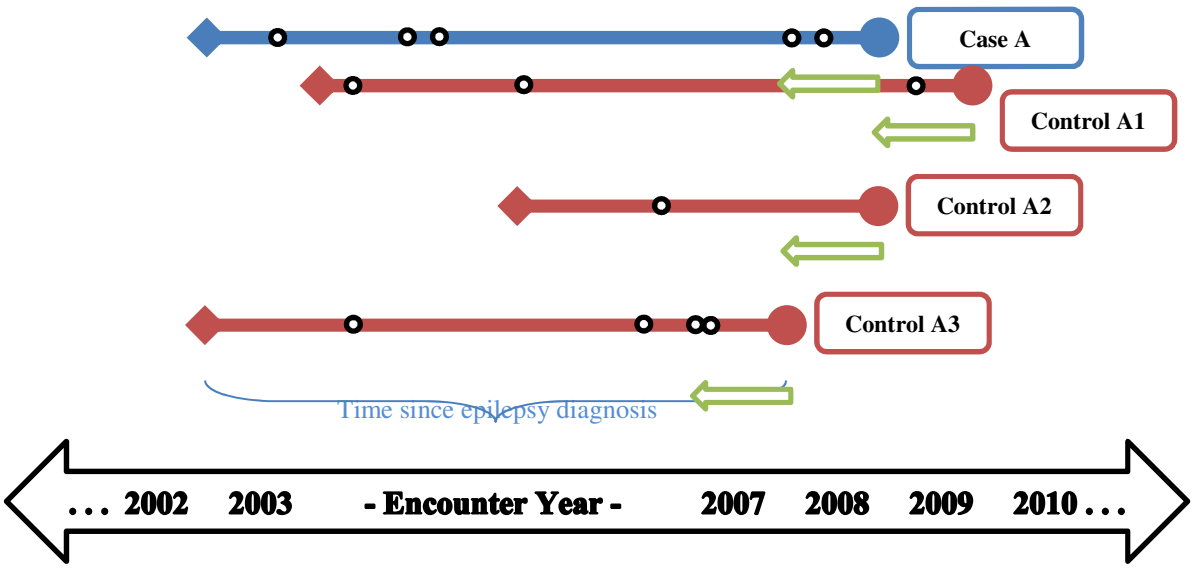

Figure 6.2. Schema describing health encounter selection across time for matched cases and controls. Cases were matched to a maximum of five controls by sex, age, healthcare facility, and index encounter year (+/-2 years). The time since epilepsy diagnosis covariate was derived by subtracting the epilepsy diagnosis encounter start date from the index encounter start date; the number of days between these events was then categorized as 90 days or less [reference], between 91 and 180 days, between 181 and 365 days, and more than 365 days. To determine the prevalence of multimorbidity in cases and in controls, diagnoses recorded during any health encounter identified in the 365 days preceding the index encounters were assessed.

Legend: O = Follow-up encounter; ● = Index encounter; ← = Look back period, 1 year; ◊ = Epilepsy diagnosis.

Control variables

Race categories included Caucasian, African American, Hispanic, Asian, and other (Native American, Pacific Islander, Mid-Eastern Indian, and mixed race/ethnicity). Health insurance payer status was categorized according to a model proposed by the Agency for Healthcare Research and Quality: private, Medicaid, Medicare, self-pay/uninsured, and other (TRICARE-CHAMPUS, international plan, research funded, Title V, and worker's compensation). Care setting characteristics for the index encounter included US census

region (Northeast, Midwest, South, and West), teaching status, and population density (rural/urban).

Assuming a minimum level of compliance with seizure-free interval policies and driving avoidance by PWE, MVA risk would be expected to be lower in the three months following a diagnosis of epilepsy. To help control for the potential effect of compliance with seizure-free period policies, the time separating the epilepsy diagnosis from the start of the index encounter was derived and categorized as follows: 90 days or less [reference], 91 to 180 days, 181 to 365 days, and more than 365 days.

Because there is strong evidence that prior MVAs and driving citations are predictive of future accidents (Hours et al., 2008; Sagberg, 2006), we constructed a dichotomous indicator describing the presence or absence of any MVA prior to the epilepsy diagnosis.

The identification of prevalent health conditions from EHR sources, such as Health Facts, is susceptible to possible misclassification. For instance, care received and diagnoses recorded at health care facilities outside the Cerner Health Facts EHR network cannot be accounted for. To help control for systemic misclassification of the exposure, three measures of health services utilization were derived for each PWE: the total number of health encounters, including the index, contributing to the morbidity assessment (henceforth lookback encounters); the confirmed number days in the lookback (henceforth lookback days); and the pooled total number of inpatient days during the lookback period (henceforth inpatient days).

Suspecting possible effect modification by sex or by age, interaction terms sex and comorbidity status, and age and comorbidity status, were introduced as complementary covariates.

Statistical Analysis

The main outcome of the study was a driver-related MVA following a diagnosis of epilepsy. To describe categorical variables, differences in patient characteristics by MVA status were reported as counts and percentages and compared with the Pearson Chi-square test and the Fisher's Exact test. For continuous variables, differences were described with means and standard deviations and compared with Student's t-test when such variables satisfied the normality requirement, which was defined as the acceptance of the null hypothesis based on the Shapiro-Wilk test. Non-normally distributed continuous variables were reported using the median and range and compared using the Wilcoxon-Mann-Whitney test. Conditional univariate logistic regressions were used to obtain crude odds ratio estimates, Wald confidence intervals, and P-value for the relationship between MVA status and 1) overall multimorbidity, 2) individual Elixhauser health conditions, and 3) control variables. To test the independent effect of multimorbidity on MVA risk, two separate adjusted models were evaluated using conditional multivariate logistic regression. In the primary model, the effect of increasing multimorbidity was tested using the total multimorbidity categorical variable as the exposure of interest. In the secondary model, the 28 eligible Elixhauser health conditions were introduced as binary indicators of multimorbidity. To be retained in the adjusted models, control variables had to display empirical evidence of confounding based on the change in estimate method using a 5% cut off (Greenland, 1989).

Data analyses were performed with SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Sensitivity analyses

In epilepsy, pharmacological treatment with antiepileptic drugs (AEDs) is generally the primary intervention for preventing seizure recurrence (Perucca & Tomson, 2011). To investigate whether cases and controls showed differences in AED exposure, Health Facts hospital pharmacy records were reviewed for: 1) any medication orders; 2) any AED orders; 3) the total number of concurrent AEDs ordered, and 4) independent AED orders for carbamazepine, divalproex sodium, ethosuximide, ethotoin, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, methsuximide, oxcarbazepine, phenobarbital, phensuximide, phenytoin (including fosphenytoin), pregabalin, primidone, rufinamide, tiagabine, topiramate, trimethadione, valproic acid, vigabatrin, and zonisamide. Medication orders were limited to those recorded as filled during the index encounter or any health care encounter in the 30 days preceding the index. The availability of pharmacy data in Health Facts is dependent on length of stay; 48 hours of inpatient care are typically required prior to the represcription of medications used outside the care setting. As a result, medications used in the outpatient setting were frequently unrecorded and it was expected that a large proportion of cases and controls would have no pharmacy data at all. We therefore limited the sensitivity analyses to patients with one or more medication orders for any drug. In this subsample, two indicators of AED exposure were created to test if pharmacological treatment of epilepsy altered the main study findings: 1) ever/never use of any AED; and 2) total number of concurrent AED orders.

Results

Of 71,371 admissible PWE, 336 MVA cases were identified and matched to 1,541 controls. Most cases—277 (82.4%)—were successfully matched to five controls (Figure 6.1). Males accounted for 51.5% of the sample and the median age was 39 years (Table 6.1). Caucasians (76.5%) made up the largest proportion of the sample. There were no significant differences in age, sex, and race between cases and controls. Time separating the epilepsy diagnosis and the index encounter differed between cases and controls. Increased MVA frequency was observed among individuals classified as being 91 to 180 days (13.1% vs 9.0%) and 181 and to 365 days (21.1% vs 15.8%) from epilepsy diagnosis compared to the reference category of 90 days or less, $\chi 2$ (3, N = 1,887) = 19.3, p <.001.

Table 6.1. PWE and care setting characteristics by MVA Status

Characteristics	*Total N = 1,877(%)*	*MVA N = 336(%)*	*No MVA N = 1,541(%)*	*P Value*
Sex (Male)	967 (51.5)	172 (51.2)	795 (51.6)	*0.894* [C]
Age	Med: 39.0 R: 73	Med: 39.0 R: 73	Med: 39.0 R: 73	*0.603* [W]
Race				*0.331* [C]
Caucasian	1,436 (76.5)	270 (80.4)	1,166 (75.7)	
African American	291 (15.5)	42 (12.5)	249 (16.2)	
Hispanic	28 (1.5)	7 (2.1)	21 (1.4)	
Asian	1 (0.1)	0 (0.0)	1 (0.1)	
Other	29 (1.5)	4 (1.2)	25 (1.6)	
Health Insurance Status				*<.001* [C]
Private	466 (24.8)	128 (38.1)	338 (21.9)	
Medicare	394 (21.0)	36 (10.7)	358 (23.2)	
Medicaid	438 (23.3)	42 (12.5)	396 (25.7)	
Uninsured	141 (7.5)	30 (8.9)	111 (7.2)	
Other	35 (1.9)	7 (2.1)	28 (1.8)	
Missing	403 (21.5)	93 (27.7)	310 (20.1)	
Time Since Epilepsy Diagnosis [T]				*<.001* [C]
90 days or less	377 (20.1)	44 (13.1)	333 (21.6)	
Between 91 and 180 days	183 (9.7)	44 (13.1)	139 (9.0)	
Between 181 and 365 days	315 (16.8)	71 (21.1)	244 (15.8)	
More than 365 days	1,002 (53.4)	177 (52.7)	825 (53.5)	
Prior MVA	20 (1.1)	8 (2.4)	12 (0.8)	*0.010* [C]
History of Alcohol Abuse	195 (10.4)	36 (10.7)	159 (10.3)	*0.829* [C]
History of Drug Abuse	252 (13.4)	54 (16.1)	198 (12.8)	*0.116* [C]
Lookback Encounters	Med: 4 R: 80	Med: 5 R: 45	Med: 4 R: 80	*0.165* [W]
Lookback Days	Med: 269 R: 365	Med: 266 R: 365	Med: 270 R: 365	*0.759* [W]
Inpatient Days	Med: 0.4 R: 141	Med: 0.7 R: 69	Med: 0.4 R: 141	*0.607* [W]
Care Setting (Index)				

Census Region				*0.772* [C]
Midwest	202 (10.8)	39 (11.6)	163 (10.6)	
Northeast	881 (46.9)	151 (44.9)	730 (47.4)	
South	743 (39.6)	135 (40.2)	608 (39.5)	
West	51 (2.7)	11 (3.3)	40 (2.6)	
Teaching Status (Teaching)	1,530 (81.5)	264 (78.6)	1,266 (82.2)	*0.125* [C]
Population Density (Urban)	1,877 (100.0)	336 (100.0)	1,541 (100.0)	*NA*

Abbreviations: C, Pearson Chi-Square test; Med, median; R, range; NA, not applicable, no difference between groups; S, Student's t-test; T, time since epilepsy diagnosis represents the difference in days between the start of the index encounter and the start of the first health encounter satisfying the epilepsy case definition; W, Wilcoxon-Mann-Whitney test.

Care setting characteristics of the index encounter were comparable between cases and controls. All index encounters occurred in urban settings: a large percentage of these were from teaching hospitals (81.5%), and the Northeast census region (46.9%) was the most frequent region of care. Cases had a greater percentage of prior MVAs than controls, 2.4% versus 0.8%, $\chi 2$ (1, N = 1,877) = 6.7, p<.010. There were no significant differences in the history of alcohol or of drug abuse between cases and controls. MVA cases and controls differed significantly by health insurance status. For instance, Medicaid (12.5%% vs 25.7%) and Medicare (10.7% vs 23.2%) insured PWE were less frequently in the MVA than the non-MVA group, $\chi 2$ (5, N = 1,877) = 78.7, p<.001. A sizeable portion of the sample—21.5%—had missing values for health insurance status and the frequency of missing values was larger in MVA cases than controls, 27.7% versus 20.1% respectively.

Health encounters available for the identification of prevalent health conditions were balanced between the cases and controls, as evidenced by the absence of significant differences in the number of lookback encounters, lookback days, and inpatients days between the groups. Most PWE (65.8%) were comorbid (Table 6.2). The median number

of prevalent comorbidities in cases (Med = 1) was similar to that of controls (Med = 1), according to the results of the Wilcoxon-Mann-Whitney test, U = 308,138, p = .401, r = -0.02. Controls did not have a greater frequency of comorbidities than MVA cases. Of the 28 pre-selected comorbid conditions investigated, 5 differed in frequency between cases and controls. Prevalent deficiency anemia, congestive heart failure, paralysis, and weight loss were less frequent in cases compared to controls. Depression was the only condition found to have a higher prevalence among MVA cases (27.4%) compared to controls (21.3%), $\chi 2$ (1, N = 1,877) = 5.9, p=0.015.

Table 6.2. Multimorbidity status and prevalence of individual health conditions by MVA status

Variable	Total N = 1,877 (%)	MVA N = 336 (%)	No MVA N = 1,541 (%)	P Value
Multimorbidity Status				*0.341* [C]
No comorbidity	642 (34.2)	115 (34.2)	527 (34.2)	
1 comorbidity	379 (20.2)	77 (22.9)	302 (19.6)	
2 comorbidities	226 (12.0)	39 (11.6)	187 (12.1)	
3 comorbidities	176 (9.4)	31 (9.2)	145 (9.4)	
4 or more comorbidities	454 (24.2)	74 (22.0)	380 (24.7)	
Number of Comorbidities				
Mean ± Standard Deviation	2.2 ± 2.7	2.1 ± 2.7	2.3 ± 2.7	NN
Median (Range)	1 (15)	1 (12)	1 (15)	0.401 [W]
Individual Health Condition Groups				
AIDS/HIV	25 (1.3)	4 (1.2)	21 (1.4)	1.000 [E]
Deficiency Anemia	**82 (4.4)**	**7 (2.1)**	**75 (4.9)**	**0.024** [C]
Rheumatoid Arthritis	58 (3.1)	13 (3.9)	45 (2.9)	0.362 [C]
Blood Loss Anemia	23 (1.2)	5 (1.5)	18 (1.2)	0.784 [E]
Cardiac Arrhythmia	242 (12.9)	45 (13.4)	197 (12.8)	0.763 [C]

Variable	Total N = 1,877 (%)	MVA N = 336 (%)	No MVA N = 1,541 (%)	P Value
Congestive Heart Failure	**118 (6.3)**	**12 (3.6)**	**106 (6.9)**	**0.024** [C]
Chronic Pulmonary Disease	402 (21.4)	74 (22.0)	328 (21.3)	0.765 [C]
Coagulopathy	82 (4.4)	16 (4.8)	66 (4.3)	0.697 [C]
Depression	**420 (22.4)**	**92 (27.4)**	**328 (21.3)**	**0.015** [C]
Diabetes w/o Complications	299 (15.9)	51 (15.2)	248 (16.1)	0.678 [C]
Diabetes w/Complications	80 (4.3)	12 (3.6)	68 (4.4)	0.489 [C]
Hypertension	604 (32.2)	107 (31.8)	497 (32.3)	0.885 [C]
Hypothyroidism	190 (10.1)	35 (10.4)	155 (10.1)	0.844 [C]
Liver Disease	103 (5.5)	18 (5.4)	85 (5.5)	0.908 [C]
Lymphoma	5 (0.3)	0 (0.0)	5 (0.3)	0.593 [E]
Fluid and Electrolyte Disorders	390 (20.8)	68 (20.2)	322 (20.9)	0.788 [C]
Metastatic Cancer	18 (1)	1 (0.3)	17 (1.1)	0.226 [E]
Other Neurological Disorders	95 (5.1)	11 (3.3)	84 (5.5)	0.099 [C]
Obesity	206 (11)	32 (9.5)	174 (11.3)	0.348 [C]
Paralysis	**101 (5.4)**	**10 (3.0)**	**91 (5.9)**	**0.031** [C]
Peripheral Vascular Disease	68 (3.6)	12 (3.6)	56 (3.6)	0.956 [C]
Psychoses	178 (9.5)	29 (8.6)	149 (9.7)	0.556 [C]
Pulmonary Circulation Disorder	41 (2.2)	7 (2.1)	34 (2.2)	0.889 [C]
Renal Failure	128 (6.8)	18 (5.4)	110 (7.1)	0.241 [C]
Solid Tumor without Metastasis	79 (4.2)	10 (3.0)	69 (4.5)	0.214 [C]
Peptic Ulcer Disease	18 (1)	2 (0.6)	16 (1.0)	0.557 [E]
Valvular Disease	78 (4.2)	13 (3.9)	65 (4.2)	0.771 [C]
Weight Loss	**86 (4.6)**	**8 (2.4)**	**78 (5.1)**	**0.033** [C]

Note: Bolded health conditions highlight statistically significant differences in frequency between cases and controls, $p \leq 0.05$.

Abbreviations: C, Pearson chi-squared test; E, Fisher Exact test; NN, Non-normal distribution, statistics not reported; S, Student's t-test; W, Wilcoxon-Mann-Whitney test.

Univariate logistic regression analyses confirmed the differential likelihood of the outcome for the five health conditions above and revealed that odds of MVA varied by health insurance status, time since epilepsy diagnosis, evidence of a prior MVA, and interaction between sex and comorbidity level (Table 6.3). Persons covered by Medicare or by Medicaid were less likely than privately insured individuals to experience an MVA. PWE diagnosed for more than 90 days were more likely than those diagnosed for less than 90 days to be involved in an MVA. Preliminary tests that evaluated the magnitude of confounding by model parameters let to the exclusion of prior MVA status from the adjusted model. The univariate analyses revealed non-significant decreasing odds of MVA with increasing multimorbidity (Table 6.3).

Table 6.3. Odds ratios (OR) and 95% confidence intervals for MVA in PWE

Model Parameter	*Crude OR (95% CI)*	*P-value*	*Adjusted OR (95% CI)*	*P-value*	*Note*
Health Insurance Status					**C**
Private (reference)	1.000	-	1.000	-	
Medicare	**0.216 (0.138 - 0.338)**	**<.001**	**0.217 (0.138 - 0.341)**	**<.001**	**A**
Medicaid	**0.241 (0.160 - 0.362)**	**<.001**	**0.232 (0.153 - 0.352)**	**<.001**	**A**
Uninsured	0.681 (0.423 - 1.097)	0.115	0.662 (0.409 - 1.07)	0.092	**A**
Other	0.505 (0.197 - 1.298)	0.156	0.513 (0.194 - 1.353)	0.177	**A**
Missing	0.815 (0.558 - 1.190)	0.290	0.805 (0.549 - 1.179)	0.265	**A**
Interaction: Sex*Multimorbidity Status	**0.917 (0.847 - 0.991)**	**0.030**	0.908 (0.814 - 1.012)	0.081	**A, C**
Time Since Epilepsy Diagnosis					**C**
90 days or less (reference)	1.000	-	1.000	-	
Between 91 and 180 days	**2.389 (1.498 - 3.809)**	**<.001**	**2.195 (1.357 - 3.551)**	**0.001**	**A**
Between 181 and 365 days	**2.222 (1.469 - 3.361)**	**<.001**	**2.269 (1.474 - 3.492)**	**<.001**	**A**
More than 365 days	**1.676 (1.160 - 2.424)**	**0.006**	**1.707 (1.167 - 2.497)**	**0.006**	**A**
Prior MVA	**2.751 (1.105 - 6.850)**	**0.030**			

Exposure					
Multimorbidity Status					
No comorbidities (reference)	1.000	-	1.000	-	
1 comorbidity	1.152 (0.825 - 1.610)	0.406	1.321 (0.925 - 1.887)	0.126	**A**
2 comorbidities	0.954 (0.632 - 1.441)	0.824	1.199 (0.769 - 1.871)	0.424	**A**
3 comorbidities	0.986 (0.625 - 1.556)	0.952	1.386 (0.826 - 2.325)	0.216	**A**
4 or more comorbidities	0.885 (0.614 - 1.276)	0.513	1.497 (0.907 - 2.47)	0.114	**A**
Congestive Heart Failure	**0.492 (0.261 - 0.925)**	**0.028**	**0.474 (0.227 - 0.986)**	**0.046**	**B**
Deficiency Anemia	**0.417 (0.189 - 0.922)**	**0.031**	0.508 (0.215 - 1.201)	0.123	**B**
Depression	**1.477 (1.113 - 1.962)**	**0.007**	**1.885 (1.341 - 2.649)**	**<.001**	**B**
Paralysis	**0.455 (0.231 - 0.895)**	**0.023**	0.724 (0.35 - 1.497)	0.384	**B**
Weight Loss	**0.463 (0.219 - 0.979)**	**0.044**	0.61 (0.266 - 1.398)	0.243	**B**

Bolded parameters and categories highlight statistically significant differences in odds of the outcome between the cases and controls, $p \leq 0.05$.
Abbreviations: A, the adjusted model controls for health insurance status, the sex*comorbidity status interaction term, and time since epilepsy diagnosis; B, the adjusted model controls for health insurance status, the sex*comorbidity status interaction term, time since epilepsy diagnosis, and the remaining Elixhauser health condition prevalence indicators; C, confounding variable confirmed empirically; OR, odds ratio.

Bivariate analyses did not show statistically significant MVA risk changes with increasing multimorbidity. Even after adjusting for health insurance status, the sex*comorbidity status interaction term, and time since epilepsy diagnosis, no relationship was identified between the exposure and outcome. In the adjusted model, MVA risk from no comorbidities to four or more comorbidities ranged from [AOR = 1.321 (95% CI: 0.925-1.887, p =.126] to [AOR = 1.497 (95% CI: 0.907-2.47, p =.114], respectively. Complimentary multivariate logistic regression modeling, in which the primary exposure variable, multimorbidity status, was substituted by the 28 individual health conditions ascertained, showed decreased odds of MVA with comorbid congestive heart failure [AOR = 0.474 (95% CI: 0.227-0.986, p =.046)] and increased odds of MVA with comorbid depression [AOR = 1.885 (95% CI: 1.341-2.649, p <.001].

Sensitivity Analyses

A subgroup analysis of 213 cases and 708 controls with available pharmacy data [49.1% of the original study sample] replicated the main study findings (Appendix B, Tables S6.1 to S6.3). In this subgroup, the observed difference in ever/never AED medication orders did not differ between cases (28.6%) and controls (35.7%), p= 0.055. In the multivariate logistic regression analyses, ever/never orders for an AED and total concurrent number of AED orders were evaluated in separate models. Controls (14.7%) were almost twice more likely than cases (7.5%) to have 2 or more concurrent AED orders [reference=0] before model adjustments, crude OR = 0.518 (95% CI 0.272-0.988), p =.046], but not after full model adjustments, [AOR = 0.664 (95% CI: 0.326-1.35, p =.258].

Discussion

To our knowledge, this is the first study to investigate the potential role of multimorbidy as a risk factor for MVA in PWE, a population disproportionally affected by comorbid diseases and with elevated risk of MVA compared to the general population. To advance knowledge on this topic, we examined the relationship between multimorbidity status and MVA risk in PWE alone. The association between 28 independent comorbid conditions and MVA risk was also tested. PWE included in this study were frequently multimorbid, with over 65% of study participants 16 to 89 years of age affected by one or more comorbidities. The high prevalence of comorbidity among PWE was expected based on prior findings from Selassie et al. (2014) that showed 56.5% of PWE indentified from South Carolina statewide health-care encounter databases had at least one somatic, psychiatric, or neurodevelopmental disorder. This difference in multimorbidity prevalence

likely results from the admissible age of participation in each study: 16 to 89 years of age in the current study compared to any age in the study by Selassie et al. (2014). Of the prevalent comorbidities identified in the current study, hypertension, depression, chronic pulmonary disease, and fluid and electrolyte disorders were diagnosed in over 20% of PWE.

Published studies based on the general population are in agreement that increasing multimorbidity compounds the risk of MVA (Fortin et al., 2017; Marshall & Man-Son-Hing, 2011; Papa et al., 2014). In this study, increasing multimorbidity and MVA risk appeared to show a slight positive exposure-outcome relationship based on multivariate analyses; however, the minor increase in odds of the outcome were not statistically significant. The previously reported difference in MVA risk from multimorbidity exposure in PWOE was not reproduced in this study limited to PWE. This is likely the result of several factors. It is known that relatively fewer PWE are licensed to drive than PWOE (McLachlan, Starreveld, & Lee, 2007; Sillanpää & Shinnar, 2005). This implies that in the absence of knowledge on driver licensing status, greater differences in patient characteristics should be expected between MVA cases and matched controls in a study limited to PWE than in one based on the general population. MVA risk differences between PWE and the general population may also reflect the historical, legal, and cultural context surrounding driving eligibility of PWE. When licensing became mandatory for driving priviledges, persons with seizure disorders were banned from driving (Steinwall, 1972). It is only through a progressive understanding of seizure-based diseases and the liberalization of licensing policies that PWE obtained the right to drive (Krumholz, Fisher, Lesser, & Hauser, 1991). Based on this historical contingency, it could be hypothesized that PWE

with comorbid diseases might be more likely to be advised by clinicians and others to avoid driving, as compared to comorbid individuals without epilepsy. In this event, PWE controls in this study would be more likely than controls in studies based on the general population to avoid driving altogether and not be at risk of a MVA. If true, this would result in artificially reduced odds of MVA in studies limited to samples of PWE.

Secondary analyses testing the relevance of 28 individual Elixahauser comorbidity groups on MVA status identified two comorbities associated with differential odds of MVA. Comorbid congestive heart failure was linked to a 47% reduction in the odds of MVA, whereas comorbid depression increased the odds of MVA by nearly 90%. Reduced odds of MVA in persons also diagnosed with congestive heart failure was more likely the consequence of a greater proportion of non-drivers among persons with heart failure being selected in the control group than a genuine protective effect. Increased risk of MVA in persons with depression and in those treated with antidepressants has been previously reported (Hours et al., 2008; Ray, Fought, & Decker, 1992; Sagberg, 2006; Vaa, 2005). A systematic review and meta-analysis by Vaa (2005) reported increased risk of MVA [RR = 1.67 (95% CI 1.10-2.55), $p<0.5$] in persons diagnosed with depression or having depressive symptoms compared to those without. Investigating crash responsibilty in a French sample of MVA survivors who were treated in hospital, Hours et al. (2008) reported increased odds [AOR = 3.61 (95% CI 1.30-10.03)] of crash responsibility in those who consumed antidepressants compared to those who had not. Comorbid depression in PWE is likely to result in treatment involving polypharmacy which may have additional effects on cognition and driving safety.

Persons covered by Medicare and Medicaid had a lower risk of MVA compared to those who were privately insured. These findings replicate those reported in a similar study of MVA risk from multimorbidity conducted in Health Facts on a general population sample by Fortin et al. (2017). Persons covered by private insurance should be more likely to be covered by an employer-sponsored health insurance plan, drive to fulfill employment obligations, and possibly be at greater risk of a MVA than those covered by public health insurance. Findings from a Finnish population-based cohort of childhood-onset epilepsy followed prospectively for more than 45 years found that PWE who where licensed to drive were more almost twice as likely to be employed [RR 1.9, 95% CI 1.2 to 3.0, p = 0.0002] (Sillanpää & Shinnar, 2005).

Findings reported in Table 6.3 show a peak risk of MVA in PWE between 91 and 365 days following epilepsy diagnosis compared to shorter (1-3 months) and longer (>12 months) periods. These observed differences are difficult to interpret without additional individual-level information on disease severity [seizure frequency, time since last seizure, seizure classification], indicators of disease progression, treatment course and compliance, driving restrictions and eligibility, and individual compliance with such restrictions. Indicators of geographic location, at the state level were not available for individual patients nor for their treatment facilities. It was therefore not possible to control for the mandatory seizure-free period requirements in each state. Conversely, prior evidence shows that some PWE prefer not to disclose their epilepsy status to transport authorities (Salinsky, Wegener, & Sinnema, 1992; Siddiqi & Jirsch, 2015) and knowingly chose not to comply with such driving requirements (Krauss, Krumholz, Carter, Li, & Kaplan, 1999; McLachlan et al., 2007). For instance, a matched case-control study by Krauss et al. (1999)

investigating seizure-related MVAs in PWE found that 54% of those involved in MVAs had not respected the applicable minimal seizure-free period.

Complementary analyses conducted on a subsample of PWE with evidence of pharmacotherapy for any drug did not identify a correlation between AED orders and MVA. Current evidence on the potential relationship between pharmaceutical treatment with AEDs and MVAs is complex and at times contradictory. A review by Classen et al. (2012) concluded that AEDs were not likely predictive of having a driver's license but taking fewer AEDs might be associated with driving. Switching or reducing AED exposure was also associated with lowered odds of seizure-related MVA for PWE in a study by Krauss et al. (1999). Results of the sensitivity analyses should be interpreted with caution as they may not accurately represent the pharmaceutical management of epilepsy by individuals in the sample: the Health Facts dataset used in the study had minimal information on outpatient prescription drug utilization.

Study Strengths

This study benefited from a large sample size comprised of 71,371 PWE distributed throughout the U.S. By matching cases to controls according to health facility and encounter year, we likely reduced unknown sources of confounding associated with coding practices across sites that may affect the recording of exposure and outcome events. Similarly, matching by age and sex aided in controlling for differences in driving habits, as well as licensing rates, that are expected to vary by these demographic indicators (Sillanpää & Shinnar, 2005). The use of EHRs as a data source for exposure and outcome ascertainment has both advantages and disadvantages. One of the advantages is that ICD-

9-CM diagnostic codes are standardized and are not prone to recall and response bias typically associated with self-reported medical histories (Jenkins, Earle-Richardson, Slingerland, & May, 2002). To limit the extent of exposure misclassification and identify health conditions missed during the index encounter, the morbidity ascertainment period was extended to include health encounters in the year preceding the index encounter (Preen et al., 2006; Zhang, Iwashyna, & Christakis, 1999). Increasing the length of the morbidity ascertainment period (lookback), in addition to including health encounter data from multiple care settings [emergency department visits, hospitalizations, outpatient care], helps counteract a discharge coding abstract bias related to the severity level of the primary condition responsible for the health care encounter: treatment for acute health conditions lowers the probability that secondary health conditions that may not be of immediate concern will be equally recorded (Elixhauser, Steiner, Harris, & Coffey, 1998; Hughes, Iezzoni, Daley, & Greenberg, 1996).

The generalizability of this study was enhanced by the inclusion of health care recipients from the entire socio-economic spectrum. Multimorbidity rates follow a social gradient with multimorbidity levels steadily decreasing with increasing educational attainment or household income (Barnett et al., 2012; Roberts, Rao, Bennett, Loukine, & Jayaraman, 2015).

Limitations

An important limitation of this study was the unavailability of information on driving habits, particularly annual distance driven (Elvik, 2011, 2013). This implies the assumption that all matched controls are drivers, which is unlikely. The likelihood that a significant

proportion of cases were non-drivers is likely very low. However, the number of non-drivers, or persons not at risk of driver-related MVAs, in the control group is probably significantly higher than in cases. Differences in licensing rates between PWE and PWOE, in some cases by as much as 20%, have been reported in Canada (McLachlan et al., 2007) and Finland (Sillanpää & Shinnar, 2005). The study findings must therefore be interpreted in this context. The observed protective effect of congestive heart failure, deficiency anemia, paralysis, and weight loss in the unadjusted analyses possibly demonstrate this point, as these health conditions may be indicative of physical driving limitations and deteriorating health status that would translate in fewer actual drivers in the control group. On a similar note, numerous studies have demonstrated the so-called 'low-mileage bias', which refers to the reported inverse relationship between accident rates and annual distance travelled (Alvarez & Fierro, 2008; Fontaine, 2003; Hakamies-Blomqvist, Raitanen, & O'Neill, 2002; Langford, Methorst, & Hakamies-Blomqvist, 2006). The MVA rate of persons driving fewer annual distance units has been repeatedly shown to be higher than the MVA rate of persons driving a larger number of annual distance units. This raises the question of whether or not PWE with a greater number of comorbidities are more likely than PWE with fewer comorbid conditions to reduce their annual driving distances.

This study was limited to MVAs resulting in the use of health services. Less serious MVAs, limited to property damage and minimal personal harm, are not likely well represented, even though they represent the bulk of all MVAs. In 2014, the U.S. Department of Transportation estimated that the majority of police-reported crashes (72.3%) were limited to property damage (NHTSA, 2016). While this figure is high, it

could be argued that MVAs causing deaths and personal harm are of relatively greater concerns to most drivers.

PWE who have been diagnosed for a longer period of time, as well as those considered to be in remission, may be less likely to be included as controls in the study due to a lower number of health encounters available for matching purposes. MVA cases may also represent PWE who have better overall health, as their crash status indicates that they are well enough to drive and be at risk of an accident in the first place. Conversely, the absence of significant differences across the three indicators of health care utilization included in this study, lookback encounters, lookback days, and inpatient days, suggest limited opportunity for differences in exposure misclassification between cases and controls.

The most recent consensus on driving in epilepsy published by the American Association of Neurology (1994) identified the misuse of alcohol and drugs in the three months prior to driving as a risk factor for MVAs in PWE. However, these indicators are likely to reflect significant levels of misclassification according to results from a study by Quan et al. (2008) that reported the sensitivity of identifying alcohol and drug misuse, using the same ICD codes, ranged from 48% to 55% when compared to chart reviews. Diagnoses of substance abuse identified in EHRs are also not likely to be good indicators of substance use at the time of an MVA or admission for medical services.

Conclusion

This study did not identify a statistically significant exposure-outcome relationship between multimorbidity and motor vehicle accident risk in a sample of persons with

epilepsy. Secondary analyses identified comorbid depression as an independent predictor for MVAs in PWE. Further studies that control for driving exposure may need to be conducted to confirm our initial finding that drivers with epilepsy diagnosed with multiple health conditions are not at greater risk of a motor vehicle accident than those with fewer comorbidities.

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Appendix A

ICD-9 CM codes selected for the identification of driver-related MVAs.

Outcome	ICD-9 CM Codes
Driver-related Motor-Vehicule Accident	E8100, E8102, E8110, E8112, E8122, E8130, E8132, E8140, E8142, E8150, E8152, E8160, E8162, E8170, E8172, E8180, E8182, E8140, E8142, E8150, E8152, E8160, E8162, E8170, E8172, E8180, E8182, E8190, E8192, E81120

Appendix B

Table S6.1: Frequency of recorded medication orders

Variable	Total N = 1,877 (%)	Case - Control: MVA N = 336 (%)	Case - Control: No MVA N = 1,541 (%)	P Value
Medication Order*				*<.001* [C]
No	956 (50.9)	123 (36.6)	833 (54.1)	
Yes	921 (49.1)	213 (63.4)	708 (45.9)	
Medication Order: Yes	**Total N = 921 (%)**	**MVA N = 213 (%)**	**No MVA N = 708 (%)**	**P Value**
AED Order				*0.055* [C]
No	607 (65.9)	152 (71.4)	455 (64.3)	
Yes	314 (34.1)	61 (28.6)	253 (35.7)	
Concurrent AED Orders				*0.021* [C]
0	607 (65.9)	152 (71.4)	455 (64.3)	
1	194 (21.1)	45 (21.1)	149 (21.0)	
2+	120 (13.0)	16 (7.5)	104 (14.7)	

* = Includes medication orders for any type of pharmaceutical drugs. Abbreviations: AED, antiepileptic medications including carbamazepine, divalproex sodium, felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, and zonisamide; C, Pearson's chi-squared test.

Table S6.2: Frequency of individual AED orders in PWE with a history of medication orders*.

	Case - Control			
AED	**Total N = 921 (%)**	**MVA N = 213 (%)**	**No MVA N = 708 (%)**	**P Value**
Carbamazepine	40 (4.3)	5 (2.3)	35 (4.9)	*0.103* [E]
Divalproex sodium	46 (5.0)	9 (4.2)	37 (5.2)	*0.557* [C]
Felbamate	1 (0.1)	0 (0.0)	1 (0.1)	*1.000* [E]
Gabapentin	31 (3.4)	3 (1.4)	28 (4.0)	*0.071* [C]
Lacosamide	4 (0.4)	0 (0.0)	4 (0.6)	*0.579* [E]
Lamotrigine	39 (4.2)	9 (4.2)	30 (4.2)	*0.994* [C]
Levetiracetam	102 (11.1)	15 (7.0)	87 (12.3)	*0.032* [C]
Oxcarbazepine	11 (1.2)	3 (1.4)	8 (1.1)	*1.000* [E]
Phenobarbital	16 (1.7)	3 (1.4)	13 (1.8)	*0.776* [E]
Phenytoin	106 (11.5)	19 (8.9)	87 (12.3)	*0.177* [C]
Pregabalin	12 (1.3)	1 (0.5)	11 (1.6)	*0.314* [E]
Primidone	4 (0.4)	0 (0.0)	4 (0.6)	*0.579* [E]
Topiramate	40 (4.3)	4 (1.9)	36 (5.1)	*0.044* [E]
Valproic acid	21 (2.3)	4 (1.9)	17 (2.4)	*0.797* [E]
Zonisamide	3 (0.3)	2 (0.9)	1 (0.1)	*0.135* [E]

* = Includes medication orders for any type of pharmaceutical drugs. No recordings of the following AEDs were identified in HF pharmacy records: ethosuximide, ethotoin, mephenytoin, mephobarbital, methsuximide, phensuximide, rufinamide, tiagabine, trimethadione, vigabatrin.
Abbreviations: AED, antiepileptic medications; C, Pearson's chi-squared test; E, Fisher's Exact test.

Table S6.3: Odds ratios (OR) and 95% confidence intervals for MVA in PWE with evidence of pharmacotherapy, 213 cases and 708 controls

Model Parameter	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Note
Health Insurance Status					**C**
Private (reference)	1.000	-	1.000	-	
Medicare	**0.256 (0.135 - 0.482)**	**<.001**	**0.275 (0.14-0.541)**	**<.001**	**A**
Medicaid	**0.169 (0.090 - 0.317)**	**<.001**	**0.139 (0.071-0.274)**	**<.001**	**A**
Uninsured	**0.495 (0.253 - 0.971)**	**0.041**	**0.465 (0.23-0.939)**	**0.033**	**A**
Other	0.272 (0.057 - 1.284)	0.100	0.238 (0.04-1.401)	0.113	**A**
Missing	0.661 (0.366 - 1.192)	0.169	0.635 (0.341-1.183)	0.153	**A**
Interaction: Sex*Multimorbidity Status	**0.851 (0.765 - 0.947)**	**0.003**	**0.814 (0.697-0.951)**	**0.010**	**A, C**
Time Since Epilepsy Diagnosis					**C**
90 days or less (reference)	1.000	-	1.000	-	
Between 91 and 180 days	**2.802 (1.475 - 5.321)**	**0.002**	**3.114 (1.500-6.462)**	**0.002**	**A**
Between 181 and 365 days	**2.475 (1.413 - 4.333)**	**0.002**	**2.727 (1.465-5.075)**	**0.002**	**A**
365 days or more	**2.442 (1.501 - 3.972)**	**<.001**	**2.763 (1.606-4.753)**	**<.001**	**A**
Prior MVA	2.734 (0.801 - 9.333)	0.108			
AED Medication Order (reference: No)	0.737 (0.498 - 1.091)	0.127	0.872 (0.563-1.351)	0.540	**D**
Concurrent AED Orders					**D**
0 (reference)	1.000	-	1.000	-	**A**
1	0.852 (0.552 - 1.313)	0.467	0.984 (0.599-1.615)	0.949	**A**
2 or more	**0.518 (0.272 - 0.988)**	**0.046**	0.664 (0.326-1.35)	0.258	**A**
Exposure					
Multimorbidity Status					
No comorbidities (reference)	1.000	-	1.000	-	
1 comorbidity	1.174 (0.694-1.988)	0.550	1.585 (0.862-2.914)	0.138	**A**
2 comorbidities	0.757 (0.420-1.364)	0.353	1.027 (0.533-1.980)	0.936	**A**
3 comorbidities	0.994 (0.512-1.932)	0.987	1.608 (0.738-3.502)	0.232	**A**
4 or more comorbidities	0.727 (0.445-1.187)	0.202	1.867 (0.934-3.732)	0.077	**A**

Bolded parameters and categories highlight statistically significant differences in odds of the outcome between the cases and controls, $p \leq 0.05$.
Abbreviations: A, the adjusted model controls for health insurance status, the sex*multimorbidity status interaction term, and time since epilepsy diagnosis; C, confounding variable confirmed empirically; D, AED medication order (yes/no) and concurrent AEDs medication order(s) were evaluated individually in separate models; OR, odds ratio.

Chapter 7 – Discussion and Conclusion

Summary of Findings

This thesis examined and characterized a hypothesized positive exposure-outcome relationship between multimorbidity and MVA. This hypothesis was tested in a general population of health services users and in a subgroup of patients living with epilepsy. Our research objectives were pursued principally through observational studies and we relied on the U.S. Cerner Health Facts data repository as our principal source of data.

In all, five independent studies were performed. The first of these studies consisted in the external validation and comparison of two competing variants of the Elixhauser comorbidity measures—the Quan and the AHRQ version 3.7—for predicting inhospital mortality at index and at 1-year in HF. The second study aimed to identify the optimal methodological parameters—lookback period and multimorbidity summary approach—for predicting the same mortality outcomes in HF. These two preliminary studies not only helped us gain a better understanding of the complexities of morbidity ascertainment in HF, it led to the first external validation of a risk adjustment method for that data source. Our third study addressed the primary thesis question directly and asked whether increasing multimorbidity is associated with increased risk of MVA. This last study was performed on a large and heterogenous adult population. Our fourth study, a systematic review of the scientific literature, identified risk factors associated with the onset and natural progression of epilepsy. Findings from this study were instrumental in understanding the etiology and consequences of epilepsy, particularly the factors that might contribute or explain differences MVA risk in that population. These findings helped to conceptualize the methodology of the fifth and final study included of the thesis. In study number five, the hypothesized relationship between multimorbidity and MVA was

investigated in a population limited to persons living with epilepsy, a group predisposed to both multimorbidity and MVAs.

We begin this discussion with a short review of the principal conclusions of the main thesis chapters. In doing so, we highlight future research avenues to further the work initiated in the thesis. Then, we focus the conversation on how our findings relate to three specific determinants of population health: socio-economic status, sex, and geography. To stimulate the debate on a possible causal pathway between morbidity and traffic accidents, we then propose a complementary explanatory model of MVA risk that accounts for the "low-mileage" bias phenomenon. Lastly, we consider conditions under which new autonomous vehicle technologies might improve traffic safety.

Performance of Comorbidity Measures

It is a commonly accepted fact in health research that statistical tools such as predictive models may not perform equally in all settings: a predictive model validated internally in a certain population, geographic context, or data source may not be generalizable to another (Altman, Vergouwe, Royston, & Moons, 2009; Collins et al., 2014; Moons, Altman, Reitsma, & et al., 2015). Measures of multimorbidity, are inherently prognosis models, and to our knowledge none of the commonly used models in health research, such as the Charlson Comorbidity Index, the Elixhauser Comorbidity Measures, and the Cumulative Illness Rating Scale (CIRS), had been validated in Health Facts. Relying on these risk adjustment tools to conduct observational studies with Health Facts data, therefore, rested on uncertain assumptions of transferable predictive performance. The first thesis study, chapter II, tested this assumption using two competing variants of the Elixhauser Comorbidity Measures: the AHRQ (version 3.7) and the Quan Enhanced ICD-9-CM. To

ensure we followed best practices, the measures of model performance we selected were aligned with the guidelines for prognostic model validation suggested in the *Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): Explanation and elaboration* statement (Moons et al., 2015). The discrimination performance, defined by the area under the receiver operating characteristic curve (AUROC), of both ECMs in Health Facts, surpassed the performance reported in the original study by Quan and colleagues (2005) by 1 to 2 percent when predicting inhospital mortality at index.

Discrimination performance for predicting longer term inhospital mortality—1 year following the index start date—was not reported in the original study by Quan and colleagues. Nevertheless, we tested the selected ECMs to investigate whether they had broader applicability and were suitable for predicting longer term mortality (1-year) in HF. We found the discrimination performance of both variants to be excellent (AUROC>0.800) according to the interpretation standards suggested by Hosmer Jr et al. (2013). Looking at the calibration performance of the ECMs in HF told another story: the accuracy of the ECMs was satisfactory when predicting inhospital mortality at index but model recalibration would be essential for more accurate predictions of inhospital mortality at 1-year. We suspect the latter result may be a consequence of significant misclassification, i.e. the under recording of mortality status at 1-year.

Data collection and management for the Cerner Health Facts database is aligned with the requirements of the 1996 Health Insurance Portability and Accountability Act (HIPAA), whose aim is to protect the privacy and personal information of individuals. As a consequence of this, deaths recorded at a health or other type of facility located outside

the Cerner privacy networks cannot be linked longitudinally. Patients who died under such circumstances were therefore misclassified as alive. Unfortunately, the frequency of outcome misclassification events in our studies could not be ascertainment and adjusted for using existing methodologies (Magder & Hughes, 1997).

To improve the accuracy of ECMs for predicting mortality beyond the index encounter in Health Facts, we suggest following the current guidelines for prognosis model validation (Altman et al., 2009; Moons et al., 2015). One such preliminary approach would be to run a bootstrapping procedure on a training subset of Health Facts data to identify the Elixhauser health condition groups most consistently associated with long-term mortality (Cenzer, Miao, Kirby, & Boscardin, 2012; Miao, Cenzer, Kirby, & Boscardin, 2013; Steyerberg, Bleeker, Moll, Grobbee, & Moons, 2003; Steyerberg & Eijkemans, 2000; Steyerberg et al., 2001; Steyerberg et al., 2010). Predictive performance measures, including indicators of discrimination and calibration, could then be generated from the revised ECM tested on a separate Health Facts validation sample.

Aside from assessing the predictive performance of the Quan and AHRQ ECMs in Health Facts, we also aimed to identify which of these ECMs was more suitable for future use in observational studies. While statistical indicators marginally favored the Quan variant over the AHRQ, these differences were more likely the consequence of a large sample size and we doubt there are any practical advantage of using one ECM variant over the other.

The relevance of ECMs in HF could also be improved by the validation of additional outcome measures that may be of greater relevance to health researchers and policy makers. Inhospital mortality is only one of many outcomes of overall patient health

and it will not be relevant in every study context. In fact, it could be argued that ECMs might not be the most appropriate methods of ascertaining multimorbidity for the purposes of estimating MVA risk because some of the conditions included in them, such as coagulopathy and blood loss anemia, have no history of being associated with MVAs. In our MVA risk study limited to PWE, the use of the Quan ECM to produce indicators of disease prevalence was driven by a previous study [design] on MVA risk comparing PWE to PWOE by Kwon et al. (2011). In the latter, PWE demonstrated greater disease prevalence than PWOE for each of the 30 Elixhauser measures. By relying on the same ECM for exposure ascertainment, this enhanced the comparability of the results between the studies. Alternative outcome measures that could be used for the validation of ECMs in HF could include hospitalizations, length of stay, hospital readmission, and costs (Yurkovich, Avina-Zubieta, Thomas, Gorenchtein, & Lacaille, 2015).

Optimizing Measures of Multimorbidity in Electronic Health Data

Studies 1 and 2, chapters II and III respectively, examined methodological conditions for which the predictive performance of ECMs might vary in Health Facts. In the first study, ECM discrimination and calibration performance was examined by patient risk group and by type of index encounter [emergency department visits versus inpatient stays]. Stratification of study results by patient risk group was done to highlight the clinical relevance of the ECMs to health providers who often rely on case mix groupings for planning purposes. High risk patients were those with prior hospitalizations and numerous prior emergency department visits. These patients typically represent a small fraction of all health care users but they are responsible for a disproportionally important segment of health services utilization and costs (Wodchis, Austin, & Henry, 2016). They are also at

greater risk of death during certain medical interventions such as surgeries (Gillies et al., 2017; Pearse et al., 2006). Because of expected differences in sample size, multimorbidity status, and mortality rates between the high and low patient risk groups, we also suspected that ECM performance would differ by risk group. Surprisingly, differences in predictive performance were practically irrelevant between risk groups when predicting inhospital mortality at index. It was a different story when predicting inhospital mortality at one year; discrimination and calibration indicators were inferior in the high-risk group compared to the low risk group. One hypothesis to explain this difference is that high-risk patients might be more likely than low risk patients to transition to palliation and end-of-life care (EOLC). In turn, these transfers may be to facilities outside the Cerner Health Facts privacy networks, thereby increasing the likelihood of outcome misclassification for high risk patients. These findings lend further support for the recalibration of ECMs for predicting mortality beyond the index encounter in HF.

In chapter II, we also examined the predictive performance of ECMs by health encounter type at index: results based on hospitalizations were compared to those from emergency department visits. We anticipated that hospitalized patients would be more likely than ED patients to be high risk and consequently have a greater frequency of deaths than the former. Two-thirds of the study index encounters were ED visits and the remainder were hospitalizations. As expected, inhospital mortality was greater in those hospitalized at index than in those seen in the ED. Overall, the predictive performance indicators of the ECMs were greater for hospitalizations than for ED visits. One explanation for this is that there may be more heterogeneity in the overall health of persons coming in for an ED visits than in those who are hospitalized. In such a situation, it is more difficult for a predictive

model based on a finite number of predictors to accurately predict an outcome in a heterogenous sample [ED visitors] than one with more similarities [hospitalized patients]. In the case of hospitalized patients, one could assume similarities based on the notion that the overall health of persons being admitted for inpatient care is compromised enough to require a minimum level of clinical supervision. We can assume greater patient heterogeneity in ED patients based on prior findings that individuals covered under certain health insurance payer classes, Medicaid enrollees for instance, often show up to the ED for non-urgent care that should have technically been administered in primary care settings (Gandhi, Grant, & Sabik, 2014; Mehrotra et al., 2009). Reasons for relying on the ED for non-emergent care is typically considered a consequence of limited access to primary care services (Cunningham & May, 2003; Pukurdpol, Wiler, Hsia, & Ginde, 2014).

The study presented in chapter III reported on the optimal methodological parameters for identifying and representing health conditions. We tested different approaches for summarized health conditions into exposure indicators and evaluated whether modifying the period used for ascertaining a patient's medical history for prevalent conditions had any relevance on the performance of our prognostic models. While the overarching objective of this study was to gain empirical evidence on the best conditions under which the Quan ECM performs in Health Facts, for both short and long-term mortality, a latent consequence of our findings has been the identification of parameters that allow for improved computational and methodological efficiency. For instance, by demonstrating the performance equivalency between a single weighted morbidity score and 30 independent dichotomous ECM health indicators, health researchers conducting HF-based studies will now have empirical evidence to ague that is not necessary to rely on

30 parameters of morbidity to control for overall health status. Fewer variables also directly translates to smaller study master files and shorter computational processing time during data analyses, a feature that is non-negligible in EHR-based epidemiological studies that often include millions of observations. Another relevant finding of that study was that simply counting a person's total number of concurrent health conditions was a significantly weaker approach [- 2 to 3%] than using a weighted score that accounts for the relative severity of the conditions ascertained. Future studies comparing summary measures of multimorbidity might also be improved by testing transformed variants of the total method since disease counts are not normally distributed in the population. For instance, frequency counts of individuals with 0, 1, 2, 3, 4, 5, and 6 or more concurrent health conditions generally decrease in that order.

The last ECM parameter investigated was the length of the patient lookback period used for morbidity ascertainment. While we found that limiting the diagnostic ascertainment of multimorbidity to the index encounter was optimal when predicting inhospital mortality at index and that including a one year of lookback period was optimal for predicting inhospital mortality at one year, these differences were clinically irrelevant (<1%). The advantage of these finding, from a EHR database research perspective, is that there is little justification for doing a lengthy and computationally demanding historical ascertainment of prevalent diagnoses to control for multimorbidity in HF.

Risk Factors for the Onset and Progression of Epilepsy

The fourth thesis study, Chapter V, was conducted as part of the National Population Health Study of Neurological Conditions (NPHSNC) sponsored by the Public Health Agency of Canada (Gaskin, Gomes, Darshan, & Krewski, 2016). The systematic review

of risk factors for the onset and natural progression of epilepsy is, to our knowledge, the first to target all possible risk factors of the disease. While several of the risk factors for epilepsy evaluated in the course of the review were Genetic Risk Factors and Epilepsy Onset or Natural Progression variables, the consequences of alcohol consumption, infections such as HIV/AIDS and ischemic stroke were confirmed as comorbid conditions particularly relevant in PWE. The identified risk of epilepsy onset following head trauma was also instrumental in the development of the methodological design of our final thesis study as it further supported decision to exclude MVA cases recorded during the same encounter as the epilepsy diagnosis. In these individuals, it could have been argued that epilepsy was a consequence of the MVA and its severity (possibly head trauma) and not the other way around.

For the second component of the systematic review, a methodological decision was made to limit the identification of risk factors to those possibly associated with the natural progression of epilepsy. Studies in which there was evidence of pharmacological interventions to treat PWE were excluded as this did not constitute natural progression of the disease in the study context. This likely resulted in the exclusion of numerous studies from Western countries since the first line of treatment in these parts of the world is often the immediate initiation of pharmacotherapy with anticonvulsants to prevent recurrent seizures and their multidimensional consequences (IOM, 2012; Kobau et al., 2008). Since most PWE are treated with AEDs in North America and Europe, studies based on populations from these geographic areas were likely excluded. We believe that this also prevented the retention of studies reporting on comorbid conditions associated with epilepsy progression; conditions possibly relevant to the final study presented in this

thesis (chapter VI). Fortunately, the scientific literature contains numerous studies detailing the extent of multimorbidity in epilepsy (Athanasios Gaitatzis, Carroll, Majeed, & Sander, 2004; A. Gaitatzis, Trimble, & Sander, 2004; Hinnell et al., 2010; Rai et al., 2012; Selassie et al., 2014). Most of the relevant comorbidities previously identified in the literature were coded in the Elixhauser comorbidity measures used for morbidity ascertainment in the final study limited to PWE.

Impact of Multimorbidity on Motor-Vehicle Accident Risk

Chapters IV and VI reported on studies that addressed the principal objective of the thesis. Both evaluated the possibility of increasing risk of MVA with increasing multimorbidity. Our third study, chapter IV, was inclusive of the general patient population in HF. In these individuals, we observed a possible exposure-outcome association between multimorbidity and MVA risk. This observation was persistent across age groups and between the sexes. Interestingly, the reported relationship was more distinct in women than in men. We hypothesize that this result might reflect the higher prevalence of several high risk driving behaviors in men that are not observed as frequently in women. We therefore suggest that there may be fewer explanatory factors of MVA competing with multimorbidity in women than in men. Since women are less likely than men to drive under the influence of alcohol, speed, and engage in risky driving, the relative effect of multimorbidity on MVA risk may be more pronounced in the former. We found that women were more frequently multimorbid than men but this finding may be misleading as it was not adjusted for age. However, the relatively higher multimorbidity of women over men was reported in 9 of 14 studies (64%) identified in a systematic review of the literature by Violan et al. (2014). Another possibly relevant factor is the notion that women may be generally more inclined

to seek care than men; in EHR data this would translate into a larger number of officially recorded diagnoses for the former. In our study, women might therefore have been more often diagnosed as multimorbid than men simply because they are more inclined to seek care in the first place; men may be more likely to be undiagnosed as multimorbid.

Perhaps one of our most policy relevant finding is that the exposure-outcome relationship between multimorbidity and MVA risk was observed in adults 25 to 64 years of age. Admittedly, a lower percentage of adults in this age range are multimorbid when compared to seniors, however, their number may not be negligible. According to recent population data from the United Nations (2015), persons aged 25 to 64 years represented the majority of Americans (52.6%) in 2015. One must keep in mind, as we described in our introduction, that the proportion of multimorbid individuals in this age group is expected to continue to increase in the coming years.

Adults aged 25 to 64 years are in their prime working years and many are at risk of an MVA by the very fact that they drive to work. Reporting results from the 2013 American Community Survey (ACS), which is administered annually by the U.S. Census Bureau, McKenzie (2015) found that approximately 86% of US working adults use a private vehicle to get to work; 76.4% of these drive alone while 9.4% carpool. Between 1980 and 2013, carpooling decreased from 19.7% to 9.4% while driving alone increased from 64.4% to 76.4%, respectively. The McKenzie (2015) report also showed that after stratifying by age, lone commuting increased in the same direction as multimorbidity rates; the percentage of commuters who drove alone in 2013 for the ages of 16 to 24, 25 to 29, 30 to 34, 35 to 44, 45 to 54, and 55 years and older was 70.1%, 74.8%, 75.6%, 77.0%, 78.6%, and 78.8%, respectively. In essence, the persons in the age groups most likely to be multimorbid were

also more likely to be driving alone to work. Certainly, these numbers do not account for the possibility that those who are multimorbid might be less likely to work in the first place or drive to work in the case of those employed. However, as a whole these numbers are not encouraging from a public health perspective if we entertain the idea of an exposure-outcome relationship between MVA risk and multimorbidity, particularly with increasing rates of driving alone appearing to be aligned with natural increases in multimorbidity across the lifespan.

The conclusions of this thesis pertaining to a potential exposure-response relationship between multimorbidity and MVA risk should be considered tentative and in need of additional validation and confirmation. For one, the interpretation of our findings was complicated by the possibility of confounding from a number of relevant factors that could not be controlled in our data source, namely, the driving habits, annual driving distance, risk taking and avoidance behaviours, car ownership, and driver's licensure status of the participants in our study samples.

Multimorbidity, MVAs, and Population Health

The implications of our primary thesis finding that multimorbidity might be associated with increased risk of MVA raises a number of complex questions for population health research and policy. We begin by discussing issues pertaining to socioeconomic status (SES), arguably one of the most important social determinant of health.

Socioeconomic Status

In HF, our study data source, the only available proxy indicator of socioeconomic status was a variable describing the health insurance status of patients. The assumption was that

health insurance categories might offer, to some extent, income level rankings whereby the privately insured would be considered the greatest earners followed by the uninsured, then by Medicare, and lastly by Medicaid recipients. While several arguments can be made against this relative ranking using exceptions surrounding the eligibility criteria for Medicaid and Medicare coverage, as well as reasons why individuals may not be covered by health insurance, we believe this relative SES ranking has some face value. For instance, in a study on disparities in health and access to care, Sabik et al. (2012) reported important differences in nominal family income across health insurance categories: the average income of the privately insured largely surpassed that of the uninsured and of Medicaid recipients at $60,447, $22,872, and $13,498 respectively.

In studies 3 and 5, chapters IV and VI respectively, we hypothesized greater odds of MVA in the privately insured. From a population health perspective, this is counter intuitive since the privately insured, e.g. the highest income earner category, should be less likely to be affected by multimorbidity (Barnett et al., 2012; Roberts, Rao, Bennett, Loukine, & Jayaraman, 2015). The privately insured should also have better access to health services and more timely care through access to primary care and preventative services (Gandhi et al., 2014; IOM, 2009; Sabik & Dahman, 2012; Stone et al., 2013). What must be remembered, however, is that in the absence of driving exposure indicators, health insurance becomes a proxy for who has the greater likelihood of having a valid driver's license, owning a car, and be required to drive for employment purposes. Without the ability to exclude non-drivers from our study and control for annual distance travelled, health insurance status not only became our proxy for SES, it was our principal proxy for driving exposure. With a single variable reflecting SES in HF, we could not properly

investigate if SES independently modified the observed relationship between multimorbidity and MVA risk. We are therefore left with the option to speculate on the implications of SES for our findings.

In our introduction, we highlighted studies that described how multimorbidity followed a social gradient based on income and educational attainment: persons with lower incomes and/or educational attainment are not only more frequently multimorbid than those with greater means and education, they typically become multimorbid earlier in life (Barnett et al., 2012; Roberts et al., 2015). Therefore, if the relationship between multimorbidity and MVA holds, this would imply that persons in the lower socioeconomic deciles would typically become at risk of MVAs earlier in their lifespan than persons in the higher socioeconomic deciles. If we assume that the majority of adults will become multimorbid by age 65 on average (Barnett et al., 2012; Ward & Schiller, 2013), those in the lower socioeconomic strata would become multimorbid sometime before the habitual age of retirement, at a time when they are likely still of working age. Conversely, since driver-related MVA risk is only relevant for persons with the means to own and operate a vehicle, the poorest of the poor would in fact be protected from MVAs due to their precarious situation. Results reported in thesis studies 3 and 5 seem to confirm this point: persons covered by Medicaid (limited financial resources) had significantly lower odds of being involved in a MVA than those covered by private health insurance (greater financial resources).

Sex

According to a Canadian study by Roberts et al. (2015), women had 30% greater odds of being multimorbid than men after adjusting for age. This might mean that women will be

at a disproportionally greater risk of MVAs due to multimorbidity than men. This relative increased risk of MVA and apparent health inequity affecting members of the female sex should, however, be contrasted with other known traffic statistics that likely disadvantage men even further. Historically, men have and continue to be at greater risk of traffic accidents than women. According to the most recent U.S. statistics, men were nearly 3 times more likely than women, per licensed driver, to be involved in a fatal motor-vehicle crash (NHTSA, 2016). Women were also proportionally less likely to be involved as drivers in injury-related crashes and accidents limited to property damage. Females also appear to be more responsible drivers than men; the former reporting lower levels of participation in risky driving behaviors than the latter (Rhodes & Pivik, 2011). A prime example is the sex differential in drinking and driving. In 2014, the overall percentage of fatal motor-vehicle accidents attributable to alcohol use was lower in women [$BAC_{0.01+}$ = 18%, $BAC_{0.08+}$=15%] than in men [$BAC_{0.01+}$ = 28%, $BAC_{0.08+}$=23%] (NHTSA, 2016). In the end, while women may be disadvantaged with regards to MVA risk from multimorbidity, they are likely better off than men in terms of their overall likelihood of suffering a car crash from any cause.

If there is inequity based on sex surrounding multimorbidity and MVAs, it may rest in the selection of policies, and their associated resources, which overwhelmingly target high risk behaviors predominantly performed by men, e.g. campaigns aimed at reducing speeding, and drinking and driving. Before prevention-based policies can target multimorbidity as a risk factor for MVAs, the weight of evidence on the purported relationship between these variables will have to increase significantly. Even then, the

complex causal network resulting in multimorbidity is likely to dissuade policy makers from targeting multimorbidity as means to lower automobile crashes.

Geography: Urban versus Rural Settings

The option to reduce or abandon driving in response to multimorbidity may be limited by geography and population density. Persons living outside of metropolitan areas typically do not have access to public transportation services and must rely on other forms of transportations such as driving to reach their destination. A report on commuting trends in the US referenced earlier confirms this hypothesis in working adults (McKenzie, 2015): the percentage of automobile commuters in persons living in the metro area of a principal city, living in a metro area outside a principal city, and living outside any metro area was 78%, 89%, and 91%, respectively. Assuming multimorbidity increases the risk of MVAs, it could therefore be posited that persons living in rural areas would be systematically disadvantage compared to those residing in principal cities large enough to have a system of public transportation. Persons living in principal cities may have a greater number of viable commuting options than those living outside metro areas if they developed concerns with their ability to drive due to health reasons or other factors.

A potentially more important source of inequity surrounding the relationship between multimorbidity, MVAs, and geography may be found in the availability of resources to prevent and treat disease in urban and rural settings. There appears to be strong evidence that access to care and other health services is more likely to be limited in rural communities than in urban centers (Sibley & Weiner, 2011; Sparks, 2012). Under this assumption, one could speculate, for instance, that a rural resident with multiple concomitant health conditions may be more likely to suffer from limiting functional

impairments than an urban resident with the same diagnoses because of unequal access to timely and appropriate care. Whether urban/rural status actually modifies the relationship between multimorbidity and MVA should be further investigated. In our study data source (HF), unfortunately, the single indicator of population density [urban/rural] was assigned to the health care facility and did not reflect the residential status of the patient. This is problematic because individuals involved in MVAs serious enough to require hospital care may be systematically transferred to urban centers better equipped than rural hospitals to treat emergency and trauma cases. For this reason, we were not confident that the population density status of HF health care facilities could be used as a proxy for the patient's residential status. We could not, therefore, test if population density modified the relationship between multimorbidity and MVA risk.

Further Perspective on the Association Between Multimorbidity and MVAs

As mentioned previously, our findings must be interpreted in light of an important limitation: the absence of controls for driving exposure. Our study designs assumed that everyone in the study population, cases and controls, were drivers. Obviously, this cannot possibly be the true, particularly in the control groups (persons without MVAs). Some might perceive this missing driving exposure data to be too limiting to draw conclusions on the relationship between multimorbidity and MVAs. To those critics, we argue that while studies based on databases from motor-vehicle authorities are likely to have reliable and detailed data on MVA outcomes and licensing status, these data sources often have limited and possibly skewed information on the overall health of drivers. When asked to disclose existing health conditions to their DMV, there may be a strong incentive for driver's license holders to not disclose previously diagnosed conditions that might lead to

the removal of their driving privileges. In addition, drivers may fail to disclose health conditions that are not explicitly referenced by the DMV or for which they do not feel there is relevance to driving. To this we add the limitations of recall and interpretations of what counts as a disclosable health condition. For instance, drivers renewing their license may have doubts as to whether conditions being treated successfully with medication should be disclosed. Together, these limitations cast doubts as to whether multimorbidity can be accurately assessed from transport databases and surveys of drivers.

To complement existing knowledge of the relationship between overall health and MVAs, the work completed as part of this thesis privileged a data source in which our exposure variable of interest, multimorbidity, is likely to be more objectively and comprehensively captured than information sources with a better capture of our outcome variable of interest, MVAs. For instance, EHR databases are poor sources of information on non-serious MVAs, those for which individuals may elect to seek care or not. The inclusion of non-drivers in our control groups is likely to have affected our model effect estimates. Persons who do not drive at all simply cannot be involved in driver-related MVAs. Of those who choose or are prevented from driving altogether due to concerns with driving safety, it would be expected that the highly multimorbid would be over represented compared to those with fewer or no health conditions. This hypothesis was confirmed by a systematic review by Marshall and Man-Son-Hing (2011) which showed that increases in multimorbidity are associated with increases in driving cessation.

We expect that the strength and dose-response nature of the relationship we observed between multimorbidity and MVAs would be even greater with the exclusion of non-drivers from the control group. The combined results of thesis studies 3 and 5, chapters

IV and VI, appear to support this point. It is a well-known fact that persons with epilepsy, as a whole, are less likely than those without the disease to hold a valid driver's licence or drive. One reason for this is that a minimum seizure-free periods is required by nearly all U.S. states for PWE to hold a valid driver's licence (Epilepsy Foundation, 2017). It would therefore be expected that a greater proportion of controls in thesis study 5 [limited to PWE] would be non-drivers compared to the sample of thesis study 3 [general population]. This expected greater proportion of non-drivers in the control group of our study limited to PWE compared to the general patient population of thesis study 3 should therefore translate into a greater attenuation of the model effect estimates observed in thesis study 5 compared to study 3. Notwithstanding the numerous differences between the study populations and sample size between those two studies, the non-significant relationship between multimorbidity and MVA risk observed in the PWE study might be an attenuated version of the significant trend observed in study 3. Having discussed issues pertaining to drivers and non-drivers, we now propose an interpretation of the relationship between multimorbidity and MVAs that accounts for annual driving distance.

While it might be intuitive to assume that those who drive more are more likely to be involved in MVAs, research findings from the last decade have somewhat invalidated this simplified understanding of the relationship between driving distance and MVA risk. Let us now introduce the concept of low-mileage bias.

In MVA studies, it was often accepted as fact that after controlling for driving exposure (e.g. miles travelled), old age results in increased crash risk (CDC, 2013; Hu, Jones, Reuscher, Schmoyer, & Truett, 2000). In the early to mid-2000's, two groups of researchers challenged the notion that; 1) older age in itself is a risk factor for MVAs, and

2) that the relationship between driving exposure and crash rates follows a positive linear relationship (Hakamies-Blomqvist, Raitanen, & O'Neill, 2002; Langford, Methorst, & Hakamies-Blomqvist, 2006). These authors identified was is now termed the 'low mileage bias' and published studies that support the notion that irrespective of age, persons who drive less annually (or below a certain distance threshold) are more likely to be involved in an MVA per unit of travel than those who travel more. They were able to show that higher crash rates in the elderly were not due to age but to a proportion of them driving below an annual distance threshold strongly associated with crashes. For instance, Langford et al. (2006) used travel survey data from 47,502 Dutch respondents collected between 1990 and 2003 to replicate the low-mileage bias findings of Hakamies-Blomqvist et al. (2002). Respondents were categorized by age (18–20, 21–30, 31–64, 65–74 and 75 years or older) and annual distance travelled: <3000 km; 3000–14,000 km, and >14,000 km. Using accident rate per million kilometers driven as their outcome, the authors found that drivers who drove the most annually (>14,000 kilometers) had the lowest crash rate per kilometer and this trend was repeated in each of the age categories. Those who drove between 3000 and 14,000 km annually had a higher crash rate than those who drove over 14,000 kilometers and this trend was again repeated across all age groups. In these two groups, those driving between 3,000 to 14,000 km and those driving over 14,000 km annually, crash rates peaked in the youngest age group and then decreased with each age group that followed; persons aged 75 years and older had the lowest crash rates. The most interesting findings were found in the low-mileage group (<3000 kilometers driven annually). Irrespective of the age category referenced, these drivers had the highest crash rate per kilometers driven when compared to those who drove more annually. Of all the

age categories, drivers 18 to 20 years, the youngest age group, had the highest accident rate per million kilometers driven. Crash rates then fell with increasing aged category until the 65 to 74 years age group when a slight increase in rate from the previous age category was recorded. This was followed by an important increase in crash rate in those aged 75 years and over. These findings highlight the existence of an annual driving distance threshold below which accident rates behave in a non-linear function with regards to age.

Assuming the low-mileage bias is a real phenomenon, one could speculate that the observed exposure-outcome relationship between multimorbidity and MVA risk could be the result of progressively decreasing annual driving distances with increasing multimorbidity. Another way of describing this alternative explanation is that each additional comorbidity increases the proportion of drivers who fall in the low annual distance driven category; the group with the highest accident rate per distance unit travelled. Under this scenario proximal cause of MVAs would be lower annual driving exposure and the distal cause of crash risk would be multimorbidity. In effect, multimorbidity would be a cause of a cause of MVA risk. To our knowledge this alternative explanation to describe the observed relationship between multimorbidity and MVA has never been proposed and should be included in the existing list of hypotheses linking MVAs and health states.

Alternatively, the relationship between multimorbidity and MVA risk observed in the general patient population may reflect selection bias pertaining to who is more likely to seek care following an MVA of low to medium severity, i.e. crashes whose consequences range from property damage to non-serious injuries. Recommendations to seek care may be amplified due to prior knowledge of a person's overall health. A good

example might be provided in the case of a pregnant women involved in an MVA compared to a non-pregnant woman with similar demographic characteristics also involved in an MVA. In such a scenario, it is easy to conceive that the former would receive greater pressure from others to pursue a medical evaluation following an MVA than the latter. In other words, if it is generally perceived that those with greater multimorbidity are likely to suffer disproportionally greater negative health outcomes from an MVA than those with lower multimorbidity, then this is likely to translate into selection bias.

Conclusion

Work completed as part of this thesis aimed to fill knowledge gaps surrounding the relationship between multimorbidity and motor-vehicle accidents. Notably, we report an exposure-outcome relationship between multimorbidity and MVA risk in adults, an association that remained after stratifying by age and sex. In persons with epilepsy, the prototypical health condition associated with driving restrictions, we identified comorbid depression as a likely risk factor for MVAs. Our findings were derived from a large repository of electronic health records, an information source that is not without its own limitations but that allowed for an objective ascertainment of prevalent comorbidities and severe MVAs in the U.S. population. The thesis conclusions therefore complement existing knowledge on MVA risk from multimorbidity previously derived from transport databases and self-reports, as well as expand on prior studies often limited to older adults. Given the increasing rate of multimorbidity in North America, findings from this thesis may signal a latent public health problem. Future studies should therefore attempt to replicate the thesis findings for less serious accidents limited to property damage, all the while, accounting for driving status and habits.

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