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Multimorbidity Among Adult Primary Health Care Patients In Canada: Examining Multiple Chronic Diseases Using An Electronic Medical Record Database

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Abstract

Introduction: The coexistence of multiple chronic diseases within an individual, also known as multimorbidity, is an ongoing challenge for patients, caregivers and primary health care (PHC) providers. An enhanced understanding of the burden of multimorbidity in Canada is needed.

Objectives: This research had two main objectives. Objective One aimed to understand the prevalence of multimorbidity among adult PHC patients, as well as the patterns of unordered and ordered clusters of multiple chronic diseases. Objective Two aimed to determine the natural progression of multimorbidity over time, as well as the patient-, provider- and practice-level predictors of progressing into more complex clinical profiles.

Methods: Data were derived from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) database. For Objective One, descriptive and computational analyses were conducted and for Objective Two, multilevel survival analyses were conducted to account for clustering. Patients with at least one encounter recorded in their EMR and who were at least 18 years of age at their first encounter were included in the analyses. Chronic disease diagnoses were identified using the International Classification of Diseases, 9th Revision (ICD-9) and a list of 20 chronic disease categories identified patients with multimorbidity.

Results: Overall, 53.3% and 33.1% of adult PHC patients were living with at least two and at least three chronic diseases, respectively. Patients with at least two chronic diseases had a mean age of 59.0 years (SD: 17.0), while the majority were female (57.8%) and living in an urban

setting (52.2%). Among female patients with multimorbidity, 6,095 unique combinations and 14,911 unique permutations were found. Among male patients with multimorbidity, 4,316 unique combinations and 9,736 unique permutations were detected. The multilevel survival analysis indicated that several patient-level (patient age, patient sex and total number of chronic diseases), provider-level (provider age) and practice-level (EMR type and practice location) variables predicted time until subsequent chronic disease diagnosis.

Conclusion: This research explored the prevalence, characteristics, patterns and natural progression of multimorbidity over time among a large cohort of adult PHC patients. When carefully assessed, these findings will help to create a more nuanced understanding of the burden of multimorbidity.

Keywords

Multimorbidity, primary health care, electronic medical records, chronic disease, prevalence, multilevel survival analysis, epidemiology

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List of Abbreviations

ACG	Adjusted Clinical Groups
AHRQ	Agency for Health Care Research and Quality
BMI	Body Mass Index
CBPHC	Community-Based Primary Health Care
CCHS	Canadian Community Health Survey
CI	Confidence Interval
CIHR	Canadian Institutes of Health Research
CIRS	Cumulative Illness Rating Scale
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
DELPHI	Deliver Primary Health Care Information
EMR	Electronic Medical Record
FSA	Forward Sortation Area
HRQOL	Health-Related Quality of Life
ICD-10	International Classification of Disease, 10th Revision
ICD-9	International Classification of Disease, 9th Revision
ICD-9-CM	International Classification of Disease, 9th Revision, Clinical Modification
ICPC	International Classification of Primary Care
ICPC-2	International Classification of Primary Care, 2nd Edition
ICPC-2-R	International Classification of Primary Care, 2nd Edition, Revised
IQR	Interquartile Range
IOM	Institute of Medicine

MeSH	Medical Subject Heading
MM	Multimorbidity
NPS	National Physician Survey
PACE in MM	Patient-Centered Innovations for Persons with Multimorbidity
PHAC	Public Health Agency of Canada
PHC	Primary Health Care
SD	Standard Deviation
WHO	World Health Organization

Chapter 1

1 Introduction

The coexistence of multiple chronic diseases within an individual, also known as multimorbidity, has been deemed the "norm rather than the exception" in primary health care (PHC) by both researchers and health care providers for many years. Beyond being recognized as the "norm", multimorbidity in fact represents one of the most complex issues in modern medicine; an increasingly common issue that requires a more effective clinical approach to respond to this complexity. To contribute towards the knowledge base in the area of multimorbidity, as well as to address notable gaps in the existing multimorbidity literature, this thesis aimed to achieve three main areas of understanding: 1) to identify the prevalence and common characteristics of multimorbidity among adult PHC patients within a pan-Canadian database; 2) to determine the patterns (both unordered clusters and ordered clusters) of multiple chronic disease occurrence among adult PHC patients with multimorbidity; and 3) to understand the natural progression of adult PHC patients as they moved to more complex clinical profiles over time, as well as the patient-, provider- and practice-level variables that may predict the time until an additional chronic disease diagnosis. The use of a national, longitudinal, de-identified electronic medical record (EMR) database from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) has allowed for this research to be possible. This exploration of a complex issue in health care, using a complex set of electronic medical record data, has provided insight that can contribute to the efforts of the international community that is working to understand the burden of multimorbidity.

Chapter 2

2 Literature Review

This chapter will introduce the three interrelated pillars of this doctoral research: primary health care, electronic medical records and multimorbidity. While each pillar is presented separately, the interrelatedness of these concepts creates the basis for this thesis.

2.1 Primary Health Care

2.1.1 Definition of Primary Health Care

According to Health Canada, the term "primary health care" refers to an approach to health and a spectrum of services that go beyond the traditional health care system (Health Canada, 2012). Primary health care serves a dual function in the broader health care system: 1) to direct provision of first-contact services by health care providers such as family physicians and nurse practitioners; and 2) to integrate and coordinate patients in need of more specialized services such as those provided by specialists or through in-patient hospital care (Health Canada, 2012; Hutchison et al., 2011; Starfield et al., 2005). The range and configuration of PHC services that are available varies from community to community, but often focusses on the prevention and treatment of common diseases and injuries, basic emergency services, referrals and coordination with other levels of care, mental health care, health promotion, maternity and early-life care, as well as palliative and end-of-life care (Health Canada, 2012). The concept of "primary care" is the element within PHC that focusses on the delivery of these health care services to achieve health promotion, illness and injury prevention (both acute and chronic illness prevention) and the diagnosis and treatment of illness and injury among populations (Health Canada, 2012). In a similar sense, the World Health Organization (WHO) Alma Ata

International Conference in 1978 and reports from the Institute of Medicine (IOM) defined primary care as "the provision of integrated, accessible health care services by clinicians who are accountable for addressing a large majority of personal health care needs, developing a sustained partnership with patients and practicing in the context of family and community" (WHO, 1978; IOM, 1978). As well, this definition of primary care has been used to measure four main features of primary care services: 1) first-contact access for each new need; 2) long-term person-focussed care (not disease-focussed care); 3) comprehensive care for most health needs; and 4) coordinated care when it must be sought elsewhere (Starfield et al., 2005; McWhinney and Freeman, 2009). The term "primary health care" is used herein and refers to the definition of all aspects of both "primary health care" and "primary care", as defined above. Indeed, a strong primary health care system is required to address the marked disparities or inequities in health across populations and evidence of the substantial influence of a strong patient-centered PHC system has been accumulating (Stewart et al., 2014; Kelley et al., 2014; Starfield et al., 2005).

In Canada, family physicians and nurse practitioners who see patients in a PHC setting (e.g., in-office clinic, walk-in clinic or emergency department) provide the first point of contact between a patient who is in need of health services and the health care system. This first-point access is distinct from secondary health care services (e.g., medical specialist or in-patient hospitalization) in which a referral or admission order is typically first required before receiving these specialized services. The ways in which PHC services are organized and delivered have been the focus of much debate. In fact, numerous studies have emphasized the importance of PHC reform, including the Romanow Report published in 2002 (Hutchison et al., 2011; Romanow, 2002). Explained further in the next section, the key feature of PHC reform was the fundamental shift from singular PHC providers in their own in-office, unattached clinics to more

robust teams of health care providers who work together to deliver multidisciplinary and comprehensive services to their patients or clients (Hutchison et al., 2011; Health Council of Canada, 2007; Starfield et al., 2005). This shift occurred based on the increasing evidence that a team of professionals working as partners could achieve positive health outcomes, as well as improved access to services, more efficient use of resources and higher satisfaction of both patients and providers (Health Canada, 2012; Hutchison et al., 2011; Health Council of Canada, 2007). In fact, a team-based approach to PHC has become the focus in Canada and helps to ensure that each health service is provided by the most appropriate professional, at the most appropriate time and in the most appropriate location.

2.1.2 Primary Health Care in Canada

Canada has thirteen provincial and territorial health care systems that operate separately, but are united under the legislative framework of the 1984 Canada Health Act. In 2010, 71% of Canada's health spending was publicly funded, but the delivery of care was largely private (Hutchison et al., 2013). This means that most providers are independent contractors who are then reimbursed by the provincial or territorial governments. In the early 2000s, despite the country's universal health care coverage, the Canadian PHC system experienced a period of lagging behind other high-income countries on many PHC access and quality indicators (Blendon et al., 2001; Hutchison et al., 2011). In an international survey examining PHC quality among five high-income countries (Australia, Canada, New Zealand, United Kingdom and United States), 61% of Canadian family physicians (the highest among all five participating countries) were "very concerned" that their quality of care would decline in the future (Blendon et al., 2001). These findings, combined with a number of federal and provincial reports, led to

PHC reform in Canada. Although the goals and objectives of the provinces and territories for PHC and its reform differ, common themes included focus on improved access to PHC services; better coordination and integration of care; expansion of team-based approaches and partnerships; improved quality of care, with an emphasis on patient engagement and self-management; and the implementation and utilization of electronic records and other health information management systems (Hutchison et al., 2011). Since this transition, several PHC reform initiatives have been implemented broadly in one or more jurisdictions to advance the quality of care received by PHC patients. For example, Family Health Teams and Community Health Centres serve as the main interprofessional models in Ontario, while Family Medicine Groups (Groupes de medicine de famille) are the main delivery models in Québec (Hutchison et al., 2011).

A common criticism of PHC is the degree of "generalism" that this field of medicine provides to their patients (McWhinney and Freeman, 2009; Stange and Ferrer, 2009). This criticism is often referred to as the "paradox of primary health care". This includes two interrelated observations: 1) that PHC providers deliver poor quality of care for specific diseases, as compared to specialists; and 2) that PHC is associated with higher value health care for the whole person, resulting in better overall health, greater equity, lower health care costs and better quality of care for the broader population (Stange and Ferrer, 2009). Quality of care is commonly measured by the application of disease-specific, evidence-based process-of-care guidelines, where PHC tends to require a more generalist approach to delivering services. To date, family physicians and (increasingly) nurse practitioners are the principal sources of primary medical care in Canada. As such, the term "primary health care provider" will be used herein and refers to both family physicians and nurse practitioners. In their roles as primary health care

providers, these professionals deliver ongoing, accessible care to their patient population and build relationships with their patients to enhance the effectiveness of preventive and therapeutic interventions over time (Martin et al., 2014; McWhinney and Freeman, 2009; van Weel, 2005). Indeed, primary health care has been promoted as the building block of a high-value health care system and should be supported to achieve its goals of providing quality care to its patients (Stange and Ferrer, 2009; Chan, 2008; Rowan et al., 2007; Starfield et al., 2005).

A recent study conducted by Stewart and Ryan (2015) provided a Canadian synthesis of health care use at the population level. This study examined health care needs and health care use among provincial jurisdictions using the 2007 Canadian Community Health Survey (CCHS). This database provided a large sample size of over 100,000 respondents from the ten Canadian provinces (territories were excluded due to small sample sizes). The "ecology of health care" was assessed by province, after age-sex standardization per 1,000 individuals for those who were 15 years of age and older (Stewart and Ryan, 2015). This study measured visits with family physicians, visits with specialist physicians, visits with nurses and hospitalizations, as well as the presence of chronic diseases. In Canada, a total of 243 contacts were reported to a family physician per month per 1,000 people (Stewart and Ryan, 2015). This represented the most frequent number of contacts per month, as there were only 70 contacts per month to a specialist physician and 8 contacts per month that involved a hospitalization (both per 1,000 people). Notable variation was observed from province-to-province. In fact, monthly contacts with family physicians per 1,000 people ranged from as low as 158 contacts in Québec to as high as 295 contacts in British Columbia (Stewart and Ryan, 2015). Interestingly, the monthly rate of having at least one chronic condition ranged from 524 per 1,000 people in Québec to 638 per 1,000 people in Nova Scotia, indicating differences in chronic disease occurrence based on

geographic location (Stewart and Ryan, 2015). This study indicates the demand placed on the primary health care system at the population-level in Canada. When these PHC services are integrated, interdisciplinary and focused on the evolving health care needs of their patients, this system is well positioned to provide the important facets of chronic disease prevention and management to the populations they serve over time. Furthermore, these PHC providers can deliver ongoing care to their patients, developing relationships that are beneficial to achieving better health outcomes.

2.1.3 Chronic Disease Management in Primary Health Care

According to the 2014 WHO Global Status Report on Noncommunicable Diseases, noncommunicable or chronic diseases are of a long duration and generally demonstrate slow progression (WHO, 2014). These are health issues that require ongoing management over a period of years or decades (WHO, 2014). The definition of "chronicity" proposed by O'Halloran et al. (2004) is a disease lasting at least six months, having a documented pattern of recurrence or deterioration, as well as an impact on an individual's quality of life. Individuals living with chronic diseases (and particularly those with multiple chronic diseases) often manage complex treatment regimens that can include multiple appointments, multiple medications, regular monitoring and adherence to different treatment and management protocols (Moffat and Mercer, 2015; Onder et al., 2015; Mercer et al., 2014; Smith et al., 2012; Sinnott et al., 2013; Fortin et al., 2007; Boyd et al., 2005). For patients who are living with chronic diseases, access to regular and effective PHC services can be highly desirable and associated with better health outcomes (Smith et al., 2012; Soubhi et al., 2010; Noël et al., 2005; Starfield et al., 2003).

In Ontario, almost two-thirds of respondents to the 2014 Commonwealth Fund International Health Policy Survey of Older Adults who were living with chronic diseases reported that they had easy access to a professional who could help with medical questions between visits (Health Quality Ontario, 2015). Similarly, the 2011 Commonwealth Fund Survey of Sicker Adults found that 96% of respondents with a chronic disease had access to a regular medical doctor (Health Council of Canada, 2011). The vast majority (95.1%) of adults aged 40 years and older in the four western Canadian provinces (British Columbia, Alberta, Saskatchewan and Manitoba) indicated they had access to a regular medical doctor (Weaver et al., 2014). Generally, these results indicate that many Canadians with a disease that is of long duration and generally slow progression are able to access their PHC provider. However, there is a need to provide a complement of health care professionals in order to achieve the most successful health outcomes for these patients (Rudland and Macey, 2013; Smith et al., 2007; Hemmelgarn et al., 2007; Noël et al., 2007). This includes the involvement of health professionals like dietitians, pharmacists, social workers, physiotherapists and occupational therapists, many of which are now actively recruited into team-based settings. Even further, these teams may involve specialist physicians, such as a psychiatrist or a geriatrician. This increasingly diverse set of professionals will help to address the multidimensional needs of many individuals who are living with chronic disease.

As stated by Barbara Starfield (2011), "Neither morbidity nor multimorbidity is randomly distributed in populations. People and populations differ in their overall vulnerability to illness and resistance to threats to their health; some have more than their share of illness and some have less". To date, a clear and comprehensive understanding of why "people and populations differ in their overall vulnerability" and why some chronic diseases tend to cluster together within

certain individuals. Indeed, this life course approach to understanding the occurrence of individual chronic diseases, as well as multiple chronic diseases, is a large area of complex and longitudinal research. More specifically, it is unclear how patients accumulate one disease after another, as compared to other patients who remain unhindered by disease throughout their lifetime (van den Akker et al., 2006). Extensive research has been conducted examining the aetiology of individual chronic diseases (Ben-Shlomo et al., 2016; Non et al., 2014; Kamphuis et al., 2013; Braveman and Barclay et al., 2009; Lynch and Smith, 2005; Barker 2004; Kuh et al., 2004), however, a small subset of studies has examined the aetiology of multiple pathologies or general disease susceptibility for multimorbidity, using a life course approach (Wister et al., 2016; Vos et al., 2015; Pavela and Latham, 2015; Tomasdottir et al., 2015; Tucker-Seeley et al., 2011). An article published more than twenty years ago by van den Akker et al. (1996) identified the need for causal explanations or description of general susceptibility for disease in observed patterns of chronic disease accumulation. Not only did this publication identify the need for a differentiation between comorbidity and multimorbidity, but it signified the need to understand the occurrence of multiple diseases in more detail.

Some patients may be more vulnerable to the co-occurrence of chronic diseases due to genetic and immunological factors, the environment in which they live and work, lifestyle behaviours and their level of adaptive or coping capacities (van den Akker et al., 1996). Individual patient characteristics, such as stressful life events, vulnerability to stress, (mal)adaptive approaches to illness and personal locus of control could be influential factors in disease accumulation (van den Akker et al., 1996). Moreover, some chronic diseases may have a common aetiology, common predisposing characteristics or a shared pathogenesis. For example, although the aging process can vary from patient-to-patient, the biological ageing of organ

systems can lead to increased general vulnerability for disease (van den Akker et al., 1996). As well, some health care providers may be more aggressive in diagnosing, treating and managing symptoms presented by their patients, due to personal or contextual influences on clinical care behaviours (Vos et al., 2015). Finally, and particularly with the use of electronic records for research, the potential influence of "detection bias" may result in increased chronic disease burden. This detection bias refers to the fact that patients who have already been diagnosed with one disease will contact the health care system more often than those who are relatively healthy. As such, these patients will likely be examined more frequently and more extensively than their healthy counterparts (van den Akker et al., 1996). Consequently, these patients are more likely to be diagnosed with additional diseases, and may be more alert in recognizing or presenting with symptoms for examination (van den Akker et al., 1996). The time elapsing between diagnoses indicates an important period to either detect further pathophysiology or to avoid the potential for overdiagnosis. While clinical judgement is intrinsic to family medicine, this represents a point of intervention to avoid further disease progression. Therefore, the management of chronic diseases over time and the assessment of variables that may influence the accumulation of chronic diseases over time is an important, yet fairly unexamined, area of research for those patients living with multiple chronic diseases.

2.2 Electronic Medical Records

2.2.1 Definition of Electronic Medical Records

Computer-based technology and the associated digital infrastructure, such as an electronic medical record (EMR), can be particularly useful in facilitating the delivery and organization of care to patients over time. An EMR is a computer-based repository of patient

information, which is securely stored and readily accessible to authorized users. These electronic records represent an important shift from traditional paper-based records and their primary purpose is to support continuous, comprehensive, efficient and high quality health care (Manca, 2015; Canada Health Infoway, 2013; Health Council of Canada, 2011; Schoen et al., 2009; Hayrinen et al., 2008). Several elements can be documented within an electronic record including patient demographics, lifestyle behaviours, presenting complaints or symptoms, past medical history, family history, physical examination findings, clinical diagnoses, laboratory tests and corresponding results, diagnostic imaging, medication administration, allergies, immunizations, referrals, hospital admission and discharge notes (Canada Health Infoway, 2013; Tu et al., 2015).

Health care systems are also increasingly offering patients the ability to access and manage their health information through their own personal health record or through companion applications such as health-related mobile applications or patient portals (Manca, 2015; Zulman et al., 2015b; Goldzweig et al., 2013). Patient portals, in particular, are designed to give patients secure access to health information (such as appointment and laboratory test results) and allow secure methods for communication and information sharing between patients and their PHC provider (Goldzweig et al., 2013). In comparison, an EMR is only accessible to an authorized health professional or health organization (Canada Health Infoway, 2013). For example, within a single PHC organization, those with access to the EMR system can be family physicians, nurse practitioners, nurses, medical trainees (e.g., residents and medical students), administrative staff and (in some cases) allied health professionals.

These EMR software programs can hold thousands of individual patient records, but allow each health care provider to enter relevant patient-level data in unique ways (e.g., highly

structured or “drop-down” data recording vs. highly unstructured or “free-text” data recording). These EMR systems can also be integrated with other software that manages activities such as billing and appointment scheduling. Canada Health Infoway is working towards the goal of one electronic medical record system for all Canadians. However, since health care is organized at the provincial and territorial level, each jurisdiction has its own EMR adoption program and policies (Tu et al., 2015). This has had three important consequences: 1) there are multiple vendors or companies that develop and sell EMR software programs to health care organizations, such as PHC practices and hospitals; 2) there are no consistent or enforced guidelines for recording clinical information within these electronic records; and 3) there is not a single repository in Canada that automatically collects all of this clinical information. The United Kingdom and its Clinical Practice Research Datalink is an excellent example of a country that has recorded health-related data for every person registered with the National Health Service, from birth to death, within a singular clinical database (Clinical Practice Research Datalink, 2016). The Canadian Primary Care Sentinel Surveillance Network (CPCSSN), which will be described further in the next chapter, was established to address this notable gap in the Canadian EMR landscape (Birtwhistle and Williamson, 2015; CPCSSN, 2016; Birtwhistle, 2011).

2.2.2 Adoption and Use of Electronic Medical Records in Canada

A systematic review conducted by Chang and Gupta (2015) indicated that the rates of adoption of EMRs in Canada have increased from about 20% of physicians in 2006 to an estimated 62% of physicians in 2013. This study found substantial regional variation in adoption rates ranging from 40% of physicians in New Brunswick and Québec to more than 75% of physicians in Alberta (Chang and Gupta, 2015; Schoen et al., 2012). As the use of EMR systems

becomes increasingly common in PHC settings throughout Canada, it is important that these EMR systems are used as effectively and efficiently as possible to maximize benefits and improve quality of care (Terry et al., 2014; Canada Health Infoway, 2013). A recent study by Paré et al. (2015) assessed the EMR use patterns of 331 family physicians in Québec and determined that EMR systems "as-used" vary substantially from one family physician to another in terms of the system capabilities that are actually mobilized in day-to-day clinical care. The group of family physicians that were most impacted by their EMR system were those who had the longest usage experience and consciously made the most use of their system's capabilities (Paré et al., 2015). However, many EMR adopters use only a fraction of their software's available functions and perceive the enhanced use of EMR systems as a substantial and underused opportunity (Paré et al., 2015; Chang and Gupta, 2015). User-cited benefits of the adoption of an EMR system into clinical care include time savings, improved record keeping, heightened patient safety and confidence in the retrieved data when EMRs are used efficiently (Chang and Gupta, 2015). In comparison, user-cited barriers to EMR adoption included financial and time constraints (particularly for initial adoption of an EMR system), lack of knowledgeable support personnel, lack of interoperability with hospital and pharmacy systems and lack of integration with other allied health professionals (Chang and Gupta, 2015).

A recent study conducted by Zulman et al. (2015b) demonstrated that from the perspective of patients living with multiple chronic diseases, the presence of an EMR can markedly alleviate challenges and create opportunities for enhanced support. In a similar sense, EMR use can support improved interactions and communications among members of the health care team, as well as between providers and patients (Canada Health Infoway, 2013). The patient-provider relationship may improve through additional opportunities for patient education

(e.g., trending of test results over time), availability of information in real-time to facilitate decision-making and options for patients and providers to communicate via secured messaging (Manca, 2015; Canada Health Infoway, 2013). In contrast, the use of EMRs may introduce challenges in building rapport between patients and providers, such as the distraction of entering information electronically during the encounter or the unsuitable placement of the computer in the examination room (Canada Health Infoway, 2013). To date, a balance between the benefits and challenges of EMR use has not been consistently achieved.

2.2.3 Use of Electronic Medical Records in Epidemiological Research

Structured electronic records provide the potential to access point-of-care data to inform clinical practice and to conduct academic research. With meaningful use, including standard and consistent data entry in specific fields, EMR data can provide valuable practice-level information (Manca, 2015). Epidemiological studies and public health assessments that measure population morbidity often rely on the development and administration of surveys, which can capture self-reported morbidity among a sample of the target population of interest. An alternative approach is to utilize information and diagnoses recorded during routine consultations in a clinical setting, particularly in a PHC setting. An advantage of PHC consultation data is that encounter-level information is collected longitudinally or at multiple time points. This information is recorded at individual encounters between the patient and their PHC provider when the patient presents for a clinical visit. This is distinct from typical population-level surveys, which are specifically designed for a one-time or cyclic administration.

However, it is important to recognize that these PHC consultations and their corresponding medical records do not necessarily reflect the "true" level of morbidity in a

population, as many of the symptoms or morbidities (e.g., conditions or diseases) a patient may be living with are not brought to the attention of the PHC provider. As well, a patient may be living with a morbidity that remains undetected by the PHC provider. In a study completed by Barber et al. (2010), the estimated population burden of multiple chronic diseases was actually very similar between a population-level survey and an electronic medical record and was more consistent for diseases with clear diagnostic features, such as diabetes mellitus. Electronic medical records provide data that can reflect the entire care experience and can be analyzed for entire populations receiving care (e.g., entire PHC practices and potentially in an ongoing and real-time basis). This source of data can also improve the depth and breadth of information available for research based on the longitudinal and patient-level data that are recorded.

Other sources of data, such as administrative data recorded for billing purposes, can be used to capture real-world clinical information from a large population of patients (e.g., even whole provinces such as Ontario or Alberta). These data, which can be held and analyzed by the Canadian Institutes for Health Information, can be very valuable for clinical and policy purposes. However, these data do not cover the breadth of clinical information from the PHC perspective and are limited to patients who appear in the administrative database after receiving adjudicated claims (e.g., prescriptions or hospital visits). In comparison, primary data collection, such as surveys, allow researchers the ability to structure data collection to capture specific variables of interest. This is particularly valuable for information that is not typically collected or contained within a medical chart or an administrative database, such as patient socioeconomic characteristics, experiences of disease or satisfaction with clinical care. The challenges of primary data collection (e.g., surveys) include the time and resources that are required to recruit a sufficient number of participants (Belletti et al., 2010).

Electronic medical records offer great potential for research, enabling the rapid identification of patients in the context of primary health care. EMRs use a combination of structured data and unstructured (or free text) data (CIHI, 2013; Orueta et al., 2012; Terry et al., 2010). The balance between these two components varies across different record systems with some EMRs consisting primarily of coded data and others are a combination of coded and free text fields. The accuracy of a diagnostic code within an electronic record depends on two steps: whether the code accurately reflects the provider's clinical opinion and whether that diagnosis was correct (Coleman et al., 2015; Nicholson et al., 2011). A valid diagnostic code indicates that a provider believes that: 1) a patient has a specific symptom, condition or disease; 2) this clinical diagnosis is correct; and 3) this diagnosis code is accurately recorded within the patient's EMR. Occasionally, a code may be entered in error and not corrected (Greiver, 2015; Nicholson et al., 2011). Alternatively, a provider may make a diagnosis, but not record it (Tu et al., 2015; Weiskopf et al., 2013; Thiru et al., 2003). The practice of recording diagnostic codes is yet to be fully understood and requires further research (Coleman et al., 2015; Orueta et al., 2012). At present, the extent of accurately identified and non-missing cases in an electronic record database can be estimated by comparison of prevalence rates obtained from within the database with those from external sources, such as administrative datasets or population-based estimates.

Increasingly, the data contained within EMRs are being used for research purposes. Although not collected for research purposes, these records contain rich, longitudinal and individual-level data for each patient visiting their PHC provider. When the quality of these data can be ensured, researchers using a PHC EMR database often have access to more robust clinical data, when compared with self-reported surveys or administrative data. For example, comprehensive and quality information can be derived from the diagnoses or referral data within

an electronic record. Work is needed to enhance the coding practices of PHC providers, as well as the technologies that are used by the PHC community, so that all data recorded in these EMRs can be put to better use in clinical and epidemiological research, health services planning and health care policy decisions (Terry et al., 2014; Hayrinen et al., 2008; Lobach and Detmer, 2007; Thiru et al., 2003).

2.3 Multimorbidity

2.3.1 Concept of Multimorbidity

The issue of multimorbidity (that is, multiple chronic diseases occurring within the same individual) is among the 21st century's major emerging health issues and poses a myriad of challenges for public health, primary health care and community care (Afshar et al., 2015; Mercer et al., 2014; Parekh and Goodman, 2013). Moving beyond the health challenges and economic burden of individual chronic diseases, the emerging prevalence of multimorbidity will potentially lead to a substantial increase in demands on our society in the near future (Stewart et al., 2013). The construct of "comorbidity" dates back to 1970, when Alvin Feinstein used the term in addressing the functional effects of comorbid conditions on the patient, as well as the combined effects of these comorbid conditions on the patient's clinical profile (Feinstein, 1970). Feinstein first defined the term "comorbidity" as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" (Feinstein, 1970). This definition implies that the index disease under study is of principal importance and is the main focus for the health care provider. Although used interchangeably in the past by many authors, there are important distinctions between the terms "comorbidity" and "multimorbidity". The concept of "multimorbidity" describes the

"coexistence of two or more chronic diseases in the same individual", in which no one disease is designated the index disease or primary focus for the health care provider (van den Akker et al., 1996; Boyd and Fortin, 2011). This conceptual difference between the terms comorbidity and multimorbidity (Boyd and Fortin, 2011) has been adapted in this thesis and can be seen in **Figure 2.1.** In this adapted figure, the patient becomes ancillary to the co-occurring chronic diseases in the concept of comorbidity, as compared to the concept of multimorbidity, which facilitates a more holistic and patient-centered approach.

2.3.2 Operationalization of Multimorbidity

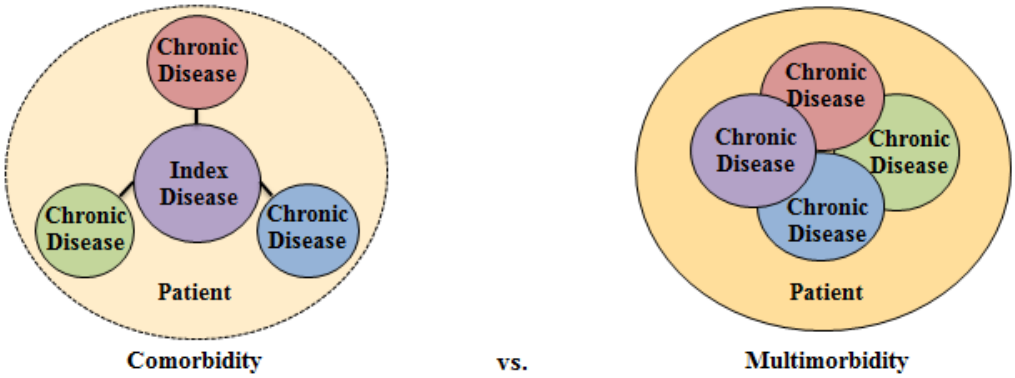
To date, there is no internationally accepted list of chronic diseases that define or capture patients with multimorbidity (Almirall and Fortin, 2013; Stewart et al., 2013; Diederichs et al., 2011). Researchers must therefore create a list that is suitable for their research purposes and corresponding data source. For this research, a list of twenty chronic disease categories and corresponding diagnostic codes were used. Based on previous international literature that examined the burden of multimorbidity among PHC patients using comprehensive national electronic health records, this list of twenty chronic diseases was created (Mercer et al., 2014; Barnett et al., 2012; Diederichs et al., 2011; George et al., 2006; Bayliss et al., 2005; Byles et al., 2005; Crabtree et al., 2000; Greenfield et al., 1993; Charlson et al., 1987). This final list was compared with more recently published definitions of multimorbidity (those studies that have published the list of individual chronic diseases), to assess consistency in diseases and disease categories that were captured. The comparison among lists is presented in **Table 2.1**.

Perhaps one of the reasons for the varying definitions and conceptualizations of multimorbidity in the literature is the lack of a clear philosophical understanding of what it

means to examine the multidimensional concept of "multimorbidity". For example, part of the problem in choosing an appropriate measure of multimorbidity is due to the abstract nature of the concept of multimorbidity and how it relates to other concepts, such as disease burden and patient complexity (Huntley et al., 2012; Valderas et al., 2009). The methodology used to measure multimorbidity is based on the underlying elements of multimorbidity that are important for research work (e.g., count numbers of chronic diseases, burden on distinct body systems, treatment burden, health system burden).

The definition of multimorbidity indicates the presence of multiple health issues within an individual. The use of the terms *disease*, *illness* or *condition* are often used interchangeably to describe these "health issues" of patients. The term *disease* refers to a defined pathological process with a characteristic set of signs and symptoms, while the term *illness* is frequently used as a synonym for disease, but in many cases it refers to the patients' personal experience of their disease (McWhinney and Freeman, 2009). In comparison, the term *condition* is a broader term that includes the concept of *disease*, as well as other health issues that fall outside of the traditional disease model (McWhinney and Freeman, 2009). For example, health issues like obesity or hypertension may be seen as pre-existing conditions and a preceding risk factor to subsequent diseases. Alternatively, they may be seen as their own chronic disease entity. In a recent study examining the various terms that have been used in research to describe multiple coexistent diseases, it was noted that the terms *disease* and *condition* were overwhelmingly used in the definition of multimorbidity and seem to be more appropriate for describing the coexistence of multiple health issues in a patient, particularly when no one disease has been identified as the index disease (Almirall and Fortin, 2013). Therefore, the term *disease* was used herein.

Figure 2.1 Conceptual diagram of the terms comorbidity and multimorbidity (adapted from Boyd and Fortin, 2010)



2.3.3 Measurement of Multimorbidity

Similar to its multiple definitions, multimorbidity can be measured in several different ways. Measures of multimorbidity broadly fall into two types: simple counts of diseases in individuals (with variation in the disease types included in this count) and indices to assess morbidity burden that differentially weight disease to account for burden of illness or number of body systems that are affected. Many commonly used indices were originally developed and validated among elderly or specialized patient populations or hospital-based populations (Brilleman and Salisbury, 2013; Huntley et al., 2012). To date, research has assessed the prevalence of multimorbidity by comparing between multiple measures (Harrison et al., 2014; Brilleman and Salisbury, 2013; Huntley et al., 2012; Diederichs et al., 2011; Valderas et al., 2009; Fortin et al., 2005).

A study that examined the predictive validity of 17 different measures (including simple disease counts, Adjusted Clinical Groups, Charlson Index of Comorbidity and Cumulative Illness Rating Scale) of multimorbidity and their relationship with related outcomes (e.g., health care utilization, health care costs, mortality and quality of life) found that simple counts of

disease performed almost as well as complex measures in predicting important outcomes in patients (Huntley et al., 2012). While the choice of measure of multimorbidity is primarily based on the suitability of the measure for the data available, this systematic review indicated that the most common approach to measuring multimorbidity is the use of simple disease counts (Huntley et al., 2012). However, it remains challenging to compare findings between studies examining the burden of multimorbidity, as different authors have utilized different lists of diseases in their measure of multimorbidity. Also hindering the comparability between studies is the fact that many publications do not include details about which diseases were included in the multimorbidity list and the criteria for inclusion (Diederichs et al., 2011). Similarly, most studies are based on counting of chronic diseases; however a definition of "chronicity" is rarely explicitly stated. This can again lead to varying lists of multiple chronic diseases.

While the simple count of chronic diseases tends to be the most common approach to examine the burden of multimorbidity, other commonly used indices to measure the burden of multimorbidity have included the Charlson Index of Comorbidity (Charlson et al., 1987), the Cumulative Illness Rating Scale (Miller et al., 1992), or indices that are applied to evaluate quality of outcomes and resource utilization, such as the Johns Hopkins University Adjusted Clinical Groups Case-Mix System (Salisbury et al., 2011). While these measures have been applied in previous research examining multimorbidity burden, they are more complex and were originally created for different purposes than estimating multimorbidity prevalence (e.g., risk of mortality or health care cost). Therefore, the simple count of chronic diseases may indeed be the useful approach to determining the prevalence of multimorbidity in a population. It may be anticipated that more complex measures of multimorbidity (e.g., the Charlson Index of Comorbidity, Cumulative Illness Rating Scale or Adjusted Clinical Group System) that

differentially weight diseases, would be more effective at predicting outcomes related to multimorbidity as compared to simple counts that weigh all diseases equally. However, some studies have concluded that simple measures, such as counts of chronic diseases, are almost as effective at predicting health care utilization and quality of life as more sophisticated measurements (Huntley et al., 2012). In fact, these approaches to measuring multimorbidity are more ideal as they are less costly (e.g., no registration or purchasing fee required) and can be more easily applied to secondary data sources (e.g., electronic records or administrative data).

To date, clear and comprehensive criteria for the selection of individual chronic diseases, which qualify for multimorbidity are still lacking. As a result, there is no clear agreement or consensus on the number and type of diseases to be included in multimorbidity research. In fact, existing definitions are characterized by their large degree of heterogeneity, considering as little as four diagnoses (stroke, coronary heart disease, hypertension and diabetes) by McGee et al. (1996) to as many as 185 diagnoses by Kadam et al. (2007). This often leads to incomparable prevalence levels across studies and a lack of a "gold standard" measure for multimorbidity. In a systematic review by Diederichs et al. (2011), researchers found that almost 60% of studies did not specify the criteria for selecting the list of diseases included in the multimorbidity measure. In these publications, a list of diseases was presented without any further explanation or justification for the list selected (Diederichs et al., 2011). Overall, the mean number of diseases that were considered in 39 multimorbidity indices was 18.5 diseases (median of 14 diseases). Interestingly, the range of the number of diseases was in fact rather small, with 87.2% of the indices including between 6 and 25 chronic diseases (Diederichs et al., 2011). When criteria were given, the most frequently used selection criterion was found to be those diseases that were "highly prevalent" in the population of interest (Diederichs et al., 2011). This systematic review

concluded that future multimorbidity indices should include and measure at least 11 diagnoses, particularly for studies that rely on ICD-10 diagnoses (Diederichs et al., 2011). It also highlighted the heterogeneity of existing indices and the need for a new, established instrument to assess multimorbidity.

Likewise, a systematic review conducted by Fortin et al. (2012) suggested that investigators designing future studies to assess the prevalence of multimorbidity should include at least 12 frequent chronic diseases and should attempt to report results for the two main definitions of multimorbidity: at least two and at least three chronic diseases. This more uniform operationalization and presentation of multimorbidity will assist in creating more comparable estimates of multimorbidity prevalence in the literature. Indeed, the comparable estimation of the burden of multimorbidity is important to fully characterizing this global health issue.

Valid comparisons of the prevalence rates of multimorbidity also require a rigorous methodological approach, with specific criteria made explicit in academic publications (Stewart et al., 2013; Schellevis, 2013; Fortin et al., 2012). According to Stewart et al. (2013), the criteria for comparability of multimorbidity studies include commonality in: 1) the definition of multimorbidity; 2) the definition of chronicity; 3) the level at which chronic diseases are defined (e.g., transient ischemic heart attack or cerebrovascular disease; split or lumped); 4) the list of chronic diseases that will be considered; and 5) the study population and data source being used (e.g., administrative, clinical or survey data). Ultimately, there is a need to establish an approach to measuring multimorbidity that balances both comprehensiveness (e.g., including all important diseases) and efficiency (e.g., particularly for use in large secondary databases) when measuring the burden of multimorbidity.

2.3.4 Prevalence of Multimorbidity in Community Populations

Managing chronic disease is a daily reality for at least one third of Canadians, with this proportion increasing as the Canadian population ages and risk factors continue to rise (Broemeling et al., 2008). These chronic diseases impact the health and wellbeing of individuals and represent a significant health system and economic burden. In their analyses of the 2005 Canadian Community Health Survey (CCHS Cycle 3.1), Broemeling et al. (2008) demonstrated that multimorbidity was a common experience as more than one-half of adults over the age of 65 years reported having at least two of seven chronic diseases (arthritis, cancer, chronic obstructive pulmonary disease, diabetes, heart disease, high blood pressure and mood disorders). This study also found that among the almost 9 million Canadian respondents (over the age of 12 years), approximately 33% had at least two of seven chronic diseases (Broemeling et al., 2008). Individuals living with chronic disease also use health care services (e.g., visits to a PHC provider) more often than individuals without chronic disease and the intensity of service use increases as the number of chronic disease diagnoses increases (Broemeling et al., 2008).

A systematic review conducted by Fortin et al. (2012) examined previously published prevalence estimates of multimorbidity in both general populations and primary health care populations from more than ten different countries, including Canada, the United States, the United Kingdom, the Netherlands and Australia. This review found that the prevalence of multimorbidity, defined as at least two diseases, ranged between less than 10% to as high as 70% in general population studies, stratified by age (Fortin et al., 2012), indicating wide variation.

In the United States, the National Health Interview Survey conducted in 2010 found that among respondents who were over the age of 18 years, 26% had at least two of ten chronic diseases and rates significantly increased among women and with advancing age (Ward and

Schiller, 2013). A study conducted by Barber et al. (2010) in the United Kingdom found similar rates of multimorbidity (defined as at least two of a possible seven chronic diseases) among more than 5,000 respondents aged 50 years of age and older who replied to a self-reported postal health survey (36.2%) and whose electronic medical record was also reviewed (32.3%). A study conducted in Spain by Violán et al. (2013) also found comparable prevalence levels of multimorbidity (defined as at least two of a possible 27 chronic diseases) among more than 15,000 respondents aged 15 years of age and older who responded to a self-reported national survey (Health Survey for Catalonia) and whose electronic medical record was reviewed for clinical chronic disease diagnoses (77.4% and 67.7%, respectively). Although conducted outside of Canada, this work indicates that there is reasonable agreement between prevalence estimates of multimorbidity derived from data sources that access general populations and primary health care populations.

2.3.5 Prevalence of Multimorbidity in Clinical Populations

Among primary health care populations, the prevalence of multimorbidity (defined as at least two diseases, ever diagnosed in the health record) has been calculated as high as 98.5% among patients aged 65 years or older (Fortin et al., 2012). In studies that included patients of all ages, an S-shaped curve was observed for the association between increasing patient age and the prevalence of multimorbidity. More specifically, multimorbidity prevalence was approximately 20% or lower before the age of 40 years, then increased dramatically between 40 and 70 years and finally plateaued around the age of 70 years (Fortin et al., 2012). Barnett et al. (2012) utilized a national EMR dataset in Scotland, which holds records for almost two million patients from 314 medical practices, representing about one-third of the entire Scottish

population. Among all patients, the prevalence of multimorbidity (defined as at least two of a possible forty chronic diseases) was found to be 23.2%, and the association between increasing patient age and prevalence showed the same S-shaped curve (Barnett et al., 2012). However, there was a notable excess of multimorbidity among those living in economically deprived areas. In fact, young and middle-aged adult patients living in economically deprived areas (measured using a deprivation score) had the same prevalence of multimorbidity 10 to 15 years earlier, as compared to adult patients living in the most affluent areas (Barnett et al., 2012). This echoed previous work that found that the most deprived people spend twice as many years in poor health before they die than those who live in affluent settings (Mercer et al., 2007).

A study conducted by Brett et al. (2013) estimated patterns and prevalence of multimorbidity across the entire age spectrum of patients attending two large metropolitan practices in Western Australia during a six-month period. Data were extracted from the medical records of 7,247 patients at the two practices and the Cumulative Illness Rating Scale was used to categorize 42 conditions into 14 domains. This study found that multimorbidity was present among 52% of patients examined. The prevalence of multimorbidity was 20.6% among patients younger than 25 years, 43.7% among patients aged 25 to 44 years, 75.5% among patients aged 45 to 64 years, 74.6% among patients aged 65 to 74 years and 92.0% among patients aged 75 years and older. These findings demonstrate the challenge and ultimate limitations of the single-disease framework by which most health care, medical research and medical education is structured. In fact, research demonstrates that the clinical care to manage multiple individual diseases can become duplicative, costly and inefficient. As well, this becomes burdensome and unsafe for patients because of poor coordination and integration of care and management plans. Better understanding of the epidemiology of multimorbidity, as well as a patient-centered

perspective to delivering this care, is necessary to develop proactive interventions to prevent or reduce the burden and to properly align health care services with patient need (Wang and Lo, 2016; Schattner et al., 2015; Green, 2013; Shippee et al., 2012; Soubhi et al., 2010). Until these changes are achieved, a significant burden will be felt by many key stakeholders: the patients and caregivers, the health care providers and the health care system.

2.3.6 Burden of Multimorbidity on Health Care System

Multimorbidity has been linked with adverse health outcomes including more frequent and longer hospitalizations (Gruneir et al., 2014; Agborsangaya et al., 2013; Gijsen et al., 2001; Librero et al., 1999), reduced functional status (Ryan et al., 2015; Vogeli et al., 2007; Bayliss et al., 2004), polypharmacy, (Smith et al., 2007; Boyd et al., 2005; Tinetti et al., 2004), compromised care and patient safety (Panagioti et al., 2015; Zulman et al., 2013; Vogeli et al., 2007; Gijsen et al., 2001), reduced quality of life (Agborsangaya et al., 2013; Boyd and Fortin, 2010; Fortin et al., 2007; Fortin et al., 2006), higher health care costs (Salisbury et al., 2011; Hartmann et al., 2011; Vogeli et al., 2007; Rapoport et al., 2004) and higher mortality (St. John et al., 2014; Gijsen et al., 2001). Studies have projected that the number of Americans living with chronic disease will increase from 125 million in 2000 to 164 million (or nearly 50% of the population) in 2030 (Anderson and Horvath, 2004). An estimated 78% of the total health care resources in the United States are devoted to individuals with chronic disease (Anderson and Horvath, 2004).

In a study conducted by Charlson et al. (2008), electronic medical records were used to construct a model that identified the demographic and clinical features (e.g., age, sex, multiple morbidities and medications) that were predictive of total yearly costs to the healthcare system.

Data were obtained for almost 6,000 patients over a one-year period and indicated a mean annual per patient health system cost of $2,655 (Charlson et al., 2008). In this predictive model, individuals with higher levels of morbidity (more disease diagnoses) incurred exponentially higher annual costs, ranging from $4,317 among patients with two morbidities to $13,326 among patients with seven or more morbidities (Charlson et al., 2008). More importantly, these predictive models help to identify those patients who are at high risk of costly and ineffective care. In fact, a study conducted by Alonso-Morán et al. (2015) found that predictive risk models for negative health outcomes (e.g., hospitalization, readmission, cost) were most accurate when measures of multimorbidity were included. This review indicated the impact of multimorbidity on adverse and repeated health care utilization (Alonso-Morán et al., 2015).

2.3.7 Burden of Multimorbidity on Primary Health Care Providers

As identified by the United States Department of Health and Human Services Initiative on Multiple Chronic Conditions, there is a need to catalyze change within the context of how chronic diseases are addressed, from an approach focussed on individual diseases to one that uses a multiple chronic disease approach. In fact, this report states that this process of evolution and refocus will require a "culture change, or paradigm shift" for PHC providers (United States Department of Health and Human Services, 2010). In a qualitative interview among 25 primary health care providers (15 physicians and 10 nurses) in the United Kingdom, providers identified tensions between delivering care to meet quality targets and fulfilling the patient's needs and these tensions were exacerbated with the presence of multimorbidity (Bower et al., 2011). Other challenges included the need for patients to coordinate and navigate their own health care path (through the health care system and with multiple appointments and providers); the difficulties of

self-management support for multiple diseases; and understanding the relationship between physical and mental health (Bower et al., 2011).

Clinical practice guidelines have been developed to guide clinical management decisions for patients and improve quality of health care delivery. However, adherence to current single morbidity-focused, single disciplinary guidelines may result in undesirable effects for those with multimorbidity, such as adverse interactions from polypharmacy and conflicting management strategies (Blozik et al., 2013; Boyd et al., 2005). Although clinical practice guidelines are not intended to replace the diagnostic, therapeutic and patient-centered priorities of the patient-provider encounter, providing health care in compliance with the current practice guidelines might in fact result in worse outcomes and increased cost for a growing population of complex (and even vulnerable) patients.

Boyd and colleagues (2005) illustrated the limitations of clinical practice guidelines by aggregating recommendations from relevant clinical guidelines for a hypothetical (yet typical) case of a 79-year-old woman with five common chronic diseases: chronic obstructive pulmonary disease, diabetes mellitus, osteoporosis, hypertension and osteoarthritis. This analysis found that most clinical practice guidelines did not modify or discuss the applicability of their recommendations for patients living with multimorbidity. If the relevant clinical practice guidelines were followed, this hypothetical patient would be prescribed 12 medications, 19 doses per day, which would cost her US$4,877 per year (assuming no prescription drug coverage). This patient would also have a complicated and often conflicting, list of 14 non-pharmacological activities, including weight bearing exercise and energy conservation (Boyd et al., 2005). Furthermore, none of the five clinical practice guidelines were patient- or family-centered as they did not discuss the burden of comprehensive treatment on the patients or caregivers. This review

provides evidence that current clinical practice guidelines do not provide an appropriate, evidence-based foundation for assessing quality of care in patients with multiple chronic diseases. In the Canadian context, Fortin et al. (2011) appraised 16 Canadian guidelines and assessed their relevance for patients with multimorbidity. This study found that although 56.2% of individual chronic disease guidelines addressed treatment for patients with multiple chronic diseases, three guidelines addressed specific recommendations for patients with two co-occurring diseases and only one addressed more than two concurrent diseases (Fortin et al., 2011). Indeed, it is widely recognized that current clinical practice guidelines provide little guidance for PHC providers on how to appropriately care for patients with multimorbidity (Tinetti et al., 2014; Blozik et al., 2013; Hughes et al., 2013; Guthrie et al., 2012; Tinetti et al., 2004). Furthermore, there is a need for PHC providers to form an ongoing and collaborative partnership with patients and their families to prioritize care efforts.

2.3.8 Burden of Multimorbidity on Patients and Caregivers

The full physical and psychological impact of multimorbidity can be highly dependent on the specific disease combinations within a patient, the severity of the coexisting conditions, the patient's age and their ability to effectively cope with multiple chronic diseases (Duguay et al., 2014; Smith and O'Dowd, 2007). Consequential impact is also felt by the family members and informal caregivers of those affected by multimorbidity. Interestingly, while support may be available in the community for single diseases (e.g., through the Heart and Stroke Foundation or the Canadian Diabetes Association), it is less likely to be available for those with multimorbidity (Smith and O'Dowd, 2007). There continues to be a lack of investigation into the longitudinality of multimorbidity, in which patients experiencing multimorbidity are followed over time to

understand their progression into more complex clinical profiles and how their associated needs evolve (Noël et al., 2005). As a result, complex patients are forced to depend on a health care system and societal resources that have been traditionally designed to serve only single diseases (Guthrie et al., 2012; Tinetti et al., 2012; Upshur et al., 2008). Moreover, there is often a mismatch between the needs and priorities as defined by patients and their caregivers and those priorities of their health care providers (Gill et al., 2014). As such, patients with multimorbidity are most in need of shared decision-making and enhanced communication with their providers.

Individuals living with multimorbidity face many challenges, including managing polypharmacy (Hughes et al., 2013; Blozik et al., 2013; Taylor et al., 2010; Noël et al., 2005; Boyd et al., 2005; Townsend et al., 2003; Bayliss et al., 2003), increased risk of drug interactions (Moffat and Mercer, 2015; Cheraghi-Sohi et al., 2013; Boyd and Fortin, 2010; Boyd et al., 2005), dealing with barriers to self-care and self-management (Kenning et al., 2015; Liddy et al., 2014; Morris et al., 2011; Bayliss et al., 2007; Boyd et al., 2005; Bayliss et al., 2003) and difficulties in coordinating health care services (Zulman et al., 2015; Gill et al., 2014; Gustafsson et al., 2013; Hartmann et al., 2011; Noël et al., 2005). Because of these challenges, research has confirmed that individuals living with multimorbidity place higher demands on the system and have poorer health outcomes. Multimorbidity can also impact an individual's overall quality of life (Agborsangaya et al., 2013; Boyd and Fortin, 2010; Fortin et al., 2007; Fortin et al., 2006). In a cross-sectional questionnaire (Health Related Quality Council of Alberta 2010 Patient Experience Survey) of almost 5,000 adult respondents in the province of Alberta, multimorbidity was associated with reduction in the health-related quality of life (HRQOL), which is a self-reported multi-attribute health utility instrument for describing and valuing health states (Agborsangaya et al., 2013). Moreover, a study conducted by Fortin et al. (2007) has detected

significant impacts on HRQOL among patients with multimorbidity, and even specific synergistic negative effects of co-occurring diseases (e.g., cluster of respiratory and cardiac morbidity). Overall, both quantitative and qualitative research demonstrates that those living with multimorbidity experience considerable pressure from the management of their chronic diseases and the maintenance of all other activities of daily life.

2.3.9 Natural History and Progression of Multimorbidity

Previous research has noted that examining how multimorbidity develops over time, as well as understanding causal mechanisms, is an important area for progress in our understanding (Boyd and Fortin, 2010; Valderas et al., 2009). The lack of prospective studies that examine the changing burden of multimorbidity over time has been highlighted in the literature (Strauss et al., 2014; France et al., 2012; Mercer et al., 2011). There is increasing recognition that clinicians must move away from the single disease management approach for patients with multiple chronic diseases and use an integrated treatment or management plan for these patients. However, greater insight is required to provide the evidence for these treatment and management plans. Research that identifies clusters of the most prevalent chronic diseases and investigates the nuanced patterns or natural history of multimorbidity could indicate areas in which evidence-based information can integrate clinical practice guidelines for multimorbidity. The study of the amount of time elapsing between chronic disease diagnoses may provide important points of focus for prevention. More specifically, identifying those patients who are considered to be most "at risk" of developing a subsequent chronic disease can allow both clinicians and researchers to focus on this cohort of patients and to create resources to potentially avoid the next occurrence of chronic disease. To date, this has not been achieved in the multimorbidity literature.

2.3.10 Clusters and Patterns of Multimorbidity

When analyzing the impacts of multimorbidity, previous literature has focused on the descriptive counting of individual diseases or the simple link between co-occurring pairs of diseases. However, the analysis of cumulative interactions and non-random associations between chronic disease diagnoses can lead to a deeper understanding of the multidimensional burden and impacts of multimorbidity (Sinnige et al., 2015; Vos et al., 2014; Garin et al., 2014; Prados-Torres et al., 2014; Prados-Torres et al., 2012). A retrospective study using an exploratory factor analysis and EMR data from 275,682 adult patients in Spain and found that five patterns of multimorbidity could be detected (Prados-Torres et al., 2012). These five patterns were: cardio-metabolic (e.g., diabetes, hypertension and heart disease); psychiatric-substance abuse (e.g., psychosis and neurosis); mechanical-obesity-thyroidal (e.g., low back pain, varicose veins of lower extremities and osteoporosis); psychogeriatric (e.g., dementia and Parkinson's disease); and depressive (e.g., depression and insomnia). In the systematic review conducted by Prados-Torres et al. (2014), 97 patterns composed of two or more diseases were detected and the three most prevalent combinations of chronic diseases were classified as: cardiovascular and metabolic diseases; mental health problems; and musculoskeletal disorders. In comparison, a systematic review conducted by Sinnige et al. (2015) found that among older adult populations, depression was the disease that was most commonly clustered with other disease diagnoses and was specifically paired with eight other diseases (hypertension, arthritis, diabetes mellitus, asthma or chronic obstructive pulmonary disease, stroke, cancer, heart failure and heart disease). This work is beginning to uncover the previously unexplored complexities of multiple chronic diseases within an individual. A comparable set of multimorbidity patterns, identified in the Canadian primary health care context, has yet to be established. This research

will work to address this gap in order to create a deeper understanding of the complexity of multimorbidity in Canada.

As demonstrated, the epidemiology of multimorbidity has been examined in international literature and a recent editorial concluded that although new descriptive epidemiological studies will likely show similar trends as seen in past multimorbidity literature (despite variations in methodology), future work should focus on statistical clustering of chronic diseases and the development of prevalence rates of multimorbidity over time (Schellevis, 2013). Studies examining the (statistical) clustering of diseases, showing higher prevalence rates of combinations of chronic diseases than can be expected by chance (observed vs. expected rates), may provide clues for further exploration of etiological factors. Moreover, the study of living with multimorbidity must take a life course view, examining the development of multiple chronic diseases over time. Such studies may provide clues for preventing or delaying the occurrence of subsequent chronic diseases, as well as support health care planning and program development to address patient needs (Schellevis, 2013; France et al., 2012; Mercer et al., 2011).

2.4 Summary

The current literature has indicated the importance of creating a more nuanced understanding of multimorbidity, the critical role of primary health care and the emerging benefits of using EMR data for epidemiological research. As such, this research will use a large national EMR data source to determine the burden of multimorbidity among adult PHC patients across Canada. The intent of this doctoral research is to add to the growing international multimorbidity literature, as well as to contribute a perspective to improving the care and well-being for this increasing and complex patient population.

Table 2.1 Comparison of multimorbidity chronic disease lists from publications in multimorbidity literature and the current list of twenty chronic disease categories

Chronic Disease Category	Pefoyo et al., 2015	Roberts et al., 2015	Tonelli et al., 2015	St. Sauver et al., 2015	Zulman et al., 2015	Fortin et al., 2014	Rocca et al., 2014	Strauss et al., 2014	Ornstein et al., 2013	Agborsangaya et al., 2012
Hypertension	++	-	++	++	++	++	++	++	++	+
Obesity	-	-	-	-	-	++	-	++	++	+
Diabetes	++	+	++	++	++	++	++	++	++	+
Chronic Obstructive Pulmonary Disease or Asthma	++	+	++	++	++	++	++	++	++	+
Hyperlipidemia	+	-	-	++	-	++	++	-	++	+
Cancer	++	+	++	++	++	++	++	-	-	+
Cardiovascular Disease	++	+	++	++	++	++	++	++	++	+
Heart Failure	++	-	++	++	++	++	++	++	++	+
Anxiety or Depression	+	+	+	++	+	++	+	-	++	+
Osteoarthritis or Rheumatoid Arthritis	++	+	+	++	+	++	+	++	++	+
Stroke or Transient Ischemic Attack	++	+	++	++	++	++	++	-	++	+
Thyroid Problem	-	-	+	-	++	++	-	++	-	-
Kidney Disease or Failure	++	-	++	++	++	++	++	++	++	+
Osteoporosis	++	-	-	++	++	++	++	++	++	-
Dementia	++	+	++	-	-	++	++	++	++	-
Musculoskeletal Problem	-	-	+	-	++	++	-	+	-	+
Stomach Problem	-	-	++	-	+	-	-	-	++	+
Colon Problem	-	-	++	-	+	-	-	-	-	-
Liver Disease	-	-	++	++	++	-	+	-	++	-
Urinary Problem	-	-	-	-	++	-	-	-	-	-

Note: ++ indicates that the definition, diagnosis codes and/or disease categories were the same or almost similar; + indicates that the definition, diagnosis codes and/or disease categories were somewhat similar; - indicates that no comparable definition, diagnosis codes or disease categories were identified

Table 2.1 Comparison of multimorbidity chronic disease lists from publications in multimorbidity literature and the current list of twenty chronic disease categories, *Continued*

Chronic Disease Category	Barnett et al., 2012	Muggah et al., 2012	Prados-Torres et al., 2012	Rizza et al., 2012	van Oostrom et al., 2012	Diederichs et al., 2011	Broemeling et al., 2008	George et al., 2006	Bayliss et al., 2005	Byles et al., 2005
Hypertension	++	++	++	++	-	++	++	-	++	++
Obesity	-	-	++	++	-	-	-	-	+	-
Diabetes	++	++	++	++	++	++	++	++	++	++
Chronic Obstructive Pulmonary Disease or Asthma	++	++	++	++	++	++	++	++	++	++
Hyperlipidemia	-	-	++	-	-	-	-	-	++	-
Cancer	++	-	++	++	++	++	++	+	++	++
Cardiovascular Disease	++	++	++	++	++	++	++	++	++	+
Heart Failure	++	++	++	++	++	-	-	+	++	++
Anxiety or Depression	++	-	++	++	++	++	+	-	++	++
Osteoarthritis or Rheumatoid Arthritis	++	-	+	++	++	++	+	-	++	++
Stroke or Transient Ischemic Attack	++	++	-	++	++	++	-	-	++	++
Thyroid Problem	++	-	++	++	-	-	-	-	++	-
Kidney Disease or Failure	++	++	++	+	-	++	-	+	-	+
Osteoporosis	-	-	++	++	++	++	-	-	++	-
Dementia	++	-	++	++	++	++	-	++	-	-
Musculoskeletal Problem	+	-	++	++	++	-	-	-	+	+
Stomach Problem	++	-	++	++	-	-	-	+	++	-
Colon Problem	++	-	++	++	+	-	-	-	++	+
Liver Disease	++	-	++	++	-	-	-	-	-	++
Urinary Problem	+	-	-	++	-	-	-	+	-	-

Note: ++ indicates that the definition, diagnosis codes and/or disease categories were the same or almost similar; + indicates that the definition, diagnosis codes and/or disease categories were somewhat similar; - indicates that no comparable definition, diagnosis codes or disease categories were identified

Chapter 3

3 Research Objectives

The objectives of this doctoral research are two-fold. Objective One is to understand the prevalence and characteristics of adult (at least 18 years of age) primary health care patients within the CPCSSN database who are living with multimorbidity as of September 30, 2013. This objective will also determine the clusters of multiple chronic diseases that tend to occur most frequently together among patients with multimorbidity. Objective Two will build on this initial understanding to provide more robust information on the natural history or progression of multimorbidity among adult PHC patients over time. Both objectives will contribute to the understanding of multimorbidity in PHC using the national and longitudinal electronic medical record database from the Canadian Primary Care Sentinel Surveillance Network.

3.1 Objective One

The first objective has three key research questions (included below), which will measure the point prevalence, characteristics and clusters of multimorbidity among adult PHC patients. More specifically, this objective will determine the prevalence (and corresponding 95% confidence intervals) of multimorbidity, defined as at least two chronic diseases and at least three chronic diseases occurring in the same individual. The characteristics of patients living with multimorbidity will also be reported. These characteristics will be compared to those characteristics found in the scientific literature. Previous research has indicated that many patients living with multimorbidity are more likely to be older, female and live in a rural or low socioeconomic setting (Barnett et al., 2012; Salisbury et al., 2011; Harrison et al., 2013; Britt et al., 2008; Uijen et al., 2008; Fortin et al., 2005; van den Akker et al., 1998).

Objective One Research Questions:

1a) What is the point prevalence of multimorbidity among adult PHC patients within the CPCSSN database as of September 30, 2013?

1b) How does this prevalence compare to those prevalence estimates reported in the scientific literature?

2a) What are the common characteristics of adult PHC patients with multimorbidity within the CPCSSN database?

2b) How do these characteristics compare to those reported in the scientific literature?

3a) Among adult PHC patients with multimorbidity, what are the most frequent combinations (that is, unordered clusters) of multiple chronic diseases?

3b) Among adult PHC patients with multimorbidity, what are the most frequent permutations (that is, ordered clusters) of multiple chronic diseases?

3.2 Objective Two

The second objective has three research questions (included below), which will examine the natural history and changing burden of multimorbidity over time among adult PHC patients. This objective will examine the time-to-event patterns of multiple chronic disease diagnoses, among a cohort of adult patients. More specifically, the amount of time elapsing (in days) between multiple chronic disease diagnoses will be determined using a multilevel recurrent event survival analysis. In order to account for clustering of events at the patient-, provider- and practice-level, the multilevel survival analysis will assess the variance contributed by each level. Research has

suggested that chronic diseases involving related body systems will lead to a quicker accumulation of related chronic disease diagnoses, beyond the effect of increasing age (Strauss et al., 2014). However, previous research has not indicated the extent to which patient-, provider- and practice-level factors will impact the subsequent rate of chronic disease accumulation.

Objective Two Research Questions:

1) Among adult PHC patients with at least one chronic disease, what is the mean time elapsing until next chronic disease diagnosis?

2) Does the mean time until next chronic disease decrease as the number of chronic disease diagnoses increase?

3) What are the patient-, provider- and practice-level variables that predict the mean time until next chronic disease diagnosis?

Chapter 4

4 Methodology

This chapter will describe the key elements of this doctoral research: the main data source, relevant database variables, database management techniques, study design and statistical analyses for Objective One and Objective Two.

4.1 Canadian Primary Care Sentinel Surveillance Network Database

Data were derived from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database located in Kingston, Ontario (CPCSSN, 2016; Birtwhistle, 2011). This network was initially funded in 2008 by the Public Health Agency of Canada (PHAC) to develop a national repository of primary health care information derived from EMRs (Queenan et al., 2016; Birtwhistle, 2011; Birtwhistle et al., 2009). This information was intended to be a resource for monitoring chronic disease in Canada, as well as for PHC-oriented research. CPCSSN's vision is to collect these point-of-care data and facilitate clinical and epidemiological research to understand the health of Canadians from the PHC perspective (CPCSSN, 2016). CPCSSN also strives to build a stronger national knowledge base on chronic disease management, in order to improve the quality of PHC delivery for millions of Canadians (CPCSSN, 2016).

CPCSSN is a growing entity with ongoing recruitment of practice-based research networks: PHC sites (nested within networks), PHC providers (nested within sites), PHC patients (nested within providers) and health care encounters (nested within patients). This multilevel structure of the CPCSSN data is presented in **Appendix A.** While this database does not include all PHC patients across Canada, these data represent the largest source of patient-level PHC data that are available in Canada. For CPCSSN, database recruitment begins at the network level

(e.g., in a specific geographic area like London, Ontario or Halifax, Nova Scotia), followed by the recruitment of PHC sites and providers in the network's geographic area. CPCSSN has attempted to achieve representativeness in their network locations (e.g., recruitment has recently begun in the Northwest Territories), as well as representative patient and provider characteristics. The participation of PHC sites and providers is not random, but instead relies on a number of related factors: self-selection of sites and providers that utilize EMR systems and are interested in participating in CPCSSN; providers who are willing to contribute their patients' EMR data; logistics of data extraction and geographic location of the sites (e.g., limiting potential participation of rural and remote sites); and financial remuneration to participating providers, which can impact initial recruitment and sustainability of participating networks. To date, the CPCSSN database includes PHC sites from inner-city, urban, suburban, small town and rural settings and is continuously looking to expand its coverage and representativeness (Queenan et al., 2016; Godwin et al., 2015).

A recent study determined the level of representativeness of both patient and provider characteristics in the CPCSSN database, as compared to the broader Canadian population. Queenan et al. (2016) identified that CPCSSN patients were slightly older than the age reported by the 2011 Canadian Census (mean age of CPCSSN patients was 3.5 years older than the mean age calculated from the 2011 Canadian Census), but followed the same patterns of sex distribution (slightly larger proportion of females in both populations) and residential location (majority of patients and respondents were living in an urban setting). The provincial-level comparison indicated a lack of representation from Québec and British Columbia within the CPCSSN database (Queenan et al., 2016). This was likely due to the health legislative requirements in Québec that has slowed recruitment and because the network located in British

Columbia is relatively new and still recruiting providers and patients (Queenan et al., 2016). Likewise, the PHC providers in the CPCSSN database had similar characteristics as those reported in the 2013 National Physician Survey (NPS). Among both populations, similar distributions were seen among provider age, provider sex and whether the providers practiced in a rural or urban location (Queenan et al., 2016). However, this study identified a larger proportion of academic primary health care centres participating in the CPCSSN database, as compared to those reported in the 2013 NPS (Queenan et al., 2016). The representation of the CPCSSN data will continue to improve as the number of sites, providers and patients increase.

Each participating CPCSSN site and provider was recruited after transitioning from paper-based to electronic-based health records. As such, each site had a pre-adopted EMR software type (e.g., Wolf or Nightingale). As well, each site varied in when the EMR was adopted and implemented (e.g., when the transition took place) and the extent to which the EMR system is used in daily clinical care. For example, some sites may rely heavily on their EMR software for scheduling appointments and ordering referrals, but may not enter complete or consistent diagnostic information during patient encounters (Coleman et al., 2015; Orueta et al., 2012; Lau et al., 2012; Hayrinen et al., 2008). Other sites may achieve a higher level of "meaningful use", in which their EMR system is used regularly as an important tool for disease prevention and ongoing disease management (Manca 2015; Terry et al., 2014; Blumenthal et al., 2010; Thiru et al., 2003). In these sites, the providers actively engage with their EMR software for each patient encounter. These patterns of meaningful use can vary from site to site and from provider to provider. Throughout this thesis, the term "software" will refer to the EMR software program (e.g., Nightingale or Wolf) used by a PHC provider, whereas the term "record" will refer to the individual patient-level data.

Every three months, de-identified data are extracted from the participating sites' EMR software by the regional CPCSSN data managers (individuals who are skilled in information technology). These extracted data are then cleaned, coded and transformed into a common data format that is compiled into the secure CPCSSN database. The exact details of these data extraction processes vary slightly from network to network (e.g., some extractions are conducted remotely, while others require in-person and manual extraction). However, each network's data extraction process, specifically the de-identification, storage and utilization of these EMR data, has been approved by their respective university research ethics boards and by the Health Canada Research Ethics Board (CPCSSN, 2016).

One element of this ethics approval is that all participating CPCSSN sites must post informational posters and distribute brochures about CPCSSN to their patients, in order to give individual patients an opportunity to learn about this database and to opt-out (or opt-in, as is the case in the network based in Québec) of contributing their personal health information to the CPCSSN database. If a patient decides to opt-out, this decision is recorded in their EMR and these patients do not have their health information extracted. At the CPCSSN central data repository in Kingston, Ontario, a variety of organizational, physical and technological safeguards are implemented to ensure that the privacy of patients is protected. These safeguards are also important to ensure that all collection, retention and use or disclosure of data complies with current privacy legislation and the 2010 Tri-Council Policy Statement, Ethical Conduct of Research Involving Humans (CPCSSN, 2016). Personal information (of both patients and providers) is removed from the data prior to being extracted from the EMR and further de-identification (e.g., removal of names from free text notes) is conducted by the data managers after data collection and before compiling the data into the CPCSSN database.

The longitudinal, clinical data held within the CPCSSN database are not only available for academic research and policy purposes, but participating PHC providers can elect to receive quarterly reports on their patient population and how their site characteristics (e.g., number of patients who smoke or who have diabetes, performance of preventive measures for patients) compare to other PHC sites in their region and across the country. This information can provide valuable insight into the characteristics of a provider's patient population, their clinical care activities and their data input behaviours. The intent of this feedback is to improve both patient care and the quality of data entered into EMRs.

As of June 2016, more than 1,500,000 de-identified electronic patient records have been collected from more than 1,000 PHC providers (referred to as "sentinels" by CPCSSN) across Canada (CPCSSN, 2016). During the data extraction period for this thesis work (known as the Q3-2013 extract), a total of 600,565 de-identified electronic patient records were collected from 475 PHC providers in ten regional networks. These ten regional networks are located in seven Canadian provinces: British Columbia, Alberta (two networks), Manitoba, Ontario (three networks), Québec, Nova Scotia and Newfoundland and Labrador. The characteristics of these ten participating networks (e.g., geographical location, number of sites, number providers, number of patients, number of recorded encounters, type of EMR systems and time since EMR adoption) at the time of data extraction are described in **Table 4.1**.

The CPCSSN data elements used for this research contain information on practice characteristics (e.g., geographical location); provider characteristics (e.g., provider birth year and provider sex); patient characteristics (e.g., patient birth year, patient sex and residential forward sortation area); and in-office encounters (e.g., encounter date, billing diagnoses codes and encounter diagnoses codes). The majority (approximately 95%) of the disease diagnosis codes

within the CPCSSN database at the time of data extraction were recorded using the International Classification of Disease, 9th Revision (ICD-9) system. As such, this coding system will be used to detect chronic disease diagnoses for both Objective One and Objective Two.

These CPCSSN data contain patient-level, point-of-care information on disease management and morbidity over time until the date of data extraction. While this information is not principally collected for research purposes, the CPCSSN database represents the only known pan-Canadian PHC EMR database. To obtain these secondary data, approval was obtained from CPCSSN Research Committee in September 2013 (Project ID: 2013DEL04). The Letter of Permission to access the CPCSSN database is provided in **Appendix B**. Ethical approval has also been obtained from the Research Ethics Board at Western University and the Approval Notice (File Number: 104705) is presented in **Appendix C**.

Table 4.1 Characteristics of ten practice-based research networks participating in CPCSSN as of Q3-2013 data extract*

Network ID	Province or Region	Number of Sites	Start of EMR	EMR Software	Number of Providers	Number of Patients	Number of Encounters
1	Southern Alberta	7	2001	Med Access, Wolf	60	55,053	1,204,548
2	Northern Alberta	5	2002	Med Access, Wolf	35	25,901	449,525
3	Southwestern Ontario	6	2005	Accuro, Healthscreen	21	19,029	516,523
4	Central Ontario	21	2006	Nightingale, Practice Solutions, Xwave	81	140,791	1,610,614
5	Eastern Ontario	9	2010	Bell, Nightingale, Oscar	102	151,531	2,641,669
6	Québec	1	2012	DaVinci	25	8,942	212,694
7	Newfoundland and Labrador	9	2005	Nightingale, Wolf	53	47,860	896,053
8	Manitoba	3	2004	Jonoke	30	47,362	1,244,319
9	Nova Scotia	19	2006	Nightingale	53	86,359	1,093,733
10	British Columbia	2	2002	Wolf	15	17,737	343,087
Total		82			475	600,565	10,212,765

* All networks had the same data extraction date of September 30, 2013

4.2 CPCSSN Data Procedures

After ethical approval and CPCSSN permission was received, a copy of the database (as of the Q3-2013 extraction date) was transferred via an encrypted and password-protected Microsoft Access database to a password-protected device at Western University. These Microsoft Access files were then imported into the Stata SE 14.1 software to conduct management, cleaning and statistical analyses of the data.

4.2.1 CPCSSN Database Management

The data dictionary of relevant CPCSSN variables is included in **Appendix D**. This codebook outlines the variable names and the general process of entry into the EMR by the PHC provider (e.g., family physician, nurse practitioner, nurse, medical resident or medical student). New variables that were created for purposes of Objective One and Objective Two are also included in the codebook and highlighted using *italics*. These new variables are described in a similar manner to the original CPCSSN variables.

4.2.2 CPCSSN Data Cleaning

Once the data were received, all of the data tables and key variables of interest were examined and explored. This "diagnostic exploration" uncovered the nuances of the data, particularly the data entry patterns that were evident among networks, sites and providers. All included variables (both original and *new*) were checked for range and consistency; consequently, potential outliers and implausible values were identified. For continuous variables, respective means, medians, range of values and standard deviations were calculated.

For categorical variables, data distribution between categories was explored graphically and statistically. The frequency and patterns of missingness were also assessed for each variable.

4.3 CPCSSN Data Elements

4.3.1 Primary Health Care Practice Characteristics

Each CPCSSN network has been assigned a unique Network ID, which is an auto-incrementing value in which a unique number is generated when a new record is inserted into the EMR table. The participating PHC practices (referred to as "sites" by CPCSSN, and these two terms will be used interchangeably in this thesis) within each network were then assigned a unique, auto-incrementing Site ID. While the network names and geographic locations (e.g., city, province or territory) are provided in the CPCSSN database and displayed on the CPCSSN website (CPCSSN, 2016), specific Site ID information remains unavailable for researchers. Instead, the geographic location of each site is recorded using the site's forward sortation area (first three characters of the site location's postal code). Finally, details of each site's EMR software are recorded, including the name of the EMR software and the date the EMR software was started within the practice. Therefore, the length of use and EMR software details for each site can be explored. Each PHC provider (referred to as "sentinels" by CPCSSN, and these two terms will be used interchangeably in this thesis) is nested within each Site ID and Network ID, and their characteristics are described further in the next section.

4.3.2 Primary Health Care Provider Characteristics

Within the CPCSSN database, both family physicians and nurse practitioners have been recruited as eligible PHC providers or sentinels. These are providers who: 1) are located at an

academic or community site; 2) practice generalized or primary health care; and 3) utilize an EMR system in their clinical work. After recruitment and consent to participate in the CPCSSN database, each provider is then assigned a unique, auto-incrementing Provider ID. Similar to Site ID, the majority of Provider ID information remains de-identified for researchers. Instead, only the provider's birth year and sex is recorded. Each patient and their health care encounters are nested within each Provider ID, and these variables are described further in the next sections.

4.3.3 Primary Health Care Patient Characteristics

Patients who seek care from the participating CPCSSN providers (and who have not refused to contribute their health data) are assigned a Patient ID, which is a unique, auto-incrementing identifier for each patient in the database. Both patient birth year and patient sex are recorded, as well as corresponding health information. As stated earlier, if a patient has decided to opt-out of any data extraction period, the patient and their respective health information are removed from subsequent data analyses. Unfortunately, details of the patient's socioeconomic characteristics, such as patient occupation, level of education, housing status, language and ethnicity are incomplete and of poor quality in the CPCSSN database. This may be because these fields within the EMR that are completed inconsistently, if at all, by the PHC providers or more complete information is contained in another area of the EMR software not extracted by the CPCSSN data managers (e.g., within clinical notes or patient profile). Examples of data entries for these characteristics can be found in **Appendix E**. Due to missingness and inconsistency, these socioeconomic variables were not a reliable source of information for use in data analyses. However, the patient residential forward sortation area (FSA) has been recorded for a larger proportion of patients and was used to identify whether a patient lived in a rural or

urban setting and their median household income. This identification was done via a link with Canada Post and Statistics Canada data and will be described further in the next two sections.

Residential Location and Forward Sortation Areas

The typical form of the Canadian postal code system is "ANA NAN", where each "A" represents an alphabetic character and each "N" represents a numeric character (Statistics Canada, 2015). The first three characters of the postal code identify the FSA (Statistics Canada, 2015), which can be used to classify individuals into rural or urban residence. The first character of the FSA (first alphabetic character) represents a province or territory, or a major region within a province, as can be seen in **Appendix F**. The second character of the FSA (numeric character) identifies whether the postal code is for a "rural" or "urban" area. For this character, a zero (0) indicates a rural area, while any other digit between 1 through 9 represents a comparatively urban area. As defined by Canada Post, "rural" residence refers to individuals living outside centres with a population of 1,000 and outside areas with 400 persons per square kilometre (Statistics Canada, 2015). In comparison, "urban" residence refers to individuals living within population centres of 1,000 or more (Statistics Canada, 2015). The third character of the FSA (second alphabetic character) narrows down the area of coverage and boundaries of each region. The last three characters of the postal code ("NAN") identify routes known as local delivery units for mail delivery. For the purposes of this research, the CPCSSN database collects residential FSA data for participating patients. The second character of each patient's FSA was used to categorize patients into rural (second character = 0) or urban (second character $\neq$ 0) residence.

Median Household Income and Forward Sortation Areas

In addition to linking with Canada Post data, the patient FSA data were linked with household income data from the National Household Survey (2011) conducted by Statistics Canada. Access to Statistics Canada data is covered through the Data Liberation Initiative licence from Western University, which is a partnership between post-secondary institutions and Statistics Canada for improving access to Canadian data resources (Western University, 2016). Source data were derived from the Income Statistics Division of Statistics Canada (CANSIM Table 202-0701), which collected information on market, total and after-tax income by economic family type and income quintiles as of 2011. As such, annual household income was determined before tax (total) and in Canadian dollars as of 2011 (Statistics Canada, 2016). More specifically, household income was recorded for economic families (defined as two or more persons who live in the same dwelling and are related to each other by blood, marriage, common law or adoption), as well as unattached individuals (defined as a person living either alone or with unrelated roommates), as of 2011 (Statistics Canada, 2016). The median annual household income measure was used, instead of the mean annual household income, to account for a non-symmetrical distribution. This median value helps to provide a better description of the central tendency of the income data distribution.

4.3.4 Primary Health Care Encounter Characteristics

Each time a participating CPCSSN patient visits or seeks care from their CPCSSN PHC provider, an encounter is recorded and assigned a unique, auto-incrementing Encounter ID. As well, an associated Encounter Date (for Encounter Diagnosis information) or Service Date (for Billing Diagnosis information) is recorded to indicate the date on which the encounter occurred.

The details of the encounter are then documented in the EMR (again, the level of detail recorded or documented within an EMR varies by site, provider and encounter). A number of characteristics, specifically linked to the encounter, can be entered into the EMR by the provider. For example, a provider has the ability to record relevant diagnostic codes, medication information and specialist referrals that are made during the encounter. These data can also be entered into various parts of a patient's electronic record, as each EMR software has its own individualized structure for clinical data input. This flexibility in data entry creates a need to identify and extract from, all relevant areas of the EMR software program and the CPCSSN database. Variability in EMR data entry requires adaptability from the researcher and the approach used to identify the main source of diagnostic information is described in **Section 4.6**.

4.4 Identifying Sample of CPCSSN Patients

As of the Q3-2013 data extraction, the complete CPCSSN database consisted of 600,565 patients from 475 providers within ten regional networks. For both objectives, the inclusion criteria required that eligible patients have at least one in-office encounter recorded in their EMR and were at least 18 years of age as of their first encounter date (calculated using the patient's birth year and first recorded encounter date). Patients who had a missing or implausible (e.g., entry of "0") Patient ID or birth year were excluded from the patient sample. A patient inclusion flowchart is included in **Figure 4.1**. After applying the inclusion and exclusion criteria, the final sample consisted of 367,743 eligible adult patients (at least 18 years of age at first encounter date) who had at least one in-office encounter with their primary health care provider.

4.5 Identifying Patients with Multimorbidity

As described in the Literature Review Chapter, there is currently no gold standard list for measuring multimorbidity. Therefore, a list of twenty chronic disease categories and corresponding ICD-9 diagnostic codes was created and used in this research to identify eligible adult patients with multimorbidity. This list was created by a supervisory committee member and an internationally recognized expert in multimorbidity research (Dr. Martin Fortin) as part of a nationally funded research project. This project is co-led by Dr. Moira Stewart (Distinguished University Professor, Western University, Ontario) and Dr. Martin Fortin (Professor, Université de Sherbrooke, Québec) and is entitled "Patient-Centered Innovations for Persons with Multimorbidity" or "PACE in MM" (PACE in MM, 2014). It is funded by the Canadian Institutes of Health Research (CIHR) as a five-year signature initiative in community-based primary health care (CBPHC), which supports innovative approaches to improve the delivery of appropriate and high-quality primary health care to Canadians. The final list is composed of chronic disease categories that are particularly relevant among clinical and general populations in Canada. For example, the ICD-9 codes of 278 and 278.01, as well as a body mass index (BMI) of thirty or greater, were used to capture patients with Obesity. The abbreviated list of chronic disease categories and their corresponding ICD-9 codes is found in **Table 4.2**, while a more detailed list is available in **Appendix G**.

To date, the performance of the list of chronic disease categories has been assessed using a combination of criterion validity (through chart reviews), construct validity (through quality of life), as well as through test-retest reliability and inter-rater reliability. This work has not yet been published, but was conducted by Maude Richards who is a Master of Science student at the Université de Sherbrooke in Québec. This study recruited 245 patients from the Family

Medicine Group in Chicoutimi, Québec. After comparing the measurement of multimorbidity with a chart review, this list of categories for multimorbidity had an overall sensitivity of 84.6% (95% CI: 77.0 – 90.9) and specificity of 84.3% (95% CI: 76.4 – 90.4). Ms. Richard's work also found a moderate correlation between the measure of multimorbidity and quality of life (-0.5). In terms of the reliability, there was fair agreement in the test-retest reliability (Cohen's Kappa coefficient of 0.64) and inter-rater reliability (Cohen's Kappa coefficient of 0.79). Overall, this research has demonstrated a fairly strong performance of this measure of multimorbidity, when compared to the gold standard of chart review. For the research described herein, it was used as a marker for multimorbidity among adult PHC patients within the CPCSSN database.

Figure 4.1 Patient inclusion flowchart to create the final sample of adult patients with at least one in-office encounter recorded during the data extraction period

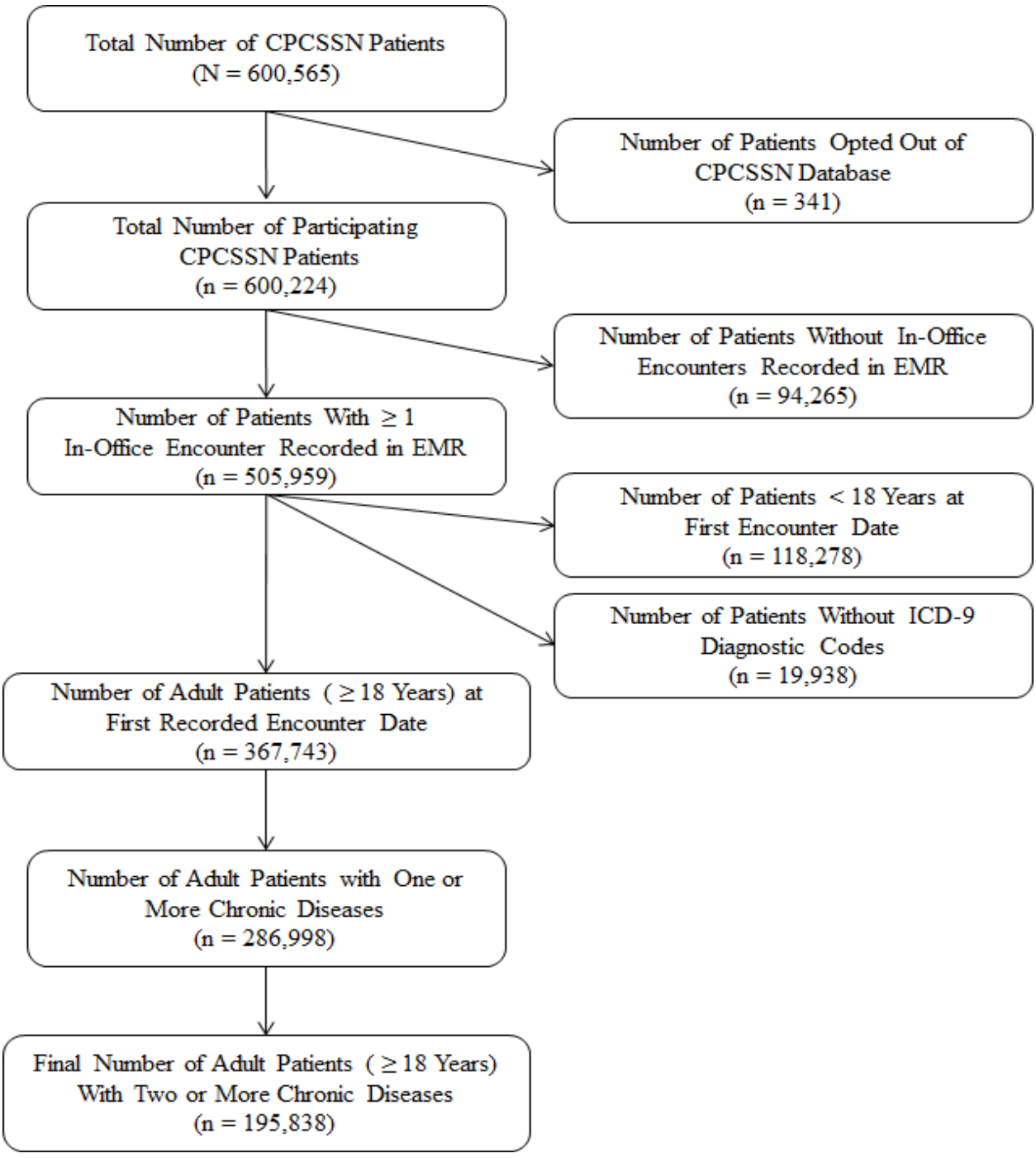


Table 4.2 List of twenty chronic disease categories and abbreviated ICD-9 disease codes*

Chronic Disease Category	ICD-9 Codes
Hypertension	401-405, 401, 401.1, 401.9, 405, 405.01, 405.09, 405.1, 405.11, 405.19, 405.9, 405.91, 405.99
Obesity	278, 278.01, BMI ≥ 30
Diabetes	250, 250.01, 250.02, 250.03, 250.1, 250.11, 250.12, 250.13, 250.2, 250.21, 250.22, 250.23, 250.3, 250.31, 250.32, 250.33, 250.4, 250.41, 250.42, 250.43, 250.5, 250.51, 250.52, 250.53, 250.6, 250.61, 250.62, 250.63, 250.7, 250.71, 250.72, 250.73, 250.8, 250.81, 250.82, 250.83, 250.9, 250.91, 250.92, 250.93
Chronic Obstructive Pulmonary Disease or Asthma	491, 491.1, 491.2, 491.21, 491.22, 491.8, 491.9, 492, 492.8, 493, 493.01, 493.02, 493.1, 493.11, 493.12, 493.2, 493.21, 493.22, 493.8, 493.81, 493.82, 493.9, 493.91, 493.92, 496
Hyperlipidemia	272, 272.1, 272.2, 272.3, 272.4
Cancer	140-239, 140-149, 150-159, 160-165, 170-176, 179-189, 190-199, 200-209
Cardiovascular Disease	412, 413, 413.1, 413.2, 440-449, 427, 427.3, 427.31, 417.32
Heart Failure	428, 394, 394.1, 394.2, 395, 395.1, 395.2, 395.9
Anxiety or Depression	296, 296.2, 296.21, 296.22, 296.23, 296.24, 296.25, 296.26, 296.3, 296.31, 296.32, 296.33, 296.34, 296.35, 296.36, 300, 300.01, 300.02, 300.09
Osteoarthritis or Rheumatoid Arthritis	714, 714.1, 714.2, 714.3, 715, 715.1, 715.2, 715.3, 715.8, 715.9
Stroke or Transient Ischemic Attack	434, 434.01, 434.1, 434.11, 433.9, 434.9, 434.91, 435, 435.1, 435.2, 435.3, 435.8, 435.9
Thyroid Problem	240-246, 240, 241, 242, 243, 244, 245, 246
Kidney Disease or Failure	585, 585.1, 585.2, 585.3, 585.4, 585.5, 585.6, 585.9
Osteoporosis	733, 733.01, 733.02, 733.03, 733.09
Dementia	290, 290.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 294, 294.1, 294.2
Musculoskeletal Problem	723, 723.1, 724, 724.1, 724.2, 724.3, 724.4, 724.5, 725, 726, 726.1, 726.2, 726.3, 726.31, 726.32, 726.33, 726.39, 726.4, 726.5, 726.6, 726.61, 726.62, 726.63, 726.64, 726.65, 726.69, 726.7, 726.71, 726.72, 726.73, 726.79, 726.9, 726.91, 727, 727.01, 727.03, 727.04, 727.05, 727.06, 727.09, 727.2, 727.3, 729, 729.1, 729.2, 729.4, 729.5
Stomach Problem	530, 530.81, 531, 531.4, 531.41, 531.5, 531.51, 531.6, 531.61, 531.7, 531.71, 531.9, 531.91
Colon Problem	555, 555.1, 555.2, 555.9, 556, 556.4, 556.5, 556.6, 556.8, 556.9, 564, 564.1
Liver Disease	571, 571.1, 571.2, 571.3, 571.4, 571.41, 571.42, 571.49, 571.5, 571.6, 571.8, 571.9
Urinary Problem	593, 593.3, 593.4, 593.5, 593.7, 593.71, 593.72, 593.73, 593.8, 593.82, 593.89, 593.9, 595, 595.1, 595.2, 595.9, 597, 597.8, 597.81, 597.82, 600, 601, 601.1, 601.3, 601.8, 601.9, 602, 602.1, 602.2, 602.3, 602.8, 602.9

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4.6 Identifying Source of Chronic Disease Diagnoses

There are two areas of the CPCSSN database where diagnostic codes for each patient are stored based on how the information was originally entered into the EMR. These are the Billing Diagnosis and Encounter Diagnosis tables. After exploration of the raw data, it was clear that the patterns of data entry for diagnostic information varied among sites and providers. There was not a consistent source of diagnostic information for all patients between these two tables, and diagnostic data had to be explored on a patient-by-patient basis. To overcome this variability, the mean number of Billing Diagnosis codes and Encounter Diagnosis codes (including both acute and chronic diagnoses) per encounter was calculated for each patient. More specifically, the total number of Billing Diagnoses codes and the total number of Encounter Diagnoses codes recorded for a patient in their EMR was divided by the total number of encounters recorded for a patient. This produced the mean number of Billing Diagnosis codes per encounter and the mean number of Encounter Diagnosis codes per encounter, respectively. From this calculation, the higher mean number of diagnoses codes was identified as the main source of chronic disease diagnoses for that individual patient. For patients with the same mean number of Billing Diagnosis codes per encounter and Encounter Diagnosis codes per encounter, the Encounter Diagnosis codes were selected as these codes were deemed more closely tied to the encounter itself and were recorded beyond purposes of billing. The number of eligible adult patients with a higher mean of Billing Diagnosis codes per encounter was 245,365 (66.7%), while 110,608 (30.1%) patients had a higher mean of Encounter Diagnosis codes per encounter. A total of 11,770 (3.2%) patients had the same mean number of Billing Diagnosis and Encounter Diagnosis codes per encounter. Consequently, Encounter Diagnosis codes were used for 122,378 (33.3%) patients. This approach aimed to capture the maximum amount of clinical

information available on a patient-by-patient basis. This produced a final prevalence estimate of 53.3%.

A three-part sensitivity analyses was conducted to detect potential differences in prevalence of multimorbidity using either the Billing Diagnoses codes only, the Encounter Diagnoses codes only or a combination of the two diagnostic sources. The results from these three sensitivity analyses are presented in **Table 4.3**, as well as the results from the original analysis. When all Billing Diagnosis codes were used to detect patients with multiple chronic diseases, the prevalence of multimorbidity was found to be 56.7%. When all Encounter Diagnosis codes were used to detect patients with multiple chronic diseases, the prevalence of multimorbidity was found to be 54.1%. For the third part of the sensitivity analysis, Billing Diagnosis codes were used for the 11,770 patients with an equal mean of Billing Diagnosis and Encounter Diagnosis codes per encounter. Consequently, Billing Diagnosis codes were used for 257,135 (69.9%) and the resulting prevalence of multimorbidity was found to be 57.2%. After conducting these analyses, the original analysis (reported in the Results Chapter) was deemed to provide the most conservative estimate of multimorbidity among adult PHC patients in Canada.

Table 4.3 Prevalence of multimorbidity (defined as patients with two or more chronic diseases), stratified by source of diagnostic code information

Original Analysis	Prevalence of Multimorbidity
Highest Mean of Billing and Encounter Diagnosis Codes Selected and Encounter Diagnosis Codes Selected for Patients with Equal Mean	53.3%
Sensitivity Analyses	**Prevalence of Multimorbidity (% Change from Original Analysis)**
All Billing Diagnosis Codes Selected for All Patients	56.7% (+3.4)
All Encounter Diagnosis Codes Selected for All Patients	54.1% (+0.8)
Highest Mean of Billing and Encounter Diagnosis Codes Selected and Billing Diagnosis Codes Selected for Patients with Equal Mean	57.2% (+3.9)

4.7 Objective One

4.7.1 Patient Sample

The first objective measured the point prevalence, characteristics and clusters of multimorbidity among adult PHC patients in Canada. The patient sample, or population at-risk of multimorbidity occurrence, was composed of participating CPCSSN patients with at least one in-office encounter recorded in their EMR and who were at least 18 years of age as of their first encounter date. As described in a previous section, this final sample consisted of 367,743 adult patients. While the clinical data for these patients were recorded prospectively as the patients consulted their PHC provider over time, the CPCSSN database created a retrospective or historic cohort. The prevalence estimates of individual chronic diseases and multimorbidity were calculated as of September 30, 2013.

4.7.2 Study Design

The first objective used a retrospective or historic observational cohort study design. Prevalence estimates and corresponding 95% confidence intervals were calculated using the

Stata SE 14.1 software (StataCorp., 2015). Prevalence estimates were stratified according to relevant patient-, provider- and practice-level predictors: patient age, patient sex, residential location, provider age, provider sex, EMR software type, practice location and CPCSSN Network. Both crude and stratified prevalence estimates of multimorbidity were reported. To identify the most frequently occurring clusters of chronic diseases accumulated by patients over time, the frequency and type of unordered and ordered clusters (also known as combinations and permutations, respectively) of chronic disease diagnoses were computed using customized Java programming and the Stata SE 14.1 software (StataCorp., 2015), which are described in more detail in **Section 4.7.3.3**.

4.7.3 Data Analyses

4.7.3.1 Research Question 1 – Prevalence of Multimorbidity

Prevalence estimates were calculated using two approaches, corresponding to the prevalence estimates that are commonly reported within the multimorbidity literature. This means that prevalence estimates of patients with *at least two* or *at least three* chronic diseases were calculated, as well as the prevalence level of patients with zero, one, two, three, four and five or more chronic diseases. Prevalence estimates and corresponding 95% confidence intervals, were calculated using the *proportion* procedure in the Stata SE 14.1 software (StataCorp., 2015). For all calculations, the denominator consisted of all adult patients (N = 367,743) in the final sample. These estimates were stratified by patient-level (age, sex, residential location, median household income and total number of chronic diseases), provider-level (age and sex) and practice-level (EMR software type, practice location and CPCSSN Network) variables to investigate distinct patterns of multimorbidity.

Patient age was calculated (in years) as of 2013, using the patient's recorded birth year. Age categories were then created to group patients into five categories: 18 – 34 years; 35 – 44 years; 45 – 64 years; 65 – 84 years; and 85 years or older. This calculation is separate from that used in the inclusion criteria, which used the date of the patient's first in-office encounter and the patient's birth year. Patient sex was recorded as a binary variable, female or male. As described earlier, residential location and median household income were determined using each patient's residential FSA. The total number of chronic diseases was summed (ranging from zero to twenty) for each patient as of September 30, 2013. Provider age was calculated (in years) as of 2013, using the provider's recorded birth year and categorized into three groups: 25 – 44 years; 45 – 64 years; and 65 years or older. Provider sex was recorded as a binary variable, female or male. Each practice's EMR type was categorized based on the EMR software name (e.g., Nightingale or Oscar). Similar to patient residential location, practice location was defined by the practice's recorded FSA. Finally, practices were categorized according to their associated CPCSSN Network (e.g., Network 1 or Network 2).

To compare prevalence estimates of multimorbidity with the existing international literature on multimorbidity, a review of the literature was conducted and relevant articles that reported prevalence of multimorbidity (defined as two or more chronic diseases and three or more chronic diseases) were selected. For this review, both the Medline and Embase electronic databases were searched for the reference period starting on January 1, 1990 and ending on April 25, 2016. As the term "multimorbidity" does not have an established Medical Subject Heading (MeSH) Term, the term "multimorbidity" was searched as a keyword (in all fields) and the term "comorbidity" was searched as a MeSH Term. The "epidemiology" and "prevalence" of multimorbidity estimates were incorporated into the search as keywords and MeSH Terms.

Similarly, the terms “characteristics”, “adult” and “humans” were all included to narrow the literature search. Details of the main search terms used in this review are included in **Table 4.4**. The final selection of published literature was identified from the titles derived from this search, as well as through the review of references from included literature. The key methodological elements (e.g., country of origin, study design, sample size, age range, sample recruitment, data source, diagnostic coding system and number of diseases considered) and corresponding prevalence estimates from relevant research articles were compiled into a summary table and presented in the Results Chapter. Separate tables were created for those studies that defined multimorbidity as at least two chronic diseases and those studies that defined multimorbidity as at least three chronic diseases. The methodological elements and prevalence estimates from the current study were also incorporated into these tables for qualitative comparison.

Table 4.4 Details of search terms to identify prevalence and characteristics of adults with multimorbidity in the published literature

("comorbidity"[MeSH Terms] OR "comorbidity"[All Fields] OR "co-morbidity"[All Fields] OR "multimorbidity"[All Fields] OR “multi-morbidity”[All Fields])
AND ("epidemiology"[Subheading] OR "epidemiology"[All Fields] OR "prevalence"[All Fields] OR "prevalence"[MeSH Terms])
AND (“characteristics”[All Fields])
AND ("adult"[MeSH Terms] OR "adult"[All Fields])
AND ("1990/01/01"[PDAT] : "2016/04/25"[PDAT])
AND ("humans"[MeSH Terms])

4.7.3.2 Research Question 2 – Characteristics of Adult PHC Patients with Multimorbidity

The characteristics of adult patients with multimorbidity were examined and compared with the published multimorbidity literature. More specifically, the distribution of patient age, patient sex, residential location, median household income and total number of chronic diseases were explored for all adult patients with multimorbidity, defined as at least two chronic diseases and at least three chronic diseases. The distribution of provider-level (provider age and provider sex) and practice-level (EMR software type, practice location and CPCSSN Network) were also explored for both definitions of multimorbidity.

In order to compare these patient characteristics with the existing multimorbidity literature, a review of the literature was conducted and relevant articles that reported characteristics of individuals with multimorbidity were selected. Similar to the previous search for multimorbidity literature, this review included both Medline and Embase electronic databases that were searched for the reference period of January 1, 1990 to April 25, 2016. Details of the main search terms used in this review are included in **Table 4.4**. The final selection of published literature was identified from the titles derived from this search, as well as through the review of references from included literature. While it would be ideal to compare all patient-level characteristics from the current research with those in the multimorbidity literature, there is a lack of consistent reporting of characteristics of individuals living with multimorbidity (e.g., residential location or level of household income). Instead, the most consistently reported characteristics in studies were in fact mean age and sex distribution. As such, these two characteristics were used as a starting point in the qualitative comparison between the current research and the published multimorbidity literature. These characteristics, as well as the key methodological elements (e.g., country of origin, study design, sample size, age range, sample

recruitment, data source, diagnostic coding system and number of diseases considered), from relevant articles were compiled into a summary table and presented in the Results Chapter. Once again, separate tables were created for those studies that defined multimorbidity as at least two chronic diseases and those studies that defined multimorbidity as at least three chronic diseases. The methodological elements and characteristics of patients with multimorbidity from the current study were also incorporated into this table for comparison.

4.7.3.3 Research Question 3 – Most Frequent Clusters of Multiple Chronic Diseases

The prevalence estimates of individual chronic disease diagnoses among patients with multimorbidity were calculated, stratified by patient age category and patient sex. Where possible, the prevalence levels of individual chronic diseases were compared to the national prevalence estimates from the 2013 Canadian Community Health Survey. Clusters of multiple chronic diseases were then examined, accounting for both combinations (unordered clusters) and permutations (ordered clusters). The frequency of unique clusters was determined in Objective One, whereas the time elapsing between diagnoses was analyzed in Objective Two (to be described in an upcoming section). A customized computational cluster analysis program was created in Java in collaboration with Dr. Michael Bauer (Professor, Department of Computer Science) at Western University. This computational program allowed for the identification and sorting of the more than 18,000 unique combinations (unordered clusters) and 55,000 unique permutations (ordered clusters) possible from our list of twenty chronic diseases. Further information about this computational cluster analysis program (both its availability and instruction for use) is provided within the Multimorbidity Cluster Analysis Toolkit, which is included in **Appendix H**. This document is also provided when the computational program is

accessed by external researchers who are interested in exploring unordered and ordered clusters of diseases in their own data.

In order to run properly, this computational cluster analysis program requires a basic data input file (in .txt format) that contains the unique Patient IDs, as well as the diagnostic codes received by each patient by the end of the observation period. From there, the analysis program detects and sorts all disease combinations and permutations into mutually exclusive groups. As such, two sets of output are created from the raw data: 1) frequency and type of all unique combinations (unordered clusters); and 2) frequency and type of all unique permutations (ordered clusters). For this research, the data input files were stratified by patient age category and patient sex to provide more specific output information. For example, the most frequently occurring combinations were explored among all female patients with multimorbidity, as well as those female patients in each of the five age categories. Likewise, the most frequently occurring permutations were explored among all female patients with multimorbidity, as well as those female patients in each of the five age categories. Similar output files were created for all male patients with multimorbidity, as well as those male patients in each of the five age categories. Finally, these results were further stratified by the total number of chronic disease diagnoses to create mutually exclusive groups (e.g., female patients aged 18 to 34 years with exactly two chronic diseases or male patients aged 45 to 64 years with exactly four chronic diseases).

To create the output files for the frequency and type of combinations, the computational analysis program detected all patients (within the input data file) with the exact same number and type of chronic disease diagnoses, regardless of the order in which these diagnoses occurred. For example, all patients who were diagnosed with Hypertension, Obesity and Musculoskeletal Problem at the end of the observation period were detected and categorized into the same

combination cluster. To create the output data files for the frequency and type of permutations, the computational analysis program detected all patients with the exact same number, type and sequence of chronic disease diagnoses. For example, all patients who were diagnosed with Obesity, then Hypertension and then Musculoskeletal Problem were detected and categorized into one permutation cluster. However, all patients who were diagnosed with Musculoskeletal Problem, then Hypertension and then Obesity were categorized into another permutation cluster. In addition to reporting the frequency of the most frequently occurring cluster in each age-sex multimorbidity subgroup (e.g., female patients aged 18 to 34 years or male patients aged 45 to 64 years), the proportion of patients living with this cluster from the subgroups was calculated.

4.8 Objective Two

4.8.1 Patient Sample

The second objective examined the natural history and the changing burden of multimorbidity over time among adult PHC patients. The sample consisted of patients with at least one in-office encounter recorded in their EMR and who were at least 18 years of age as of their first encounter date. For this objective, patients with one or more chronic disease diagnoses were included in order to assess both the onset and progression of multimorbidity over time. This created a final sample of 286,998 adult patients. All patients were followed over time to calculate the time elapsing (in days) between chronic disease diagnoses (regardless of disease type). These patients were observed prospectively from one chronic disease diagnosis until a subsequent chronic disease diagnosis or the end of the observation period, which was September 30, 2013. The beginning of the observation period occurred when a patient was diagnosed with their first chronic disease, which is depicted in **Figure 4.2**.

4.8.2 Study Design

The second objective used a prospective cohort study design. To determine time elapsing between chronic diseases, the corresponding encounter date for each chronic disease diagnosis was determined, as described in a previous section and **Appendix I**. These dates were ordered chronologically and the time difference (in days) between each diagnosis date was calculated. Patients were stratified into subgroups to examine both "Time Until Multimorbidity" and "Time Until Advancing Multimorbidity". To examine "Time Until Multimorbidity", the time elapsing between a patient's first chronic disease diagnosis and their second chronic disease diagnosis was calculated. As such, this was calculated for the first patient subgroup shown in **Figure 4.2**. The "Time Until Advancing Multimorbidity" was assessed for the remaining patient subgroups. In these analyses, the observation period for the second patient subgroup began on the date of a patient's second chronic disease diagnosis; the observation for the third patient subgroup began on the date of a patient's third chronic disease diagnosis; the observation period for the fourth patient subgroup began on the date of a patient's fourth chronic disease diagnosis; and the observation period for the fifth patient subgroup began on the date of a patient's fifth chronic disease diagnosis. As seen in **Figure 4.2**, the end of the observation period was when a patient was diagnosed with a subsequent chronic disease diagnoses (referred to as the "event" in the survival analysis) or as of September 30, 2013 if the patient did not receive another chronic disease diagnosis (referred to as "right censoring" in the survival analysis).

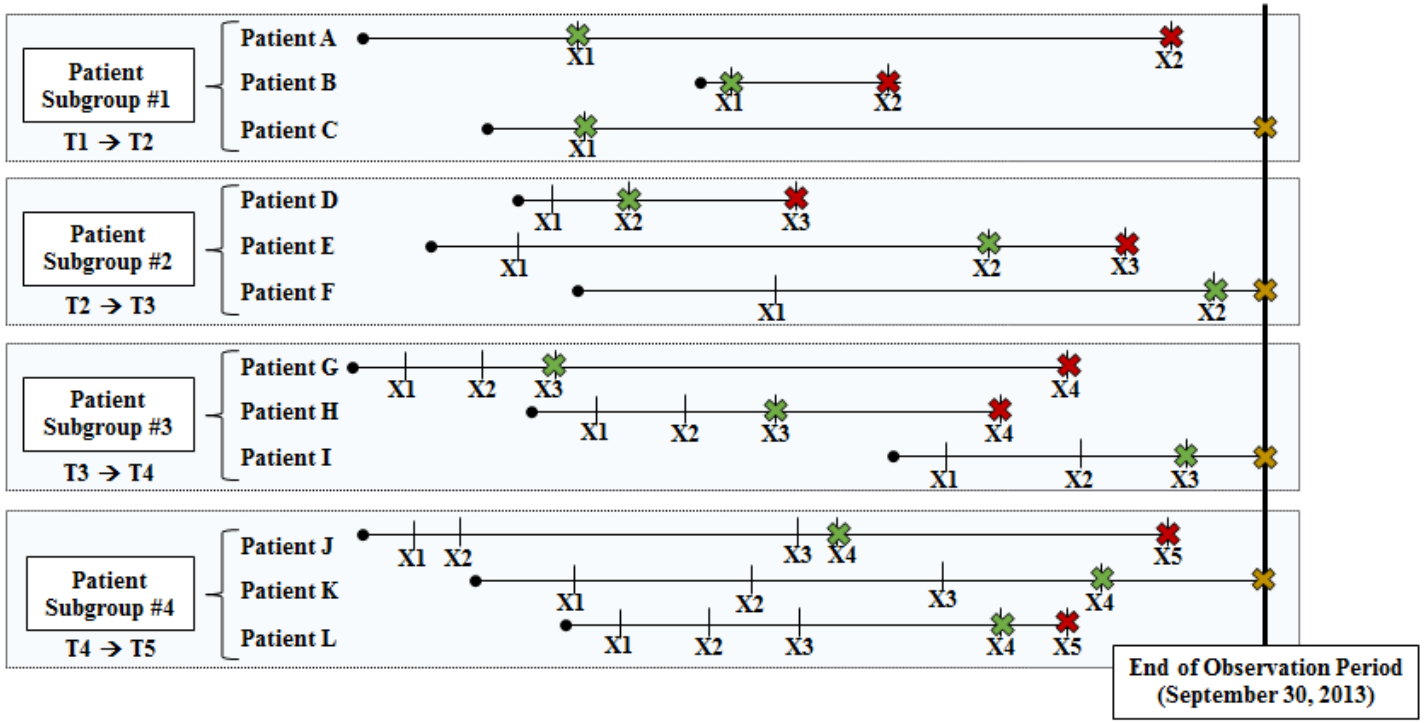
If more than one chronic disease diagnosis was documented for a patient on the same date (likely within the same encounter), the time elapsing between chronic disease diagnoses was calculated to be zero days. For example, if a patient was diagnosed with Hypertension, Diabetes and Depression or Anxiety at the same encounter, the time elapsing between all three diagnoses

was equal to zero days. However, these data points did not necessarily depict a clear transition from one chronic disease state to another. More specifically, there were three possible reasons of the zero days elapsing between chronic disease diagnoses: 1) the patient was diagnosed with two or more chronic diseases after a series of tests and clinical observations (therefore accurate diagnoses of multiple chronic diseases occurred at the same encounter); 2) the patient was new to the PHC practice and the provider was updating the patient's EMR with their current health status information (therefore inputting multiple chronic disease diagnoses at the same encounter); or 3) data entry error into the patient's EMR (that is, the second and third diagnoses were entered by mistake at the same encounter). The second and third potential reason for zero days elapsing between diagnoses would indicate an artefact in the EMR data, which cannot be clearly differentiated from the first reason. Instead, the first reason is of interest for this research.

Exploration of the data was conducted to determine the proportion of patients with at least one chronic disease who had at least one data point of zero days elapsing between subsequent chronic disease diagnoses. While these data points (where time = 0) were maintained in the complete dataset and contributed to the overall prevalence estimates of multimorbidity, they were dropped from the computational cluster analysis previously described in Objective One and the longitudinal analysis in Objective Two. This was done to ensure that the analysis described a "true" transition from one chronic disease state to the next. The distribution of time elapsing between incident chronic disease diagnoses are displayed in **Figure 4.3** and **Figure 4.4** and those patients with at least one data point of zero days were removed from the cluster and time-to-event analyses. In total, 65,828 female patients had at least one data point of zero days elapsing between chronic disease diagnoses, whereas 52,144 male patients had at least one data point of zero days elapsing between chronic disease diagnoses. The approach of case-wise

deletion of these patients was selected due to the large sample size, but more importantly, because the sequence between the chronic disease diagnoses could not be reasonably assessed if the pattern between two or more chronic disease diagnoses was not clear. However, sensitivity analyses were conducted by including these excluded data points and similar patterns were seen in both the cluster and longitudinal analyses (described further in the Results Chapter).

Figure 4.2 Depiction of time elapsing (in days) between chronic disease diagnoses, as well as the corresponding start and end of observation periods, among separate subgroups of patients with at least one chronic disease diagnosis



Legend:

- = Start of EMR Data Collection
- = Start of Patient Observation Period (Unique for Each Patient Subgroup)
- = Event of Interest (Subsequent Chronic Disease Diagnosis)
- = Right Censoring (No Event)

X1 = First Chronic Disease Diagnosis
X2 = Second Chronic Disease Diagnosis
X3 = Third Chronic Disease Diagnosis
X4 = Fourth Chronic Disease Diagnosis
X5 = Fifth Chronic Disease Diagnosis

Patient Subgroup #1 = Patients with ≥ 1 Chronic Disease
Patient Subgroup #2 = Patients with ≥ 2 Chronic Diseases
Patient Subgroup #3 = Patients with ≥ 3 Chronic Diseases
Patient Subgroup #4 = Patients with ≥ 4 Chronic Diseases

Figure 4.3 Distribution of time elapsing until subsequent chronic disease diagnoses among female patients with multimorbidity

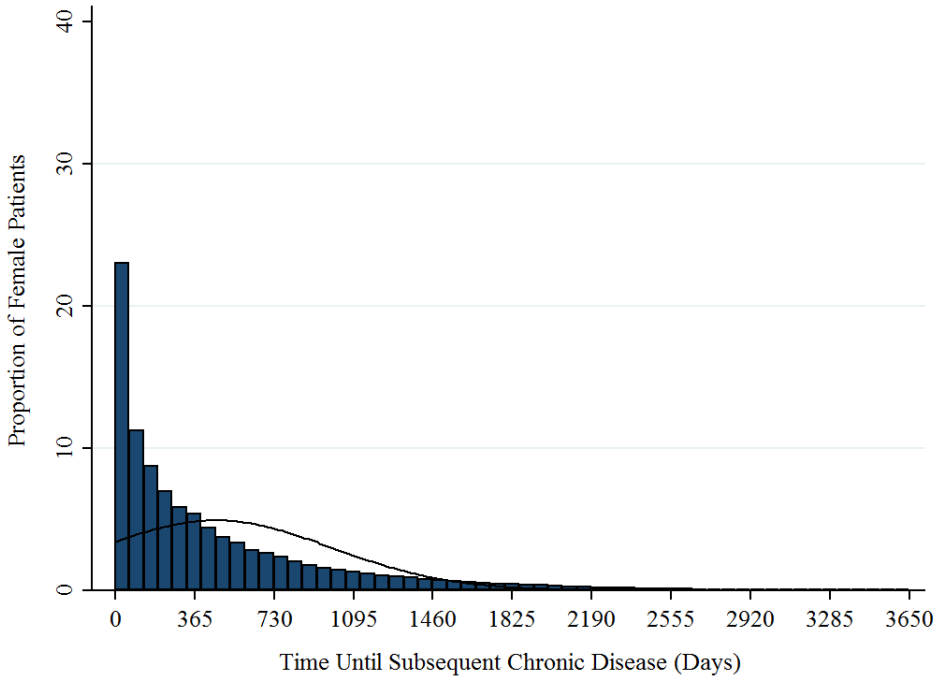
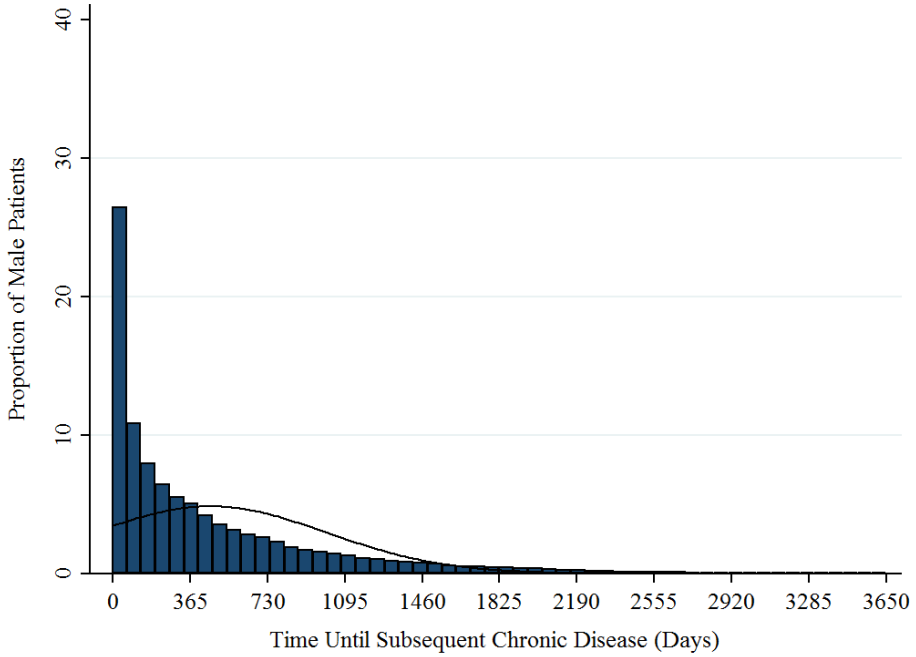


Figure 4.4 Distribution of time elapsing until subsequent chronic disease diagnoses among male patients with multimorbidity

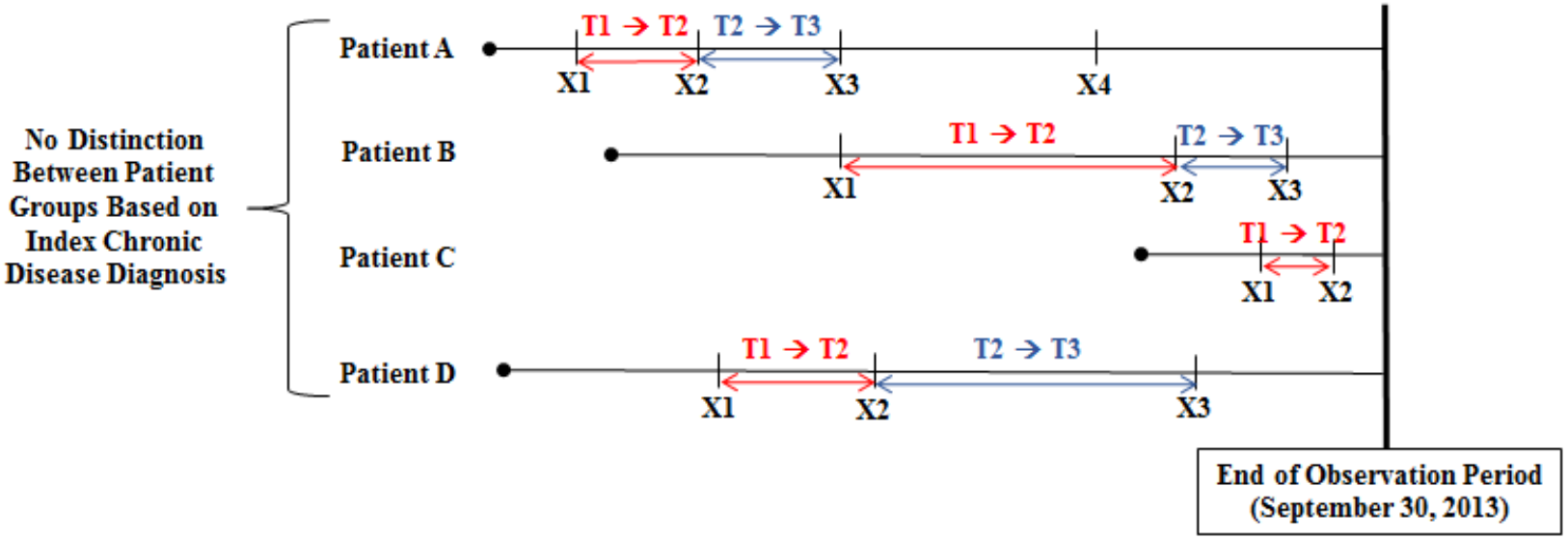


4.8.3 Data Analyses

4.8.3.1 Research Question 1 – Time Until Multimorbidity

Descriptive statistics were used to examine the time (in days) that elapsed between chronic disease diagnoses. The time elapsing between the first (or index) and second chronic disease diagnosis was designated as the "Time Until Multimorbidity", indicating the onset of multimorbidity (defined as two or more chronic diseases). The time elapsing between the subsequent chronic disease diagnoses was defined as the "Time Until Advancing Multimorbidity". As seen in **Figure 4.5**, the "Time Until Multimorbidity" observation period began when a patient received their first chronic disease diagnosis (T1) and ended on the date the patient received their second chronic disease diagnosis (T2). Likewise, the "Time Until Advancing Multimorbidity" observation period began when a patient received their second chronic disease diagnosis (T2) and ended on the date the patient received their third chronic disease diagnosis (T3). The time elapsing was calculated using the *summarize* procedure in the Stata SE 14.1 software (StataCorp., 2015) and was assessed by patient age category and between females and males. As seen in **Figure 4.6**, "Time Until Multimorbidity" was stratified by index chronic disease type in order to explore whether variations in time elapsing until subsequent chronic disease diagnoses varied by a patient's index chronic disease. For example, the "Time Until Multimorbidity" was reported among patients who were first diagnosed with Hypertension, as compared to those patients who were first diagnosed with Cancer or Cardiovascular Disease. As described in **Section 4.8.2**, the data points where time elapsing between diagnoses was equal to zero days were dropped from this analysis. This was done to ensure this described a "true" transition from one chronic disease state to the next. A sensitivity analyses was conducted to examine the impact of excluding these data points (described further in the Results Chapter).

Figure 4.5 Time elapsing (in days) between first and second chronic disease diagnoses, as well as second and third chronic disease diagnoses, among adult patients with at least one chronic disease diagnoses



Legend:

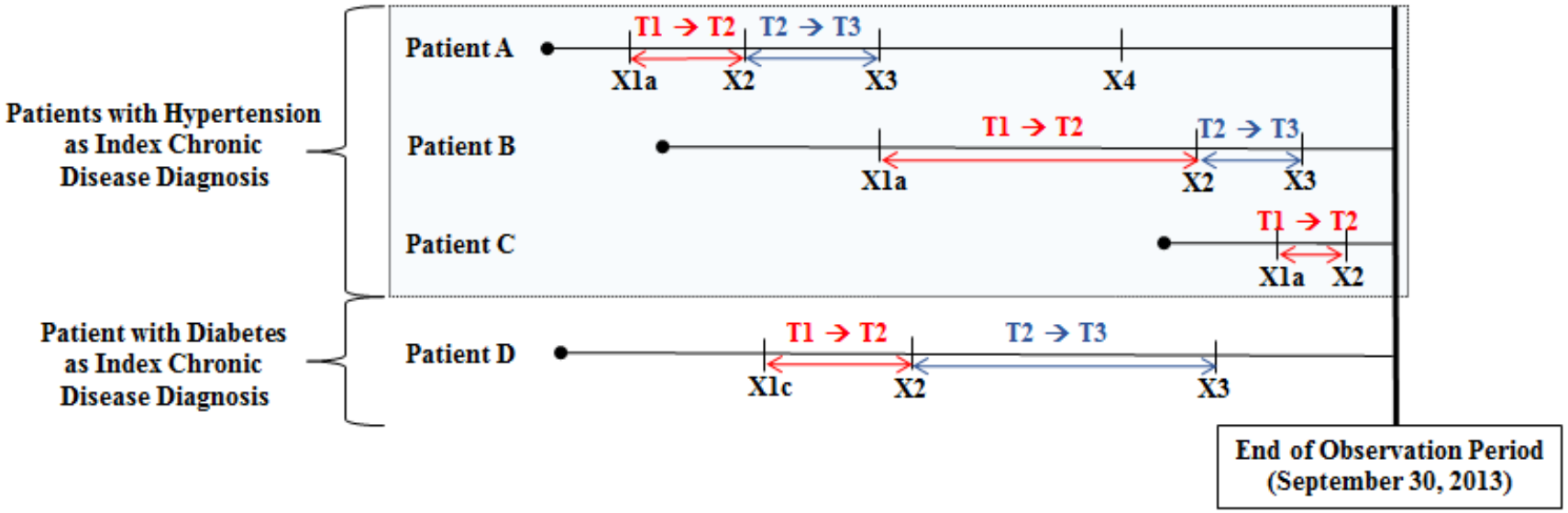
● — = Start of EMR Data Collection

X1 = Index Chronic Disease Diagnosis

T1 → T2 = Time Elapsing Between First and Second Chronic Disease Diagnoses (Time Until Multimorbidity)

T2 → T3 = Time Elapsing Between Second and Third Chronic Disease Diagnoses (Time Until Advancing Multimorbidity)

Figure 4.6 Time elapsing (in days) until subsequent chronic disease diagnoses, stratified by index chronic disease type among adult patients with at least one chronic disease diagnoses



Legend:

●— = Start of EMR Data Collection

X1a = Index Chronic Disease Diagnosis (Hypertension)

X1c = Index Chronic Disease Diagnosis (Diabetes)

T1 → T2 = Time Elapsing Between First and Second Chronic Disease Diagnoses (Time Until Multimorbidity)

T2 → T3 = Time Elapsing Between Second and Third Chronic Disease Diagnoses (Time Until Advancing Multimorbidity)

4.8.3.2 Research Question 2 – Time Until Advancing Multimorbidity

The approach described in the previous section was replicated for Research Question 2, in which the mean time (in days) until subsequent chronic disease was explored among all patients with at least two chronic disease diagnoses. As such, the "Time Until Advancing Multimorbidity" was assessed in more detail. The mean time (in days) elapsing between the penultimate and final chronic disease diagnosis was stratified among patients living with at least two, at least three, at least four and at least five chronic diseases. These non-mutually exclusive patient subgroups (except those patients with at least five chronic diseases) are presented in **Figure 4.2** and indicate the start and end of the observation period for each subgroup. This analysis was conducted to determine whether the mean time until subsequent chronic disease decreases when the number of chronic disease diagnoses increases. In each analyses, the time elapsing was calculated using the *summarize* procedure in the Stata SE 14.1 software (StataCorp., 2015) and was assessed among patient age categories and between females and males. As described in **Section 4.8.2**, the data points where time elapsing between diagnoses was equal to zero days were dropped from this analysis. This was done to ensure that this analysis described a "true" transition from one chronic disease state to the next. A sensitivity analyses was conducted to examine the impact of excluding these data points (described further in the Results Chapter).

4.8.3.3 Research Question 3 – Predicting Time Until Subsequent Chronic Disease

The time elapsing between multiple chronic disease diagnoses was further examined in Research Question 3. To observe patient progression into a more complex clinical profile, a multilevel survival analysis was conducted using the Stata SE 14.1 software (StataCorp., 2015).

Survival analysis, or time-to-event analysis, has historically been used in epidemiological research to observe health-related events in patients. A multilevel survival analysis was used to adjust for patient-, provider- and practice-level predictors and the data analyses plan followed the recommended sequential process (Hosmer et al., 2008; Hosmer and Lemeshow, 2000). This technique allowed for staggered entry dates of patients into the study period, as well as a non-normal distribution in the time-to-event data. These non-normal data violate the normality assumption of most commonly used statistical approaches, such as a multiple regression model.

A multilevel, mixed-effects parametric survival model was fit using the *mestreg* command in the Stata SE 14.1 software (StataCorp., 2015), which can be used with single- or multiple-record survival data. As patients were nested within PHC providers and providers were nested within PHC practices, observations from the same cluster may have been correlated and may have shared common cluster-level random effects. As such, a random effects model was used to account for this intra-cluster correlation. An ordered, recurrent event (also known as multivariate or multi-failure) analysis was conducted because two or more events (also referred to as "failures") may have occurred within one patient and the first chronic disease diagnosis must have occurred before the second chronic disease diagnoses event could occur. As a result, failure times were further correlated within PHC patients, which violated the independence of failure times assumption required in traditional survival analysis and these dependencies between failure times were accounted for using a variance-corrected model.

The event of interest was the point at which a patient received their subsequent chronic disease diagnosis (regardless of the disease type). Once again, an ordered, recurrent event analysis was conducted, in which patients were included more than once in the analysis if they had more than two chronic disease diagnoses before the end of the observation period. For all

analyses, the level of significance was set to 0.05. Consequently, this longitudinal analysis utilized all relevant data (that is, including information for all patients diagnosed with more than two chronic disease diagnoses). Right censoring occurred when a patient did not have another event of interest during the observation period either because: 1) the observation period was not long enough (that is, the patient would have received a subsequent chronic disease diagnosis after September 30, 2013); or 2) the patient simply would never have the event of interest (that is, the patient would not have been diagnosed with another chronic disease diagnosis after September 30, 2013). The basic or reference structure of the survival analysis model is included below:

$$h(t) = h_0(t) \exp(B_1X_1 + B_2X_2 + \dots B_kX_k)$$

where $h(t)$ = hazard rate at time *t*

$h_0(t)$ = hazard for a patient with value of 0 for all independent variables (baseline hazard function)

B_i = regression coefficient for independent variable X_i

X_i = independent variable

As previously described in **Section 4.8.2**, the data points where time elapsing between diagnoses was equal to zero were dropped from this multilevel survival analysis. This was done to ensure that the final results described the predictors that were relevant in the time elapsing until a true transition from one chronic disease state to the next. A sensitivity analyses was conducted to examine the impact of excluding these data points and a similar pattern of findings were found between the two approaches (described further in the Results Chapter).

4.8.3.4 Conceptual Model for Multilevel Variables

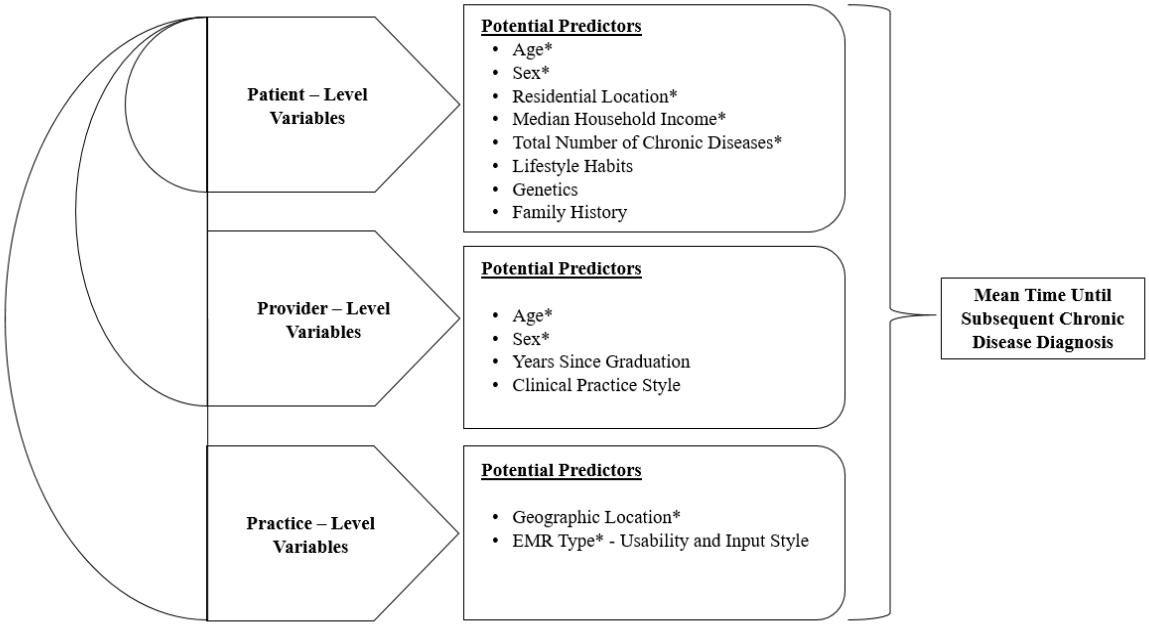
The multilevel predictors that were included in the multilevel survival analysis are presented in **Figure 4.7**. This conceptual model was developed for the purposes of this research and has not been published previously. Instead, the identification of these relevant independent variables was informed by the existing multimorbidity literature, as well as those variables that were available within the CPCSSN EMR database. For example, the patient-level variables listed in **Figure 4.7** have been reported previously to be associated with the occurrence of multimorbidity (Barnett et al., 2012; Salisbury et al., 2011; Harrison et al., 2013; Britt et al., 2008; Uijen et al., 2008; Fortin et al., 2005; van den Akker et al., 1998). Beyond the field of multimorbidity, however, research has demonstrated patient-, provider- and practice-level non-clinical influences on clinical decision-making and diagnostic behaviour (Hajjaj et al., 2010).

While most clinical decisions are based on "traditional" clinical criteria, they are also influenced by a wide range of non-clinical factors. At the patient-level, these influences can include a patient's personal characteristics, such as age (Bond et al., 2003; Little et al., 1999; Haug and Ory, 1987), sex (Bertakis, 2009; Verbruggei and Steiner, 1981; Bernstein and Kane, 1981), culture (Waldman et al., 2009) and faith (Silvestri et al., 2003); socioeconomic status (Bernheim et al., 2008; Dunlop et al., 2000); attitudes and behaviours (Steinmetz and Tabenkin, 2001; Jackson and Kroenke, 1999); concerns and worries about their health (Petursson, 2005; Escher et al., 2004); and influences of a patient's family members or friends (Franz et al., 2007). At the provider-level, these influences can include a physician's personal characteristics, such as age (McKinlay et al., 2002), sex (Bertakis, 2009; Tracy et al., 2005; Franks and Bertakis, 2003; Bertakis et al., 2003; Bensing et al., 1993), culture (Modi et al., 2007) and faith (Modi et al., 2007); time constraints and workload (Hajjaj et al., 2010); demands from the patients or their

caregivers (Franz et al., 2007; Petursson, 2005; Escher et al., 2004); and whether the physician prefers to use an "interventionist" or "wait and see" approach (Hajjaj et al., 2010; Forrest et al., 2006). Finally, practice-level influences can include characteristics of the practice organization, such as practice size and type (McKinlay et al., 1996); management policies or culture within the practice (Schumock et al., 2004; Prosser and Walley, 2003); geographic location of the practice and availability of health resources (Iverson et al., 2005; McKinlay et al., 1996). Consequently, the patient-, provider- and practice-level domains were considered to be relevant layers to capture and explore in this time-to-event analysis.

The variables that comprise the conceptual model for this thesis are those variables that were deemed to be relevant in predicting the time until subsequent chronic disease diagnoses. More specifically, these variables were informed by the existing multimorbidity literature and the variables that were available within the CPCSSN EMR database were highlighted and selected for use in the multivariable analysis. The final patient-level variables included: Age (continuous), Sex (binary), Residential Location (binary), Median Household Income (continuous) and Total Number of Chronic Diseases (discrete). The final provider-level variables included: Age (continuous) and Sex (binary). The final practice-level variables included: Practice Location (binary) and EMR Type (categorical). These independent variables were first explored in the univariate and bivariate analyses (described further in the next sections) and were used to predict the dependent variable of interest, which was the time until subsequent chronic disease diagnosis.

Figure 4.7 Conceptual model depicting the patient-, provider- and practice-level variables used to predict mean time until subsequent chronic disease diagnosis



* Variable available within CPCSSN EMR database

4.8.3.5 Univariate Analyses

All independent variables were explored using individual univariate analyses that summarized the patterns and distribution for both continuous and categorical variables. For the continuous variables (patient age, median household income, total number of chronic diseases and provider age), the mean, median, range of values and standard deviations were reported. For the binary and categorical variables (patient sex, residential location, provider sex, EMR type and practice location), the distribution among categories were calculated. The continuous dependent variable (time until subsequent chronic disease) was also explored. The characteristics of all independent variables, as well as the main dependent variable, are presented in **Table 4.5**.

Table 4.5 Characteristics of all variables included in Objective Two analyses

Independent Variable	Variable Characteristics
Patient-Level	
Age	Continuous, Measured in Years
Sex	Binary, Female or Male
Residential Location	Binary, Rural or Urban
Median Household Income	Continuous, Measured in Canadian Dollars
Total Number of Chronic Diseases	Count, Range from 0 to 20
Provider-Level	
Age	Continuous, Measured in Years
Sex	Binary, Female or Male
Practice-Level	
EMR Type	Categorical, Based on EMR Software Name
Practice Location	Binary, Rural or Urban
Dependent Variable	
Time Until Subsequent Chronic Disease	Continuous, Measured in Days

4.8.3.6 Bivariate Analyses

All independent variables were explored using bivariate analyses to determine the joint distribution between each independent variable and the continuous dependent variable. The dependent variable was non-normally distributed. As a result, non-parametric tests were conducted to explore relationships between variables. A Spearman correlation was conducted for all continuous independent variables using the *spearman* command in the Stata SE 14.1 software (StataCorp., 2015), whereas a Wilcoxon-Mann-Whitney test was conducted using the *ranksum* command for all binary independent variables. For the remaining categorical independent variables, a Kruskal Wallis test was conducted using the *kwallis* command in the Stata SE 14.1 software (StataCorp., 2015).

4.8.3.7 Creation and Interpretation of Final Survival Analysis Model

Due to sufficient sample size (ratio of 9 independent variables to 286,998 patients), all independent variables remained in the final survival analysis. To date, published multimorbidity literature has not explored potential interaction among variables that may predict the occurrence of multimorbidity. While included interaction terms can also be theory-driven, the eventual interpretation of these interaction terms must be carefully considered. Among the independent variables included in the final analysis, the potential interaction between patient age and patient sex and the joint influence on the mean time until subsequent chronic disease diagnoses was considered to be the only interpretable interaction. Consequently, this interaction term was included in the final analysis. The final survival analysis model demonstrated the time elapsing among recurrent events (that is, multiple chronic disease diagnoses) and all predictor variables at the patient-, provider- and practice-level were included in the final model. Both crude and adjusted hazard rates were calculated. The hazard rate described the probability that a patient would experience the event of interest during time, *t*, at-risk.

4.9 Summary

In summary, this research utilized a national, longitudinal EMR database to examine the prevalence, patterns and progression of multimorbidity among adult PHC patients within the CPCSSN database. The point prevalence, patient characteristics and most frequently occurring unordered and ordered clusters of multimorbidity were assessed in Objective One. The progressing burden of multimorbidity was assessed in Objective Two, which analyzed the amount of time elapsing between chronic disease diagnoses and potential patient-, provider- and practice-level predictors of this progression were explored. A summary of the similarities and

differences between the methodological approaches used for these two distinct, yet interrelated, objectives is presented in **Table 4.6**.

Table 4.6 Summary of methodological elements for Objective One and Objective Two

Methodological Element	Objective One	Objective Two
Final Patient Sample	Patients with at least one in-office encounter recorded in their EMR and who are at least 18 years of age as of their first encounter date	
Chronic Disease Diagnoses	All twenty chronic disease categories presented in **Table 4.2**	
Study Design	Retrospective or historic observational cohort (retrospectively analyzed data)	Multilevel mixed-effects recurrent event survival analysis (prospectively analyzed data)
Eligible Patients	All patients from final sample (N = 367,743)	All patients from final sample with at least one chronic disease diagnosis (n = 286,998)
Patient Groups	Mutually exclusive groups (patients with only two, only three, only four and five or more chronic diseases)	Non-mutually exclusive group (patients with one or more chronic diseases)
Start of Observation Period	Date of "first occurrence" chronic disease diagnosis	
End of Observation Period	September 30, 2013	Next chronic disease diagnosis or September 30, 2013 (if no event)

Chapter 5

5 Results

5.1 Objective One

The results for Objective One present the overall patient sample characteristics, as well as the prevalence patterns, patient characteristics, individual chronic disease distribution and the most frequently occurring clusters among patients with multimorbidity.

5.1.1 Overall Patient Sample Characteristics

Following the inclusion and exclusion criteria, a total of 367,743 patients had at least one in-office encounter recorded in their electronic record and were at least 18 years of age as of their first encounter date. The characteristics of this final sample of adult PHC patients are presented in **Table 5.1**. The mean number of chronic diseases and the prevalence of multimorbidity (defined as two or more chronic diseases) for all adult PHC patients are also presented in **Table 5.1**. The mean age of these patients was 52.3 years (SD: 18.3 years), with a range between 18 and 114 years. Approximately 73.7% of the patients included in this sample were under the age of 65 years and 36.6% of patients were between the ages of 45 and 64 years. The majority (58.0%) of patients were female and were living in an urban setting (56.3%), according to the first three letters of their residential postal code. While only thirty patients in the sample were missing data on whether they were female or male, 27.4% of patients did not have a suitable FSA recorded in their electronic record; therefore, whether they lived in a rural or urban setting could not be determined. After linking with the Statistics Canada data, the adult patient sample had a median household income of $60,310 per year, ranging from as low as

$22,457 to $181,454 per year. Once again, 27.4% of patients could not be linked with the income data as they did not have a suitable FSA recorded within their EMR.

Table 5.1 Patient-level variables for all eligible adult PHC patients (N = 367,743)

	Patient Characteristics		
Patient-Level Variable	**n (%) of Patients**	**Mean Number of Chronic Diseases (SD)**	**Prevalence (95% CI) of Multimorbidity****
Age (Years)			
Mean (SD)	52.3 Years (18.3 Years)		
Range (Minimum – Maximum)	18 Years – 114 Years		
18 – 34	74,539 (20.3%)	0.9 (1.1)	23.4% (23.1% – 23.7%)
35 – 44	61,783 (16.8%)	1.4 (1.3)	38.6% (38.2% – 39.0%)
45 – 64	134,550 (36.6%)	2.1 (1.7)	59.1% (58.9% – 59.4%)
65 – 84	77,816 (21.2%)	3.2 (2.0)	78.0% (77.7% – 78.3%)
≥ 85	19,055 (5.2%)	3.2 (2.2)	74.8% (74.2% – 75.4%)
Sex			
Female	213,402 (58.0%)	2.0 (1.8)	53.0% (52.8% – 53.3%)
Male	154,311 (42.0%)	2.0 (1.8)	53.5% (53.3% – 53.8%)
Missing	30 (0.0%)	1.1 (1.5)	23.3% (11.4% – 41.8%)
Residential Location			
Rural	59,740 (16.3%)	2.1 (2.0)	54.6% (54.2% – 55.0%)
Urban	207,192 (56.3%)	1.9 (1.9)	49.3% (49.1% – 49.5%)
Missing	100,811 (27.4%)	2.2 (1.6)	60.6% (60.3% – 60.9%)
Median Household Income (Canadian Dollars)			
Median (IQR)	$60,130 ($12,497)		
Range (Minimum – Maximum)	$22,457 – $181,454		
Missing	100,811 (27.4%)	2.2 (1.6)	60.4% (60.1% – 60.7%)

* SD = Standard deviation, CI = Confidence interval, IQR = Interquartile range

** Multimorbidity defined as patients with two or more chronic diseases

The demographic characteristics of the PHC providers for the final sample of adult patients are presented in **Table 5.2**. The mean number of chronic diseases and the prevalence of multimorbidity, stratified by provider-level variables, for all adult patients are also presented in

Table 5.2. As demographic data for providers are not commonly recorded in the EMR, missing data existed for both provider variables. The PHC providers for these patients had a mean age of 50.5 years (SD: 10.4 years) as of September 30, 2013 and a large proportion of these providers were between the ages of 45 and 64 years. For patients with a mean of 2.0 chronic diseases, their PHC providers were over the age of 65 years. In comparison, those patients with a mean of 1.7 chronic diseases had a PHC provider who was between the ages of 25 and 44 years. For patients with a mean of 1.9 chronic diseases, their PHC providers were female. For those patients with the highest mean number of chronic diseases, their PHC providers were missing information on their age (these patients had a mean of 2.2 chronic diseases) or whether they were female or male (these patients had a mean of 2.3 chronic diseases).

Table 5.2 Provider-level variables for all eligible adult PHC patients (N = 367,743)

Provider-Level Variable	n (%) of Patients	Mean Number of Chronic Diseases (SD)	Prevalence (95% CI) of Multimorbidity**
Age (Years)			
Mean (SD)	50.5 Years (10.4 Years)		
Range (Minimum – Maximum)	27 Years – 72 Years		
25 – 44	52,383 (14.2%)	1.7 (1.8)	42.7% (42.3% – 43.2%)
45 – 64	101,864 (27.7%)	1.8 (1.8)	49.0% (48.7% – 49.3%)
≥ 65	15,077 (4.1%)	2.0 (1.9)	51.3% (50.5% – 52.1%)
Missing	198,419 (54.0%)	2.2 (1.8)	58.4% (58.2% – 58.6%)
Sex			
Female	116,039 (31.6%)	1.9 (1.9)	42.8% (42.5% – 43.1%)
Male	92,319 (25.1%)	1.6 (1.7)	50.3% (50.0% – 50.6%)
Missing	159,385 (43.3%)	2.3 (1.7)	61.5% (61.2% – 61.7%)

* SD = Standard deviation, CI = Confidence interval

** Multimorbidity defined as patients with two or more chronic diseases

The characteristics of the PHC practices for the final sample of adult patients are presented in **Table 5.3**. The mean number of chronic diseases and the prevalence of multimorbidity among all adult PHC patients, stratified by practice-level variables, can also be seen in **Table 5.3**. For 28.0% of adult patients, their PHC practices were using the Nightingale EMR software. The majority of patients received care from urban PHC practices, according to the first three letters of the practices' postal code. The largest proportion of patients belonged to Network 4 (21.7%) and Network 5 (23.3%), which were located in Central Ontario and Eastern Ontario, respectively. While all adult PHC patients were allocated to one of the ten CPCSSN Networks, missing data were present for both the EMR software type and PHC practice location variables. For patients with a mean of 2.5 chronic diseases, their PHC practice was using the Jonoke EMR software, while those patients with a mean of 0.9 chronic diseases were based at a PHC practice that was using the DaVinci EMR software. Those patients who received care at a rural PHC practice had an average of 2.2 chronic diseases, while those patients who received care at an urban PHC practice had an average of 1.9 chronic diseases. For those patients with a higher mean number of chronic diseases, their PHC practices were missing information on their EMR software (these patients had a mean of 2.4 chronic diseases) or whether the practices were rural or urban (these patients had a mean of 2.3 chronic diseases). The range of the mean number of chronic diseases and the prevalence of multimorbidity were also explored among CPCSSN Network locations. The crude prevalence of multimorbidity, defined as two or more chronic diseases, is presented geographically among all ten regional networks and can be seen in **Figure 5.1**.

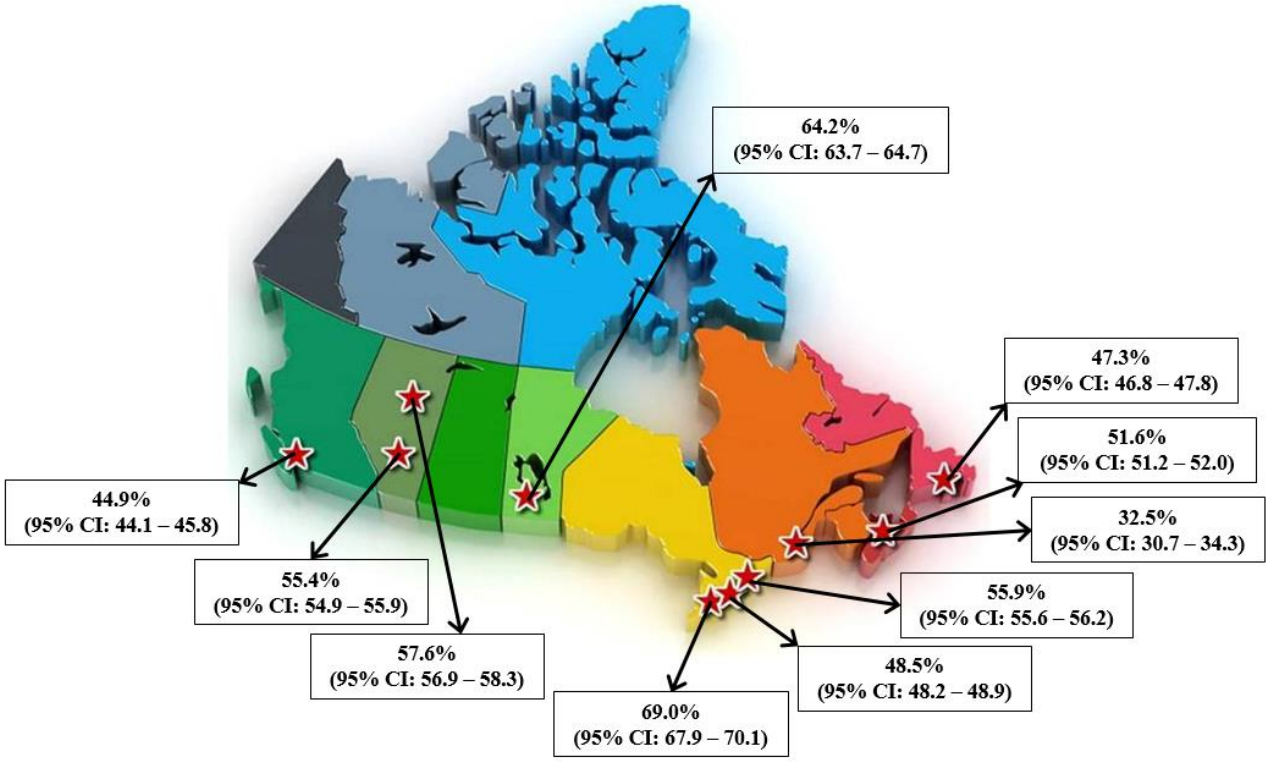
Table 5.3 Practice-level variables for all eligible adult PHC patients (N = 367,743)

Practice-Level Variable	n (%) of Patients	Mean Number of Chronic Diseases (SD)	Prevalence (95% CI) of Multimorbidity**
EMR Type			
Accuro	36,480 (9.9%)	1.7 (1.8)	43.9% (43.4% – 44.4%)
Bell	27,178 (7.4%)	2.2 (1.9)	57.4% (56.8% – 58.0%)
DaVinci	1,431 (0.4%)	0.9 (1.0)	26.3% (24.1% – 28.6%)
Jonoke	20,862 (5.7%)	2.5 (2.1)	62.1% (61.4% – 62.7%)
Med Access	12,548 (3.4%)	2.1 (2.2)	51.3% (50.4% – 52.2%)
Nightingale	103,031 (28.0%)	1.9 (1.8)	49.5% (49.2% – 49.8%)
Oscar	16,537 (4.5%)	1.4 (1.5)	37.5% (36.8% – 38.3%)
Practice Solutions	20,095 (5.5%)	1.6 (1.5)	43.4% (42.7% – 44.1%)
Wolf	38,056 (10.4%)	2.0 (2.1)	49.2% (48.7% – 49.7%)
Xwave	821 (0.2%)	2.4 (1.8)	64.3% (61.0% – 67.5%)
Missing	90,704 (24.7%)	2.4 (1.5)	65.4% (65.0% – 65.7%)
Practice Location			
Rural	35,390 (9.6%)	2.2 (2.0)	55.0% (54.5% – 55.5%)
Urban	233,744 (63.6%)	1.9 (1.9)	48.4% (48.2% – 48.6%)
Missing	98,609 (26.8%)	2.3 (1.5)	64.1% (63.8% – 64.4%)
CPCSSN Network			
1	38,031 (10.3%)	2.2 (1.9)	55.4% (54.9% – 55.9%)
2	19,253 (5.2%)	2.3 (2.1)	57.6% (56.9% – 58.3%)
3	6,954 (1.9%)	2.8 (2.1)	69.0% (67.9% – 70.1%)
4	79,941 (21.7%)	1.8 (1.6)	48.5% (48.2% – 48.9%)
5	85,834 (23.3%)	2.0 (1.7)	55.9% (55.6% – 56.2%)
6	2,507 (0.7%)	1.2 (0.9)	32.5% (30.7% – 34.3%)
7	36,391 (9.9%)	1.9 (1.9)	47.3% (46.8% – 47.8%)
8	31,741 (8.6%)	2.5 (1.9)	64.2% (63.7% – 64.7%)
9	53,624 (14.6%)	1.9 (1.7)	51.6% (51.2% – 52.0%)
10	13,467 (3.7%)	1.8 (2.0)	44.9% (44.1% – 45.8%)

* SD = Standard deviation, CI = Confidence interval

** Multimorbidity defined as patients with two or more chronic diseases

Figure 5.1 Crude prevalence estimates of multimorbidity (defined as two or more chronic diseases) among all ten regional networks of the CPCSSN database



5.1.2 Objective One, Research Question 1 – Prevalence of Multimorbidity

The patient-level variables, stratified by the total number of chronic diseases, among all adult patients are presented in **Table 5.4**. While the largest proportion (24.8%, 95% CI: 24.6 – 24.9) of adult patients were living with one chronic disease diagnosis, 22.0% (95% CI: 21.8 – 22.1) of adult patients had no chronic disease diagnoses and 20.1% (95% CI: 20.0 – 20.2) of adult patients had been diagnosed with two chronic diseases as of September 30, 2013. A total of 14.0% (95% CI: 13.9 – 14.1) of these patients were living with three chronic disease diagnoses; 8.9% (95% CI: 8.8 – 9.0) were living with four chronic diseases; and 10.2% (95% CI: 10.1 – 10.3) had been diagnosed with five or more chronic disease diagnoses. Among our final adult patient sample, the prevalence of multimorbidity defined as patients with two or more

chronic diseases was 53.3% (95% CI: 53.1% – 53.4%), whereas the prevalence of multimorbidity defined as patients with three or more chronic diseases was 33.1% (95% CI: 33.0 – 33.3). These results can be found in **Table 5.5**.

As seen in **Table 5.4**, an increasing mean age of patients was observed as the total number of chronic disease diagnoses increased. For example, the mean age of patients with no chronic disease diagnoses was 41.8 years (SD: 16.1 years) and the mean of age of patients with five or more chronic diseases diagnoses was 68.4 years (SD: 14.1 years), indicating an increase of 26.6 years on average between these two groups of patients. The proportion of female and male patients did not change notably as the number of chronic diseases increased, in that the majority of patients in all six categories were female (representing from 56.6% to 60.7% of the patient sample). The largest proportion of patients living in a rural setting was seen in the five or more chronic disease category (21.2% of those living with five or more chronic diseases), while the largest proportion of patients living in an urban setting was seen in the category of patients with no chronic disease diagnoses (73.9% of those living without any chronic disease diagnoses). The median household income was fairly consistent among the six categories of patients, and did not produce a clear trend between the categories.

Table 5.4 Patient-level variables, stratified by total number of chronic diseases, among final adult patient sample (N = 367,743)

	Total Number of Chronic Diseases					
Patient-Level Variable	**Zero**	**One**	**Two**	**Three**	**Four**	**Five or More**
Number of Patients	80,745	91,160	73,974	51,608	32,866	37,390
Prevalence (95% CI)	22.0 (21.8 – 22.1)	24.8 (24.6 – 24.9)	20.1 (20.0 – 20.2)	14.0 (13.9 – 14.1)	8.9 (8.8 – 9.0)	10.2 (10.1 – 10.3)
Age (Years)						
Mean (SD)	41.8 (16.1)	47.3 (17.0)	53.1 (16.9)	58.4 (16.3)	62.9 (15.3)	68.4 (14.1)
Range (Minimum – Maximum)	18 – 114	18 – 111	18 – 114	18 – 108	20 – 114	20 – 114
Sex (% of Patients)						
Female	59.8	56.9	56.6	57.4	57.9	60.7
Male	40.2	43.1	43.4	42.6	42.1	39.3
Residential Location (% of Patients)						
Rural	18.6	13.3	14.0	16.3	18.1	21.2
Urban	73.9	49.8	50.2	52.0	53.8	54.9
Missing	7.5	36.9	35.8	31.7	28.1	23.9
Median Household Income (Canadian Dollars)						
Median (IQR)	59,980 (13,867)	60,310 (12,497)	60,952 (12,497)	61,130 (12,497)	60,480 (12,497)	61,221 (12,953)
Range (Minimum – Maximum)	22,457 – 181,454	23,370 – 181,454	22,457 – 181,454	23,972 – 181,454	23,972 – 181,454	22,457 – 181,454
Missing (% of Patients)	7.8	37.1	36.0	31.8	28.3	24.0

* SD = Standard deviation, CI = Confidence interval, IQR = Interquartile range

The proportion of patients living with multimorbidity, stratified by patient-level variables and the two definitions of multimorbidity, are presented in **Table 5.5**. For patients with two or more chronic diseases, 40.6% of patients were between the age of 45 and 64 years and 57.8% were female. The majority of these patients were living in an urban setting (52.2%) and the median of the median household income was $60,952 per year (Canadian dollars). In fact, these patients were living with a mean of 3.3 chronic diseases, ranging from two to fourteen chronic disease diagnoses. For patients with three or more chronic disease, 39.6% of patients were between the age of 45 and 64 years and 58.5% were female. The majority of these patients were living in an urban setting (53.4%) and the median of the median household income was $61,175 per year (Canadian dollars). Similar to the group of patients with two or more chronic diseases, the group of patients with three or more chronic diseases were living with a mean of 4.2 chronic diseases, ranging from three to fourteen chronic disease diagnoses. These results will be discussed further in the next section, which will compare the characteristics of patients with multimorbidity in this research with those that have been reported in the published multimorbidity literature.

The demographic characteristics of the PHC providers for patients stratified by the two definitions of multimorbidity are seen in **Table 5.6**. Once again, as demographic data for providers are not commonly recorded in the EMR, missing data existed for both provider variables. However, for both definitions of multimorbidity, the PHC providers of these patients were a mean age of about 51.0 years and tended to be between 45 and 64 years. However, contrast was observed based on whether the PHC provider was female or male: about 30.0% of patients with two or more chronic diseases were being cared for by a male provider, while about 31.0% of patients with three or more chronic diseases were being cared for by a female provider.

Table 5.5 Prevalence of multimorbidity, defined as two or more and three or more chronic diseases, and corresponding patient-level characteristics for Objective One

Patient-Level Variable	Two or More Chronic Diseases (n = 195,838)	Three or More Chronic Diseases (n = 121,864)
Prevalence (95% CI)	53.3% (53.1% – 53.4%)	33.1% (33.0% – 33.3%)
Age (Years)		
Mean (SD)	59.0 Years (17.0 Years)	62.7 Years (15.9 Years)
Range (Minimum – Maximum)	18 Years – 114 Years	18 Years – 114 Years
Age Category, n (%) of Patients		
18 – 34	17,466 (8.9%)	6,119 (5.0%)
35 – 44	23,855 (12.2%)	10,719 (8.8%)
45 – 64	79,571 (40.6%)	48,254 (39.6%)
65 – 84	60,696 (31.0%)	45,961 (37.7%)
≥ 85	14,250 (7.3%)	10,811 (8.9%)
Sex, n (%) of Patients		
Female	113,209 (57.8%)	71,319 (58.5%)
Male	82,629 (42.2%)	50,545 (41.5%)
Residential Location, n (%) of Patients		
Rural	32,607 (16.7%)	22,274 (18.3%)
Urban	102,151 (52.2%)	65,026 (53.4%)
Missing	61,080 (31.2%)	34,564 (28.4%)
Median Household Income (Canadian Dollars)		
Median (IQR)	$60,952 ($12,497)	$61,175 ($12,497)
Range (Minimum – Maximum)	$22,457 – $181,454	$22,457 – $181,454
Missing, n (%) of Patients	61,263 (31.3%)	34,662 (28.4%)
Total Number of Chronic Diseases		
Mean (SD)	3.3 (1.5)	4.2 (1.4)
Range (Minimum – Maximum)	2 – 14	3 – 14

* SD = Standard deviation, CI = Confidence interval, IQR = Interquartile range

Table 5.6 Prevalence of multimorbidity, defined as two or more and three or more chronic diseases, and corresponding provider-level characteristics for Objective One

Provider-Level Variable	Two or More Chronic Diseases (n = 195,838)	Three or More Chronic Diseases (n = 121,864)
Age (Years)		
Mean (SD)	51.2 Years (10.2 Years)	51.5 Years (10.1 Years)
Range (Minimum – Maximum)	27 Years – 72 Years	27 Years – 72 Years
Age Category, n (%) of Patients		
25 – 44	22,402 (11.4%)	13,589 (11.2%)
45 – 64	49,871 (25.5%)	31,158 (25.6%)
≥ 65	7,730 (4.0%)	5,152 (4.2%)
Missing	115,835 (59.2%)	71,965 (59.1%)
Sex, n (%) of Patients		
Female	39,517 (20.2%)	23,738 (31.1%)
Male	58,364 (29.8%)	37,931 (19.5%)
Missing	97,957 (50.0%)	60,195 (49.4%)

* SD = Standard deviation, CI = Confidence interval

The characteristics of the PHC practices for patients stratified by the two definitions of multimorbidity are seen in **Table 5.7**. For both definitions of multimorbidity, the PHC practices of these patients tended to use the Nightingale EMR software (26.0% and 26.5%, respectively) and the majority were based in an urban setting (57.8% and 59.2%, respectively). Almost one quarter of those patients with two or more chronic diseases and three or more chronic diseases were from Network 5 (24.5% and 23.5%, respectively).

Table 5.7 Prevalence of multimorbidity, defined as two or more and three or more chronic diseases, and corresponding practice-level characteristics for Objective One

Practice- Level Variable	Two or More Chronic Diseases (n = 195,838)	Three or More Chronic Diseases (n = 121,864)
EMR Type, n (%) of Patients		
Accuro	16,001 (8.2%)	10,115 (8.3%)
Bell	15,601 (8.0%)	10,467 (8.6%)
DaVinci	376 (0.2%)	109 (0.1%)
Jonoke	12,953 (6.6%)	9,407 (7.7%)
Med Access	6,437 (3.3%)	4,553 (3.7%)
Nightingale	50,998 (26.0%)	32,287 (26.5%)
Oscar	6,208 (3.2%)	3,192 (2.6%)
Practice Solutions	8,723 (4.5%)	4,738 (3.9%)
Wolf	18,732 (9.6%)	12,949 (10.6%)
Xwave	528 (0.3%)	355 (0.3%)
Missing	59,281 (30.3%)	33,692 (27.7%)
Practice Location, n (%) of Patients		
Rural	19,471 (9.9%)	13,744 (11.3%)
Urban	113,120 (57.8%)	72,085 (59.2%)
Missing	63,247 (32.3%)	36,035 (29.6%)
CPCSSN Network, n (%) of Patients		
1	21,060 (10.8%)	13,743 (11.3%)
2	11,081 (5.7%)	7,507 (6.2%)
3	4,801 (2.5%)	3,430 (2.8%)
4	38,797 (19.8%)	21,946 (18.0%)
5	47,986 (24.5%)	28,612 (23.5%)
6	814 (0.4%)	181 (0.2%)
7	17,218 (8.8%)	11,136 (9.1%)
8	20,374 (10.4%)	13,831 (11.4%)
9	27,656 (14.1%)	17,555 (14.4%)
10	6,051 (3.1%)	3,923 (3.2%)

* SD = Standard deviation, CI = Confidence interval

To place the prevalence of multimorbidity found in this research within the context of the prevalence estimates reported in the existing multimorbidity literature, a review of the literature was conducted. A summary of the methodological characteristics, as well as the reported prevalence of multimorbidity, are presented in **Table 5.8** (for the definition of two or more chronic diseases) and **Table 5.9** (for the definition of three or more chronic diseases). The methodological characteristics and prevalence estimates from this research were also included and separated between the two definitions of multimorbidity. A total of 23 studies that defined multimorbidity as two or more chronic diseases, as well as 15 studies that defined multimorbidity as three or more chronic diseases, were included in the prevalence comparison.

Table 5.8 Key methodological elements and prevalence estimates from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Nicholson et al., 2016	**Canada**	**Retrospective cohort**	**367,743**	**≥ 18**	**Adult PHC patients**	**CPCSSN EMR database**	**ICD-9**	**20**	**53.3%****
Pefoyo et al., 2015	Canada	Retrospective cohort	10,336,297	≥ 18	All residents of Ontario	Administrative claims data	ICD-9; ICD-10	16	**30.2%****
Roberts et al., 2015	Canada	Cross-sectional	105,416	≥ 20	General adult population in Canada	2011/2012 Canadian Community Health Survey	Self-report	9	**12.9%**
Stewart et al., 2013	Canada	Retrospective cohort	2,998	≥ 18	Adult PHC patients	Deliver Primary Health Care Information EMR database	ICPC-2-R	98	**34.0%**
Agborsangaya et al., 2012	Canada	Cross-sectional	5,010	≥ 18	General adult population in Alberta	2010 Patient Experience Survey	Self-report	14	**18.8%****
Muggah et al., 2012	Canada	Cross-sectional	28,450,000	≥ 20	All residents of Ontario	Administrative claims data	ICD-9	9	**15.9%****
Fortin et al., 2005	Canada	Cross-sectional	980	≥ 18	Adult PHC patients from consecutive encounters	Health charts review	Count; CIRS	14	**89.3%****

* CIRS = Cumulative Illness Rating Scale; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-10 = International Classification of Disease, 10th Revision; ICPC-2-R = International Classification of Primary Care, 2nd Edition, Revised; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.8 Key methodological elements and prevalence estimates from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Harrison et al., 2014	Australia	Prospective cohort	8,707	≥ 20	Randomly selected PHC patients	Health charts review	ICD-10	20	**43.7%**
Taylor et al., 2010	Australia	Cross-sectional	6,411	≥ 20	Randomly selected adults	Northwest Adelaide Health Study	Self-report	7	**17.1%**
Wang et al., 2015	China	Cross-sectional	21,435	18 – 79	Community-dwelling adults	Questionnaire and interview	Self-report; ICD-10	18	**24.7%**
Chung et al., 2015	Hong Kong	Cross-sectional	25,780	≥ 15	General adult population	Hong Kong Thematic Household Survey	Self-report; ICD-10	46	**12.5%**
Pati et al., 2015	India	Cross-sectional	1,649	≥ 18	Adult patients from PHC facilities	Multimorbidity Assessment Protocol Survey	Self-report	22	**28.3%**
van Oostrom et al., 2012	The Netherlands	Retrospective cohort	173,958	≥ 15	PHC patients	Network of General Practice EMR database	ICPC	29	**12.9%**

* CIRS = Cumulative Illness Rating Scale; EMR = Electronic medical record; ICD-10 = International Classification of Disease, 10th Revision; ICPC = International Classification of Primary Care; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.8 Key methodological elements and prevalence estimates from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
van den Akker et al., 1998	The Netherlands	Cross-sectional	47,140	≥ 20	Adult PHC patients	RegistratieNet Huisartspraktijken EMR database	ICPC	335	**35.4%****
Prazeres et al., 2015	Portugal	Cross-sectional	1,993	≥ 18	Adult PHC patients	Questionnaire	ICPC-2	147	**72.7%**
Jovic et al., 2016	Serbia	Cross-sectional	13,103	≥ 20	Community-dwelling adults	2013 National Health Survey	Self-report	12	**26.8%**
Orueta et al., 2014	Spain	Cross-sectional	1,923,156	≥ 18	Adult PHC patients	Population Stratification Programme EMR database	ICD-9-CM; ACG	40	**23.6%**
Prados-Torres et al., 2012	Spain	Retrospective cohort	275,682	≥ 15	PHC patients	Spanish National Health System EMR database	ICPC; ICD-9-CM; ACG	114	**36.8%****
Rizza et al., 2012	Switzerland	Retrospective cohort	66,212	≥ 20	Adult PHC patients	Swiss Family Medicine ICPC Research using EMR database	ICPC-2	147	**14.5%**

* ACG = Adjusted Clinical Groups Case-Mix System; EMR = Electronic medical record; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; ICPC= International Classification of Primary Care; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.8 Key methodological elements and prevalence estimates from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Barnett et al., 2012	United Kingdom	Cross-sectional	1,751,841	All ages	All PHC patients	National EMR database	Read codes	40	**23.2%**
Salisbury et al., 2011	United Kingdom	Retrospective cohort	99,997	≥ 18	Randomly selected adult PHC patients	General Practice Research Datalink	ACG	114	**58.0%**
Rocca et al., 2014	United States	Cross-sectional	100,833	≥ 20	Adult PHC patients	Rochester Epidemiology Project EMR database	ICD-9	20	**22.6%****
Ornstein et al., 2013	United States	Cross-sectional	667,379	≥ 18	Adult PHC patients	Practice-Based Research Network EMR database	ICD-9-CM	24	**45.3%**
Ward et al., 2013	United States	Cross-sectional	27,157	≥ 18	Randomly selected community-dwelling adults	2010 National Health Survey	Self-report	10	**26.0%**

* ACG = Adjusted Clinical Groups Case-Mix System; EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.9 Key methodological elements and prevalence estimates from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Nicholson et al., 2016	**Canada**	**Retrospective cohort**	**367,743**	**≥ 18**	**Adult PHC patients**	**CPCSSN EMR database**	**ICD-9**	**20**	**33.1%****
Pefoyo et al., 2015	Canada	Retrospective cohort	10,336,297	≥ 18	All residents of Ontario	Administrative claims data	ICD-9; ICD-10	16	**13.6%****
Roberts et al., 2015	Canada	Cross-sectional	105,416	≥ 20	General adult population in Canada	2011/2012 Canadian Community Health Survey	Self-report	9	**3.9%**
Agborsangaya et al., 2012	Canada	Cross-sectional	5,010	≥ 18	General adult population in Alberta	2010 Patient Experience Survey	Self-report	14	**11.1%****
Muggah et al., 2012	Canada	Cross-sectional	28,450,000	≥ 20	All residents of Ontario	Administrative claims data	ICD-9	9	**5.6%**
Fortin et al., 2005	Canada	Cross-sectional	980	≥ 18	Adult PHC patients from consecutive encounters	Health charts review	Count; CIRS	14	**75.6%****
Harrison et al., 2014	Australia	Prospective cohort	8,707	≥ 20	Randomly selected PHC patients	Health charts review	ICD-10	20	**27.4%**

* CIRS = Cumulative Illness Rating Scale; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-10 = International Classification of Disease, 10th Revision; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.9 Key methodological elements and prevalence estimates from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Taylor et al., 2010	Australia	Cross-sectional	6,411	≥ 20	Randomly selected community-dwelling adults	Northwest Adelaide Health Study	Self-report	7	**5.3%****
Wang et al., 2015	China	Cross-sectional	21,435	18 – 79	Community-dwelling adults	Questionnaire and interview	Self-report; ICD-10	18	**12.0%**
Chung et al., 2015	Hong Kong	Cross-sectional	25,780	≥ 15	General adult population	Hong Kong Thematic Household Survey	Self-report; ICD-10	46	**5.4%****
Prazeres et al., 2015	Portugal	Cross-sectional	1,993	≥ 18	Adult PHC patients	Questionnaire of PHC patients	ICPC-2	147	**57.2%**
Jovic et al., 2016	Serbia	Cross-sectional	13,103	≥ 20	Community-dwelling adults	2013 National Health Survey	Self-report	12	**14.3%****
Prados-Torres et al., 2012	Spain	Retrospective cohort	275,682	≥ 15	PHC patients	Spanish National Health System EMR database	ICPC; ICD-9-CM; ACG	114	**20.2%****

* ACG = Adjusted Clinical Groups Case-Mix System; EMR = Electronic medical record; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; ICD-10 = International Classification of Disease, 10th Revision; ICPC= International Classification of Primary Care; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.9 Key methodological elements and prevalence estimates from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Study Design	Sample Size	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System	Number of Diseases Considered	MM Prevalence
Rizza et al., 2012	Switzerland	Retrospective cohort	66,212	≥ 20	Adult PHC patients	Swiss Family Medicine ICPC Research using EMR database	ICPC-2	147	**7.3%**
Zulman et al., 2015	United States	Retrospective cohort	5,233,994	All ages	United States military veterans	Veterans Affairs health care system database	AHRQ Chronic Condition Indicator	33	**28.5%**
Ornstein et al., 2013	United States	Cross-sectional	667,379	≥ 18	Adult PHC patients	Practice-Based Research Network EMR database	ICD-9-CM	24	**30.4%**

* AHRQ = Agency for Health Care Research and Quality; EMR = Electronic medical record; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

5.1.3 Objective One, Research Question 2 – Characteristics of Adult PHC Patients with Multimorbidity

The proportion of patients living with multimorbidity, stratified by patient-level variables and the two definitions of multimorbidity, are presented in **Table 5.5**. Among patients with two or more chronic diseases, 40.6% were between the ages of 45 and 64 years. When age categories were grouped together, almost two-thirds (61.7%) of patients living with two or more chronic diseases were under the age of 65 years. The majority of these patients were female (57.8%) and lived in an urban setting (52.2%), while the median of the median household income was approximately $60,950 per year (Canadian dollars). While all patients were living with at least two chronic diseases, these patients in fact had a mean of 3.3 chronic disease diagnoses (SD: 1.5) and the total number of diagnosed chronic diseases ranged from 2 to as many as 14 diagnoses.

Similar characteristics were seen among patients with three or more chronic diseases. For example, the mean age of these patients was 62.7 years (SD: 15.9 years) and the largest proportion (39.6%) of patients were between the ages of 45 and 64 years. Once again, the majority of patients were female (58.5%) and living in an urban setting (53.4%), while the median of the median household income was approximately $61,175 per year (Canadian dollars). Similar to those patients living with two or more chronic diseases, while all patients within this definition of multimorbidity were living with three or more chronic diseases, these patients in fact had a mean of 4.2 chronic disease diagnoses (SD: 1.4), indicating a slightly higher burden of chronic diseases than required within the definition itself.

To place the characteristics of those with multimorbidity found in this research within the context of the characteristics reported in the existing multimorbidity literature, a review of the literature was conducted. A summary of the methodological characteristics, as well as the

characteristic category with the highest prevalence of multimorbidity, are presented in **Table 5.10** (for the definition of two or more chronic diseases) and **Table 5.11** (for the definition of three or more chronic diseases). Due to the heterogeneity of methodology and reporting in the multimorbidity literature, the main patient characteristics that were possible to consistently compare with the existing literature were the prevalence estimates stratified by age and sex category. A total of 21 studies that defined multimorbidity as two or more chronic diseases, as well as 8 studies that defined multimorbidity as three or more chronic diseases, were included in the characteristic comparison.

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Nicholson et al., 2016	**Canada**	**≥ 18**	**Adult PHC patients**	**CPCSSN EMR database**	**ICD-9**	**20**	**53.3%****	18 – 34 35 – 44 **45 – 64: 40.6%**** 65 – 84 ≥ 85	**Female: 57.8%****
Pefoyo et al., 2015	Canada	≥ 18	All residents of Ontario	Administrative claims data	ICD-9; ICD-10	16	30.2%**	18 – 44 45 – 64 65 – 74 75 – 89 **≥ 90: 83.2%**	Not Reported
Roberts et al., 2015	Canada	≥ 20	General adult population in Canada	2011/2012 Canadian Community Health Survey	Self-report	9	12.9%	20 – 34 35 – 49 50 – 64 **≥ 65: 31.3%**	**Female: 15.1%**
Stewart et al., 2013	Canada	≥ 18	Adult PHC patients	Deliver Primary Health Care Information EMR database	ICPC-2-R	98	34.0%	18 – 34 45 – 64 **≥ 65: 55.8%****	**Male: 40.4%****

* CPCSSN = Canadian Primary Care Sentinel Surveillance Network; EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-10 = International Classification of Disease, 10th Revision; ICPC-2-R = International Classification of Primary Care, 2nd Edition Revised; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Agborsangaya et al., 2012	Canada	≥ 18	General adult population in Alberta	2010 Patient Experience Survey	Self-report	14	18.8%**	18 – 24 25 – 44 45 – 64 **≥ 65: 35.8%**	**Female: 20.6%**
Fortin et al., 2005	Canada	≥ 18	Adult patients from consecutive encounters	Health charts review	Count; CIRS	14	89.3%**	18 – 44 45 – 64 **≥ 65: 98.6%****	**Male: 89.4%****
Harrison et al., 2014	Australia	≥ 20	Randomly selected PHC patients	Health charts review	ICD-10	20	43.7%	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79 80 – 89 **≥ 90: 93.2%**	Not Reported
Taylor et al., 2010	Australia	≥ 20	Randomly selected adults	Northwest Adelaide Health Study	Self-report	7	17.1%	20 – 39 40 – 59 **≥ 60: 57.9%**	Not Reported

* CIRS = Cumulative Illness Rating Scale; ICD-10 = International Classification of Disease, 10th Revision; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Wang et al., 2015	China	18 – 79	Community-dwelling adults	Questionnaire and interview	Self-report; ICD-10	18	24.7%	18 – 44 45 – 59 **60 – 79: 51.2%**	**Female: 29.6%**
Pati et al., 2015	India	≥ 18	Adult patients from PHC facilities	Multimorbidity Assessment Protocol Survey	Self-report	22	28.3%	18 – 29 30 – 39 40 – 49 50 – 59 60 – 69 **≥ 70: 44.4%**	**Female: 32.5%**
van Oostrom et al., 2012	The Netherlands	≥ 15	PHC patients	Network of General Practice EMR database	ICPC	29	12.9%	15 – 24 25 – 54 55 – 64 65 – 74 **≥ 75: 59.2%**	**Female: 15.0%**
van den Akker et al., 1998	The Netherlands	≥ 20	Adult PHC patients	RegistratieNet Huisartspraktijken EMR database	ICPC	335	35.4%**	20 – 39 40 – 59 60 – 79 **≥ 80: 78.2%****	**Female: 37.9%****

* EMR = Electronic medical record; ICD-10 = International Classification of Disease, 10th Revision; ICPC = International Classification of Primary Care; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Prazeres et al., 2015	Portugal	≥ 18	Adult PHC patients	Questionnaire	ICPC-2	147	72.7%	18 – 34 35 – 49 50 – 64 **≥ 65: 92.6%**	**Male: 75.9%**
Jovic et al., 2016	Serbia	≥ 20	Community-dwelling adults	2013 National Health Survey	Self-report	12	26.8%	20 – 44 45 – 64 **≥ 65: 57.4%****	Not Reported
Orueta et al., 2014	Spain	≥ 18	Adult PHC patients	Population Stratification Programme EMR database	ICD-9-CM; ACG	40	23.6%**	18 – 34 35 – 44 45 – 54 55 – 64 65 – 69 70 – 74 75 – 79 **80 – 84: 76.4%** ≥ 85	**Female: 25.9%**
Prados-Torres et al., 2012	Spain	≥ 15	PHC patients	Spanish National Health System EMR database	ICPC; ICD-9-CM; ACG	114	36.8%**	15 – 44 45 – 64 **≥ 65: 67.5%****	**Female: 40.1%**

* ACG = Adjusted Clinical Groups Case-Mix System; EMR = Electronic medical record; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; ICPC = International Classification of Primary Care; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Rizza et al., 2012	Switzerland	≥ 20	Adult PHC patients	Swiss Family Medicine ICPC Research using EMR database	ICPC-2	147	14.5%	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79 **≥ 80: 37.7%**	**Male: 14.8%**
Barnett et al., 2012	United Kingdom	All ages	All PHC patients	National EMR database	Read codes	40	23.2%	0 – 24 25 – 44 45 – 64 65 – 84 **≥ 85: 81.5%**	**Female: 26.2%**
Salisbury et al., 2011	United Kingdom	≥ 18	Randomly selected adult PHC patients	General Practice Research Datalink	ACG	114	58.0%	18 – 24 25 – 34 35 – 44 45 – 54 55 – 64 65 – 74 **≥ 75: 64.0%****	Not Reported

* ACG = Adjusted Clinical Groups Case-Mix System; EMR = Electronic medical record; ICPC = International Classification of Primary Care; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.10 Key methodological elements and sample characteristics from multimorbidity literature (defined as two or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Rocca et al., 2014	United States	≥ 20	Adult PHC patients	Rochester Epidemiology Project EMR database	ICD-9	20	22.6%**	20 – 39 40 – 49 50 – 59 60 – 69 70 – 79 **≥ 80: 87.9%**	**Female: 23.4%**
Ornstein et al., 2013	United States	≥ 18	Adult PHC patients	Practice-Based Research Network EMR database	ICD-9-CM	24	45.3%	18 – 34 35 – 44 45 – 54 55 – 64 65 – 74 **75 – 85: 81.0%** ≥ 85	Not Reported
Ward et al., 2013	United States	≥ 18	Randomly selected community-dwelling adults	2010 National Health Survey	Self-report	10	26.0%	18 – 44 45 – 64 **≥ 65, Female: 61.9%****	**Female, ≥ 65 Years: 61.9%****

* EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.11 Key methodological elements and sample characteristics from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Nicholson et al., 2016	**Canada**	**≥ 18**	**Adult PHC patients**	**CPCSSN EMR database**	**ICD-9**	**20**	**33.1%****	18 – 34 35 – 44 **45 – 64: 39.6%**** 65 – 84 ≥ 85	**Female: 58.5%****
Pefoyo et al., 2015	Canada	≥ 18	All residents of Ontario	Administrative claims data	ICD-9; ICD-10	16	13.6%**	18 – 44 45 – 64 65 – 74 75 – 89 **≥ 90: 66.0%****	Not Reported
Roberts et al., 2015	Canada	≥ 20	General adult population in Canada	2011/2012 Canadian Community Health Survey	Self-report	9	3.9%	20 – 34 35 – 49 50 – 64 **≥ 65: 11.3%**	**Female: 4.5%**
Fortin et al., 2005	Canada	≥ 18	Adult PHC patients from consecutive encounters	Health charts review	Count; CIRS	14	75.6%**	18 – 44 45 – 64 **≥ 65: 95.4%****	**Female: 77.4%****

* CIRS = Cumulative Illness Rating Scale; CPCSSN = Canadian Primary Care Sentinel Surveillance Network; EMR = Electronic medical record; ICD-9 = International Classification of Disease, 9th Revision; ICD-10 = International Classification of Disease, 10th Revision; MM = Multimorbidity; PHC = Primary health care

** Prevalence estimate extracted and calculated by author

Table 5.11 Key methodological elements and sample characteristics from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group (Years) with Highest Prevalence	Sex Category with Highest Prevalence
Harrison et al., 2014	Australia	≥ 20	Randomly selected PHC patients	Health charts review	ICD-10	20	27.4%	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79 **80 – 89: 81.8%** ≥ 90	Not Reported
Taylor et al., 2010	Australia	≥ 20	Randomly selected adults	Northwest Adelaide Health Study	Self-report	7	5.3%**	20 – 39 40 – 59 **≥ 60: 14.5%**	Not Reported
Prazeres et al., 2015	Portugal	≥ 18	Adult PHC patients	Questionnaire of PHC patients	ICPC-2	147	57.2%	18 – 34 35 – 49 50 – 64 **≥ 65: 82.7%**	**Male: 61.6%**
Rizza et al., 2012	Switzerland	≥ 20	Adult PHC patients	Swiss Family Medicine ICPC Research using EMR database	ICPC-2	147	7.3%	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79 **≥ 80: 22.7%**	**Male: 7.6%**

* ICD-10 = International Classification of Disease, 10th Revision; ICPC = International Classification of Primary Care; ICPC-2 = International Classification of Primary Care, 2nd Edition; MM = Multimorbidity; PHC = Primary health care

Table 5.11 Key methodological elements and sample characteristics from multimorbidity literature (defined as three or more chronic diseases), as compared to elements and prevalence from current research, *Continued*

Citation	Country of Origin	Age Range	Sample Recruitment	Data Source	Diagnostic Coding System*	Number of Diseases Considered	MM Prevalence	Age Group with Highest Prevalence	Sex Category with Highest Prevalence
Ornstein et al., 2013	United States	≥ 18	Adult PHC patients	Practice-Based Research Network EMR database	ICD-9-CM	24	30.4%	18 – 34 35 – 44 45 – 54 55 – 64 65 – 74 75 – 85 **≥ 85: 69.0%**	Not Reported

* EMR = Electronic medical record; ICD-9-CM = International Classification of Disease, 9th Revision, Clinical Modification; MM = Multimorbidity; PHC = Primary health care

5.1.4 Objective One, Research Question 3 – Most Frequent Clusters of Multiple Chronic Diseases

In addition to presenting the most frequently occurring combinations (that is, unordered clusters) and permutations (that is, ordered clusters) among all adult patients with multimorbidity (stratified by both patient age and patient sex), the prevalence of the twenty individual chronic disease diagnoses (included within the measure of multimorbidity) will first be presented.

Prevalence of Individual Chronic Diseases

The prevalence of individual chronic disease diagnoses among all adult patients, as well as patients with multimorbidity, is displayed in **Table 5.12** and includes the prevalence of all twenty chronic disease diagnoses. Among all three patient groups (that is: 1) all adult patients; 2) patients with two or more chronic diseases; and 3) patients with three or more chronic diseases), the most prevalent chronic disease diagnosis was Obesity, ranging from a prevalence of 24.6% (95% CI: 24.5 – 24.8) among all adult patients to a prevalence of 30.2% (95% CI: 30.0 – 30.4) among patients with two or more chronic diseases. Once again for all three patient groups, the second most prevalent chronic disease diagnosis was Hypertension, ranging from a prevalence of 10.5% (95% CI: 10.4 – 10.6) among all adult patients to a prevalence of 18.9% (95% CI: 18.6 – 19.1) among patients with three or more chronic diseases. The third most prevalent chronic disease among all three patient groups was the diagnosis for Musculoskeletal Problem, which ranged from a prevalence of 8.9% (95% CI: 8.8 – 9.0) among all adult patients to a prevalence of 10.2% (95% CI: 10.1 – 10.4) among patients with two or more chronic diseases. The least prevalent chronic disease diagnoses among all three patient groups were

Stroke or Transient Ischemic Attack, Kidney Disease or Failure and Liver Disease. Each of these chronic diseases had a prevalence of about 0.1% within each patient group.

The prevalence of individual chronic disease diagnoses among all patients with multimorbidity, defined as two or more chronic diseases and stratified by patient age and patient sex, are presented in **Figure 5.2** to **Figure 5.7**. When compared, these six Figures indicate a changing distribution of prevalent chronic disease diagnoses as patients age, regardless of patient sex. Among all female patients with multimorbidity (n = 113,209), the most prevalent chronic disease diagnoses were Obesity (28.4%, 95% CI: 28.1 – 28.7); Hypertension (16.0%, 95% CI: 15.7 – 16.2); Anxiety or Depression (10.5%, 95% CI: 10.4 – 10.7); Musculoskeletal Problem (10.3%, 95% CI: 10.2 – 10.5); and Cancer (5.8%, 95% CI: 5.6 – 5.9). Among all male patients with multimorbidity (n = 82,622), the most prevalent chronic disease diagnoses were Obesity (32.7%, 95% CI: 32.4 – 33.0); Hypertension (16.7%, 95% CI: 16.5 – 17.0); Musculoskeletal Problem (10.1, 95% CI: 9.9 – 10.3); Diabetes (7.4%, 95% CI: 7.2 – 7.6); and Anxiety or Depression (6.4%, 95% CI: 6.3 – 6.6).

Among both female and male patients aged 18 to 34 years, the most prevalent chronic diseases were Obesity, Anxiety or Depression and Musculoskeletal Problem. For young female patients, the prevalence of Obesity was 32.7% (95% CI: 31.8 – 33.5); of Anxiety or Depression was 19.8% (95% CI: 19.1 – 20.6); and of Musculoskeletal Problem was 12.6% (95% CI: 12.0 – 13.2). For young male patients, the prevalence of Obesity was 33.1% (95% CI: 32.5 – 34.9); of Anxiety or Depression was 16.8% (95% CI: 15.9 – 17.8); and of Musculoskeletal Problem was 16.7% (95% CI: 15.8 – 17.7). Interestingly, these three chronic disease diagnoses remained the most prevalent among both female and male patients aged 35 to 44 years. However, in this age group, the overall prevalence of these diseases decreased as the frequency of other chronic

diseases increased (except for Obesity, which had a rise in prevalence). The prevalence of Obesity was 34.1% (95% CI: 33.3 – 34.9) and 36.4% (95% CI: 35.4 – 37.4) for female and male patients aged 35 to 44 years, respectively. Among female patients, the prevalence of Anxiety or Depression was 17.1% (95% CI: 16.5 – 17.7) and the prevalence of Musculoskeletal Problem was 13.3% (95% CI: 12.8 – 13.9). For male patients of the same age, the prevalence of Anxiety or Depression was 12.4% (95% CI: 11.7 – 13.1) and the prevalence of Musculoskeletal Problem was 16.3% (95% CI: 15.6 – 17.1). Among female patients aged 45 to 64 years, the most prevalent chronic diseases were Obesity (31.3%, 95% CI: 30.9 – 31.7); Hypertension (12.8%, 95% CI: 12.5 – 13.1); and Musculoskeletal Problem (12.4%, 95% CI: 12.0 – 12.7). This was followed closely by Anxiety or Depression, which had a prevalence of 11.3% (95% CI: 11.0 – 11.6). Among male patients aged 45 to 64 years, the most prevalent chronic diseases were also Obesity (36.3%, 95% CI: 35.8 – 36.8); Hypertension (15.4%, 95% CI: 15.1 – 15.8); and Musculoskeletal Problem (11.6%, 95% CI: 11.3 – 12.0).

Female and male patients who were between the ages of 65 and 84 years were most likely to be living with Obesity, Hypertension and Diabetes. For female patients, the prevalence of Obesity was 24.6% (95% CI: 24.1 – 25.1); of Hypertension was 24.9% (95% CI: 24.4 – 25.3); and of Diabetes was 7.4% (95% CI: 7.2 – 7.7). For male patients, the prevalence of Obesity was 29.5% (95% CI: 29.0 – 30.1); of Hypertension was 22.2% (95% CI: 21.7 – 22.7); and of Diabetes was 10.9% (95% CI: 10.5 – 11.2). With the exception of the prominent diagnoses of Obesity and Hypertension, prevalence estimates were more evenly distributed among a number of other chronic diseases, such as Musculoskeletal Problem, Hyperlipidemia, Cancer and Cardiovascular Disease. Likewise, those patients who were 85 years of age and older were most likely to be living with Obesity and Hypertension. However, the most prevalent chronic disease

in this age group was Hypertension with a prevalence of 33.9% (95% CI: 32.9 – 34.9) and 26.9% (95% CI: 25.8 – 28.2) among female and male patients, respectively. While the next prevalent chronic disease diagnosis was Obesity, the prevalence estimates were again more evenly distributed among a number of other chronic diseases, such as Cardiovascular Disease, Diabetes, Cancer and Osteoarthritis or Rheumatoid Arthritis.

Prevalence estimates of individual chronic diseases within the CPCSSN EMR database were also compared with the 2013 Canadian Community Health Survey (CCHS), which can be seen in **Appendix J**. These prevalence estimates were stratified by patient age and patient sex. Before comparison, it was important to consider the marked differences in the methodology between these prevalence estimates. For example, the 2013 CCHS data were derived from a cross-sectional survey of community-dwelling respondents and data were collected directly from survey respondents via self-report. In comparison, the CPCSSN EMR data were derived from longitudinal clinical patient records that were recorded prospectively by PHC providers. Despite these key methodological differences, the national estimates of relevant chronic diseases were compared. Overall, Diabetes and Hypertension were the most comparable categories of diseases between the CCHS and CPCSSN EMR data. This was because of the most concise overlap between the definitions of both diseases. For example, the term "High Blood Pressure", which was used in the CCHS survey is commonly interchanged with the more clinical term of "Hypertension". However, there may have been considerable disparities between a respondent's interpretation of "Heart Disease" in the CCHS survey and whether their definition corresponded to the diagnoses for "Cardiovascular Disease" in the CPCSSN EMR data. This is supported by a study conducted by Muggah et al. (2013), which examined the accuracy of self-reported diseases from the 2005 CCHS and confirmed that the highest agreement between the self-reported

chronic diseases and administrative data (specifically within the province of Ontario) were for Diabetes and Hypertension (Kappa range: 0.66 – 0.80). This was followed by a moderate level of agreement for Myocardial Infarction and Asthma, while the remaining self-reported chronic diseases (Stroke, Congestive Heart Failure and Chronic Obstructive Pulmonary Disease) showed a poor level of agreement (Muggah et al., 2013).

The prevalence estimates of Diabetes between the CCHS and the CPCSSN EMR data were within 10% throughout the age categories. The prevalence of Hypertension was comparable for individuals aged 18 to 34 years and 35 to 44 years in the two datasets, however, this prevalence was drastically lower in the CPCSSN EMR data (approximately 20% difference in prevalence) among individuals who were 45 years and older. For both categories, the CPCSSN EMR data reported a lower prevalence level as compared to the 2013 CCHS data. While these differences in prevalence estimates are notable, it is not clear whether these prevalence estimates were artefacts of the methodological differences between the survey and EMR data, or whether these differences demonstrate the true prevalence of chronic disease within these two study populations.

Table 5.12 Prevalence of individual chronic disease diagnoses among all adult patients and those with multimorbidity, defined as two or more and three or more chronic diseases

	Prevalence (95% CI)		
Chronic Disease Category	**All Adult Patients (N = 367,743)**	**Among Patients with Two or More Chronic Diseases (n = 195,838)**	**Among Patients with Three or More Chronic Diseases (n = 121,864)**
Obesity	24.6 (24.5 – 24.8)	30.2 (30.0 – 30.4)	27.5 (27.3 – 27.8)
Hypertension	10.5 (10.4 – 10.6)	16.3 (16.1 – 16.5)	18.9 (18.6 – 19.1)
Musculoskeletal Problem	8.9 (8.8 – 9.0)	10.2 (10.1 – 10.4)	9.5 (9.4 – 9.7)
Anxiety or Depression	8.1 (8.0 – 8.2)	8.8 (8.7 – 8.9)	7.5 (7.4 – 7.7)
Cancer	4.8 (4.7 – 4.9)	5.1 (5.0 – 5.2)	4.6 (4.5 – 4.7)
Diabetes	3.7 (3.6 – 3.8)	5.9 (5.8 – 6.0)	7.0 (6.8 – 7.1)
Chronic Obstructive Pulmonary Disease or Asthma	3.1 (3.0 – 3.2)	3.9 (3.8 – 4.0)	3.7 (3.6 – 3.8)
Hyperlipidemia	3.1 (3.0 – 3.1)	4.4 (4.4 – 4.5)	4.9 (4.8 – 5.0)
Osteoarthritis or Rheumatoid Arthritis	2.3 (2.3 – 2.4)	3.3 (3.3 – 3.4)	3.9 (3.8 – 4.0)
Thyroid Problem	2.1 (2.1 – 2.2)	2.9 (2.8 – 3.0)	3.0 (2.9 – 3.1)
Cardiovascular Disease	1.9 (1.8 – 1.9)	2.8 (2.7 – 2.8)	3.2 (3.1 – 3.3)
Urinary Problem	1.6 (1.6 – 1.6)	2.0 (1.9 – 2.1)	2.0 (1.9 – 2.1)
Colon Problem	1.0 (1.0 – 1.1)	1.2 (1.2 – 1.3)	1.2 (1.1 – 1.2)
Stomach Problem	0.9 (0.8 – 0.9)	1.1 (1.1 – 1.2)	1.2 (1.1 – 1.2)
Osteoporosis	0.5 (0.4 – 0.5)	0.7 (0.6 – 0.7)	0.8 (0.7 – 0.8)
Dementia	0.5 (0.4 – 0.5)	0.5 (0.4 – 0.5)	0.4 (0.4 – 0.4)
Heart Failure	0.2 (0.2 – 0.2)	0.3 (0.3 – 0.3)	0.3 (0.3 – 0.4)
Kidney Disease or Failure	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.2)
Liver Disease	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.1)
Stroke or Transient Ischemic Attack	0.1 (0.1 – 0.1)	0.1 (0.1 – 0.2)	0.2 (0.1 – 0.2)

* CI = Confidence interval

Figure 5.2 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, all ages

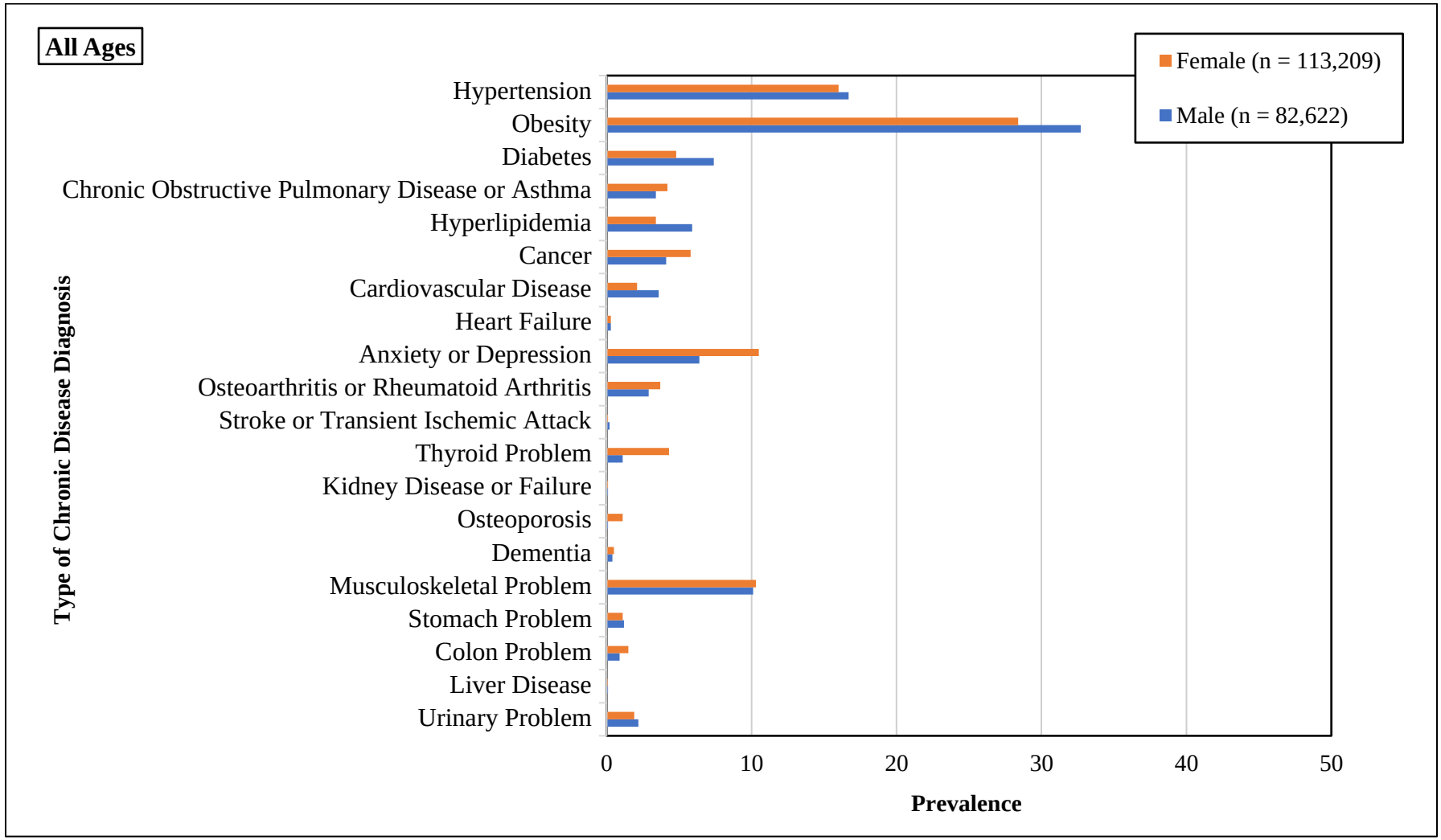


Figure 5.3 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, aged 18 – 34 years

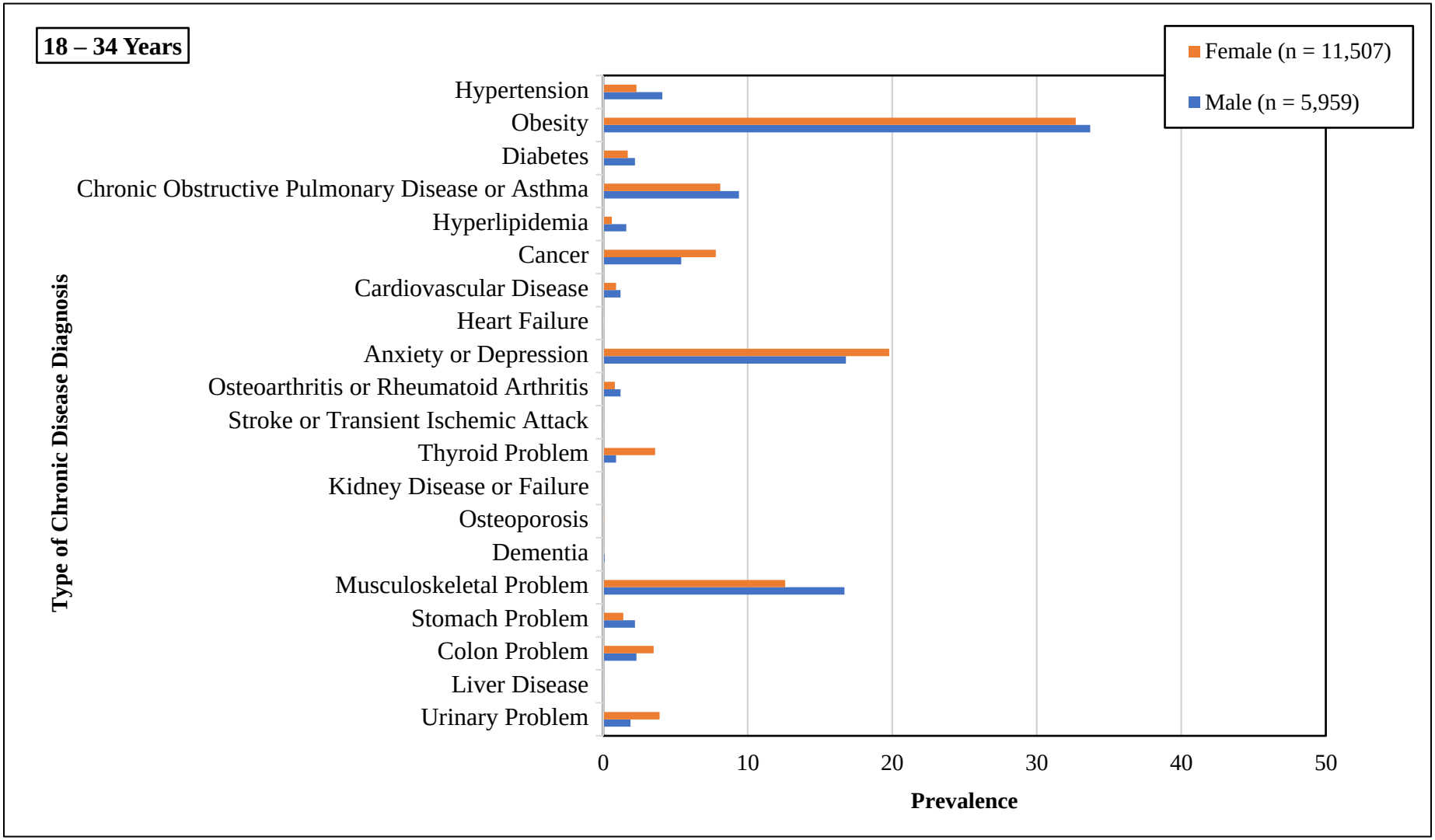


Figure 5.4 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, aged 35 – 44 years

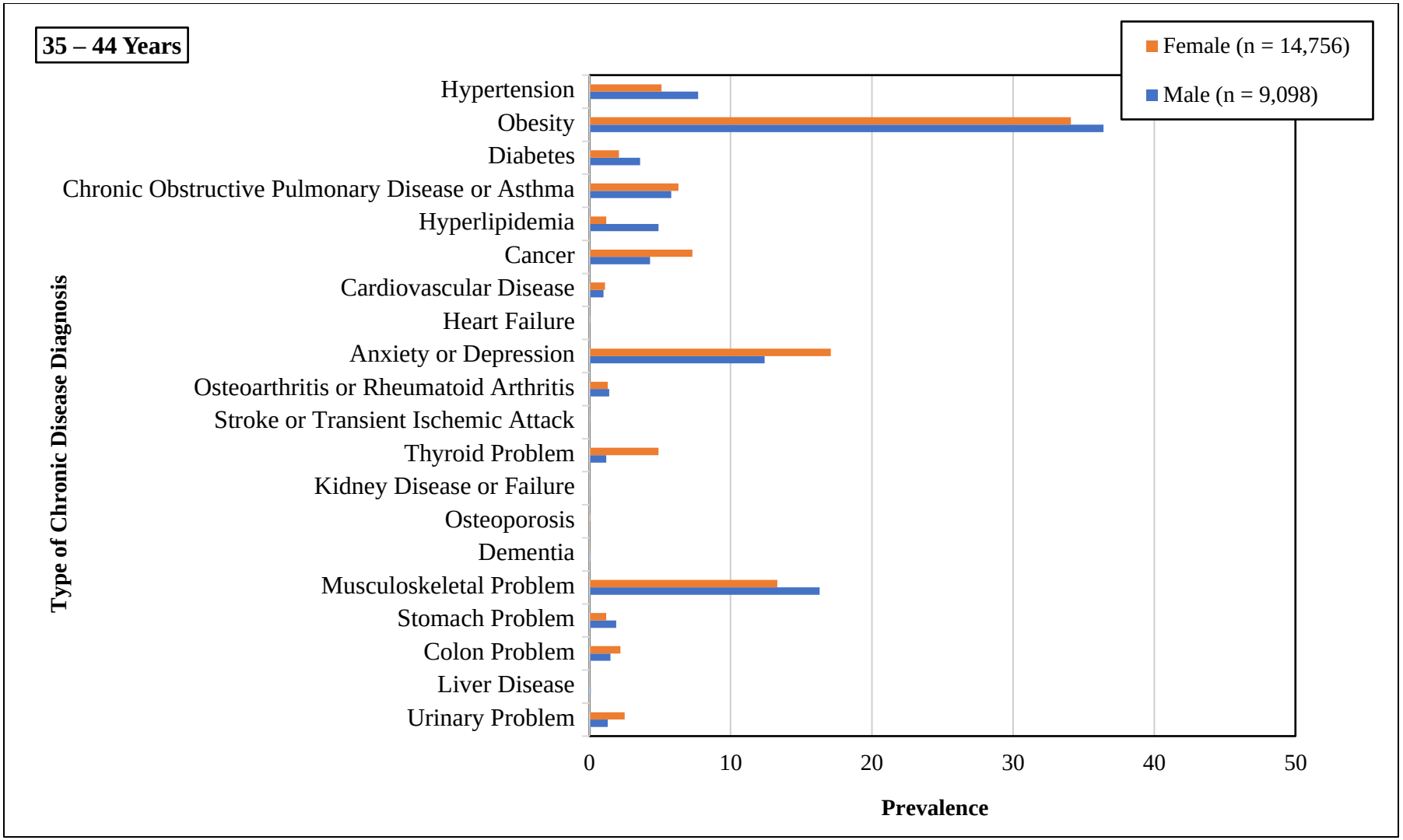


Figure 5.5 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, aged 45 – 64 years

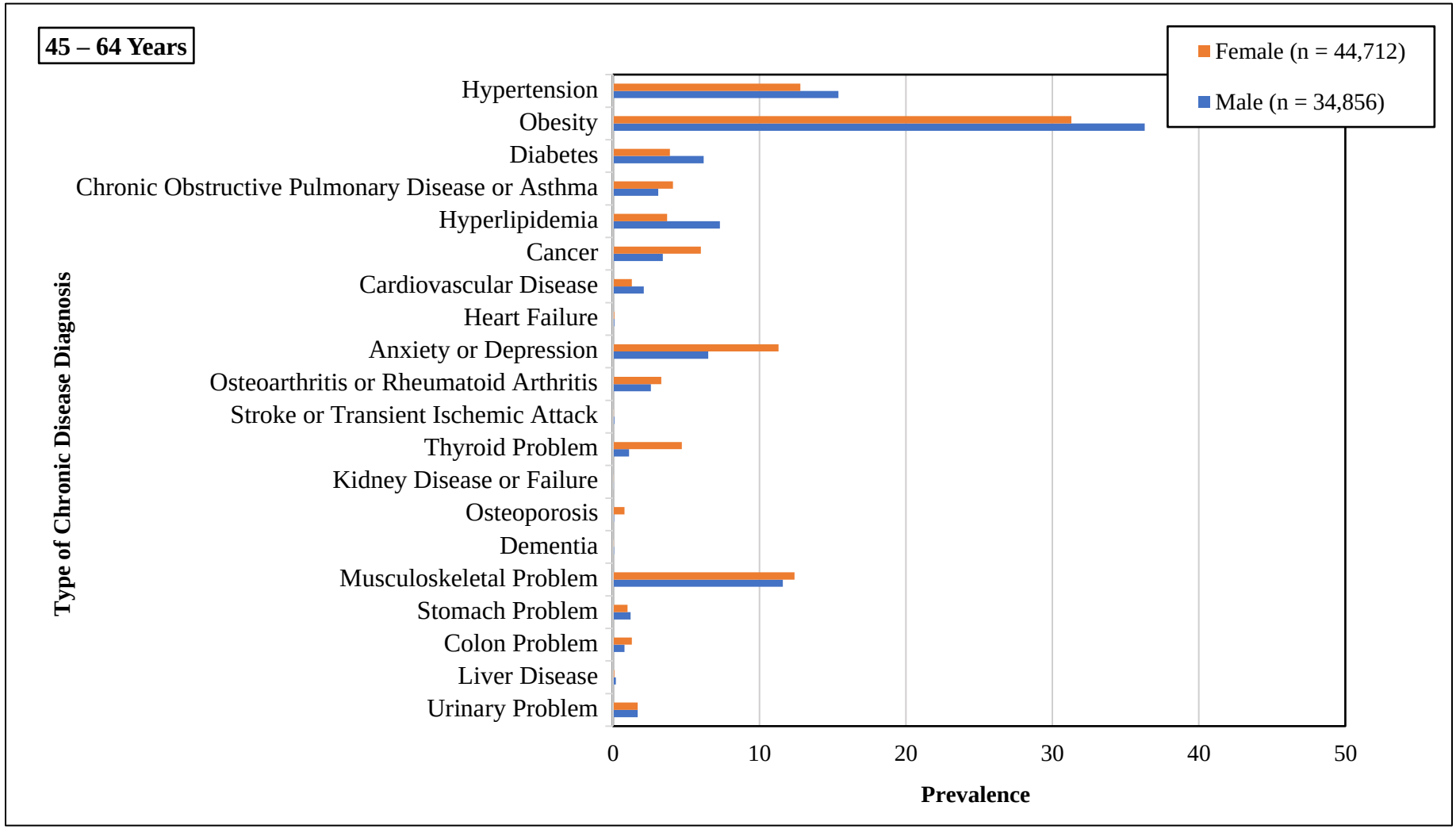


Figure 5.6 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, aged 65 – 84 years

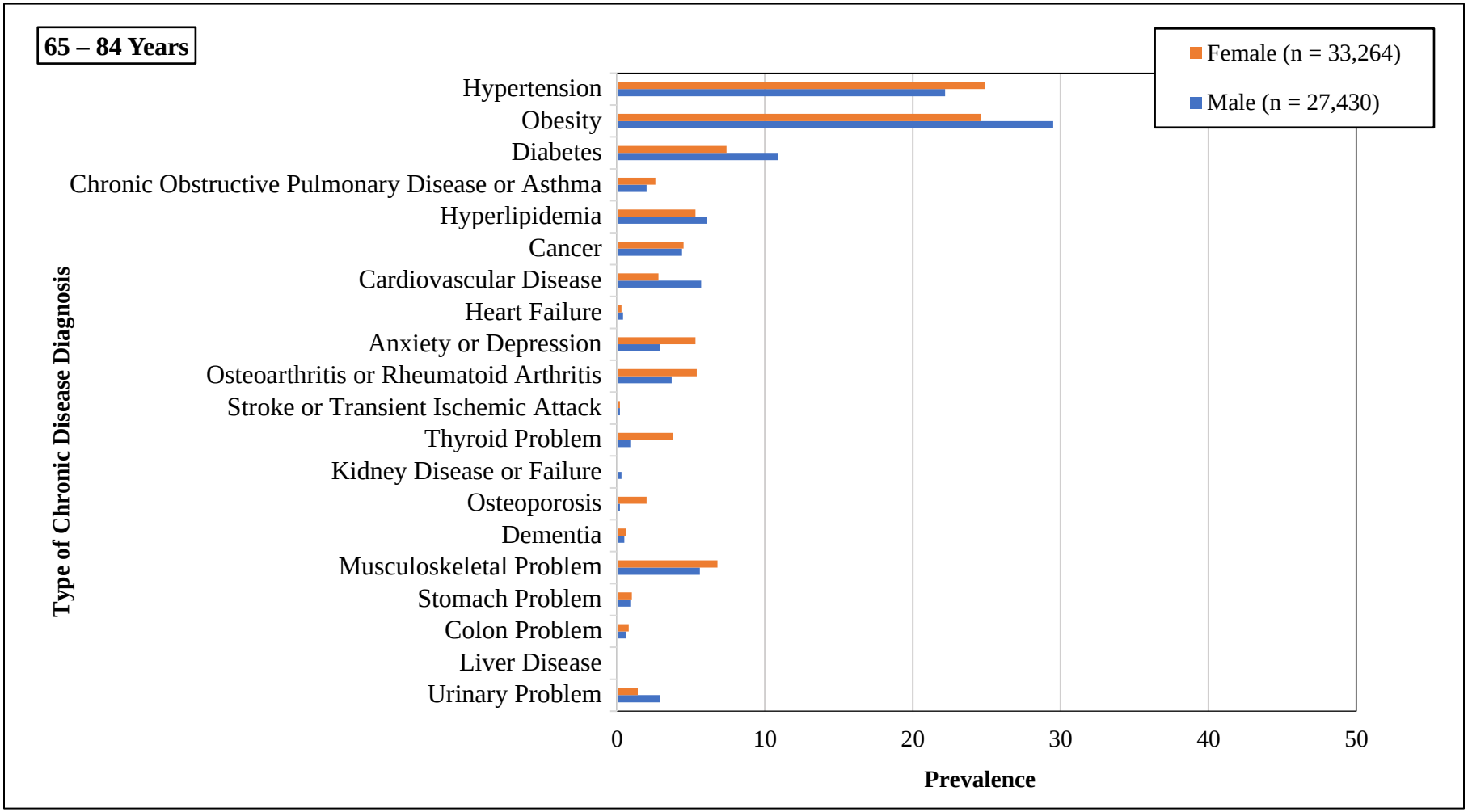
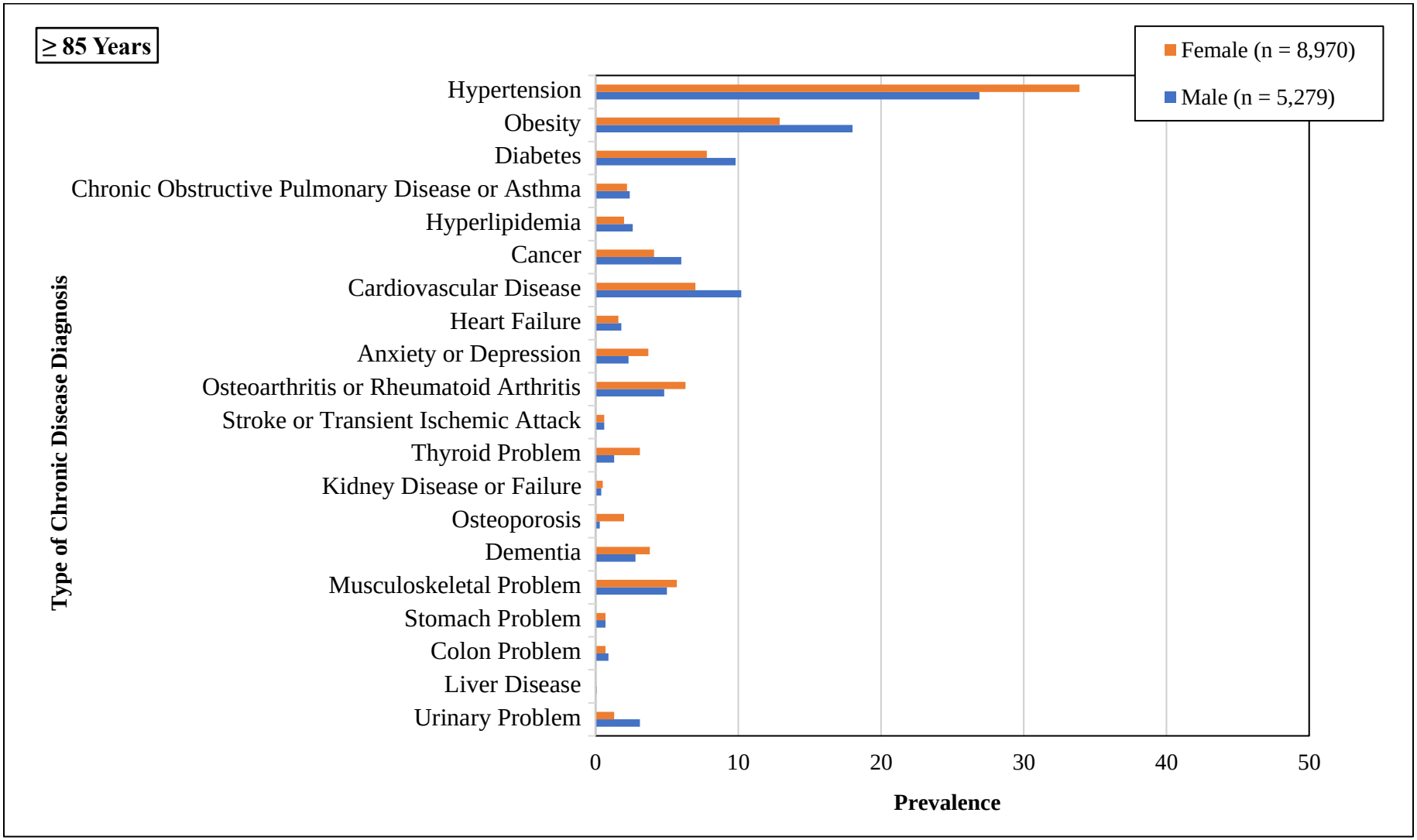


Figure 5.7 Type of chronic disease diagnoses among patients with multimorbidity, stratified by patient sex, aged ≥ 85 years



Most Frequent Combinations of Multimorbidity

Total Number of Combinations

Following the computational cluster analysis, the total number of combinations among patients with multimorbidity are presented in **Table 5.13**. After stratifying the results by patient age, patient sex and total number of chronic diseases, a large number of combinations were detected in each group. As described in **Section 4.8.2**, only those patients with at least one chronic disease and with at least one day elapsing between chronic disease diagnoses were included in this analysis. A combination is an unordered cluster of multiple chronic diseases where the sequence in which the chronic disease diagnoses occurred is not assessed. Essentially, these are co-occurring chronic diseases. The specific sequence in which the chronic disease diagnoses occurred is explored in the *Total Number of Permutations* section. Overall, a total of 6,095 combinations were found among female patients of all ages with multimorbidity (n = 47,381) and a total of 4,316 combinations were found among male patients of all ages with multimorbidity (n = 30,478). While these results may indicate a mean of 7.8 female patients and 7.1 male patients who had the same combination of multiple chronic diseases, the spread of patients across combination type was not normally distributed.

Among patients aged 18 to 34 years (n = 8,189 patients), there were 645 combinations found among females and 379 combinations among males. For those patients aged 35 to 44 years (n = 10,330 patients), 964 and 589 combinations were detected among females and males, respectively. Among patients aged 45 to 64 years (n = 30,798 patients), the number of patients and number of combinations approximately tripled as compared to the previous age group. For female and male patients, 2,769 combinations and 1,863 combinations were detected, respectively. Among both females and males, the largest numbers of combinations were

detected among patients aged 65 to 84 years (n = 22,471 patients). For female patients aged 65 to 84 years, there were 3,765 combinations detected and among males, there were 2,780 combinations detected. For female patients aged 85 years and older, a total of 1,804 combinations were identified and among male patients aged 85 years and older, a total of 1,241 combinations were identified. While the total number of combinations decreased among patients aged 85 years and older (n = 6,071 patients), these combinations represented increasingly unique clusters.

As seen in **Table 5.13**, for both female and male patients, the total number of combinations stratified by age category does not add up to the total number of combinations among all ages. For example, male patients of all ages could be grouped into the same combination, which would reduce the amount of potential combinations occurring among males of all patients. In contrast, more combinations were observed when stratified by patient age category due to the categorization by patient age and combination type. Therefore, there were a total of only 6,095 combinations and 4,316 combinations detected among female and male patients, respectively. Finally, to assess the differences that occurred when excluding cases in which the time elapsing between diagnoses was zero days, the same computational analysis was conducted for all patients and for all data points (that is, even when time elapsing between chronic disease diagnoses was equal to zero). These results are included in **Appendix K** to **Appendix V**. While there were differences in the total number of combinations found among the stratified groups, a large number of combinations (as well as similar patterns of combination types among females and males, stratified by patient age category) were detected among all patients with multimorbidity.

Table 5.13 Total number of combinations, stratified by patient age category and patient sex, among patients with multimorbidity

Patient Sex	Patient Age Category	n	Total Number of Combinations*
Females	All Ages	47,381	6,095
	18 – 34 Years	5,565	645
	35 – 44 Years	6,747	964
	45 – 64 Years	18,426	2,769
	65 – 84 Years	12,819	3,765
	≥ 85 Years	3,824	1,804
Males	All Ages	30,478	4,316
	18 – 34 Years	2,624	379
	35 – 44 Years	3,583	589
	45 – 64 Years	12,372	1,863
	65 – 84 Years	9,652	2,780
	≥ 85 Years	2,247	1,241

* The total number of combinations, stratified by age category among female and male patients, will not add to the total number of combinations among female and male patients of all ages

Most Frequently Occurring Combinations Among Female Patients

The most frequently occurring combinations were explored according to patient age and total number of chronic diseases among female patients. These results include only those chronic diseases that had at least one-day elapsing between the associated dates of diagnoses. Among adult female patients of all ages (n = 47,381 patients), the most common combination of chronic diseases was Anxiety or Depression and Musculoskeletal Problem (1,694 patients). This meant that 1,694 female patients were either diagnosed first with Anxiety or Depression and then Musculoskeletal Problem, or first Musculoskeletal Problem and then Anxiety or Depression. This was followed by a combination of Anxiety or Depression and Obesity (1,179 patients) and Musculoskeletal Problem and Obesity (1,132 patients). Among patients with three chronic diseases, the most common combination was Anxiety or Depression, Musculoskeletal Problem

and Obesity (675 patients). For patients with four chronic disease diagnoses, the most frequently occurring combination was Anxiety or Depression, Cancer, Musculoskeletal Problem and Obesity (180 patients). Lastly, for female patients living with five or more chronic diseases, the most frequently occurring combination was present in 58 patients and was a cluster of Anxiety or Depression, Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis. These results are presented in **Table 5.14**.

Among the youngest group of female patients aged 18 to 34 years (n = 5,565 patients), the most commonly occurring combination was again Anxiety or Depression and Musculoskeletal Problem (443 patients). Likewise, this was followed by a combination of Anxiety or Depression and Obesity (397 patients) and Musculoskeletal Problem and Obesity (253 patients). Among those patients with three chronic diseases, the most frequently occurring combination was Anxiety or Depression, Musculoskeletal Problem and Obesity among 157 patients. For female patients with four chronic disease diagnoses, the most common combinations were Anxiety or Depression, Cancer, Musculoskeletal Problem and Obesity (36 patients) and Anxiety or Depression, Chronic Obstructive Pulmonary Disease or Asthma, Musculoskeletal Problem and Obesity (28 patients). For female patients aged 18 to 34 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Anxiety or Depression, Cancer, Chronic Obstructive Pulmonary Disease or Asthma, Musculoskeletal Problem and Obesity (8 patients). These results are presented in **Table 5.15**.

Among female patients aged 35 to 44 years (n = 6,747 patients), the most commonly occurring combination was again Anxiety or Depression and Musculoskeletal Problem (497 patients). This was followed by a combination of Anxiety or Depression and Obesity (333 patients) and Musculoskeletal Problem and Obesity (330 patients). Among those female patients

with three chronic diseases, the most frequently occurring combinations were Anxiety or Depression, Musculoskeletal Problem and Obesity (203 patients) and Anxiety or Depression, Cancer and Musculoskeletal Problem (115 patients). For patients with four chronic disease diagnoses, the most common combination was Anxiety or Depression, Cancer, Musculoskeletal Problem and Obesity among 50 patients. Lastly, for female patients aged 35 to 44 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Anxiety or Depression, Cancer, Musculoskeletal Problem, Obesity and Thyroid Problem, which was present among 13 female patients. These results are presented in **Table 5.16**.

For female patients aged 45 to 64 years (n = 18,426 patients), the most commonly occurring combination was Anxiety or Depression and Musculoskeletal Problem (674 patients). This was followed by a combination of Musculoskeletal Problem and Obesity (472 patients) and Cancer and Musculoskeletal Problem (404 patients). Among those female patients with three chronic diseases, the most frequently occurring combinations were Anxiety or Depression, Musculoskeletal Problem and Obesity (291 patients) and Hypertension, Musculoskeletal Problem and Obesity (205 patients). For patients with four chronic disease diagnoses, the most common combination was Anxiety or Depression, Hypertension, Musculoskeletal Problem and Obesity, which was present among 88 patients. For female patients aged 45 to 64 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Anxiety or Depression, Cancer, Hypertension, Musculoskeletal Problem and Obesity (28 patients). These results are presented in **Table 5.17**.

Among female patients aged 65 to 84 years (n = 12,819 patients), the most commonly occurring combination was Hypertension and Obesity (323 patients). This was followed by the combinations of Hyperlipidemia and Hypertension (158 patients) and Cancer and Hypertension

(147 patients). Among those female patients with three chronic diseases, the most frequently occurring combinations were Diabetes, Hypertension and Obesity (129 patients) and Hypertension, Musculoskeletal Problem and Obesity (100 patients). For patients with four chronic disease diagnoses, the most common combination was Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis (73 patients). For female patients aged 65 to 84 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Hyperlipidemia, Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis, which was present among 32 patients. These results are presented in **Table 5.18**.

Finally, among female patients aged 85 years and older (n = 3,824 patients), the most commonly occurring combination was Dementia and Hypertension (76 patients). This was followed by the combinations of Cardiovascular Disease and Hypertension (69 patients) and Hypertension and Obesity (63 patients). Among those older female patients with three chronic diseases, the most frequently occurring combinations were Hypertension, Obesity and Osteoarthritis or Rheumatoid Arthritis (31 patients) and Hypertension, Musculoskeletal Problem and Obesity (26 patients). For female patients with four chronic disease diagnoses, the most common combination was Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis (17 patients). For female patients aged 85 years and older who were living with five or more chronic diseases, the most common combination was a diagnosis of Cardiovascular Disease, Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis, which was present among only 8 patients. These results are presented in **Table 5.19**.

It is important to note that all unique combinations found among female patients constituted mutually exclusive groups. This was because the results were stratified by the total number of chronic diseases. For example, among all female patients, the 675 patients with Anxiety or Depression, Musculoskeletal Problem and Obesity (three chronic diseases) or the 180 female patients with Anxiety or Depression, Cancer, Musculoskeletal Problem and Obesity (four chronic diseases) are not subsets of the 1,694 female patients with only Anxiety or Depression and Musculoskeletal Problem or the 1,179 female patients with Anxiety or Depression and Obesity (two chronic diseases). This ensured that all clusters represented unique, unordered clinical profiles among female patients with multimorbidity.

Table 5.14 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among all eligible female patients with multimorbidity (n = 47,381)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, All Ages
2	Anxiety or Depression & Musculoskeletal Problem	1,694	3.6
(n = 19,168)	Anxiety or Depression & Obesity	1,179	2.5
	Musculoskeletal Problem & Obesity	1,132	2.4
	Hypertension & Obesity	850	1.8
	Anxiety or Depression & Cancer	834	1.8
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	675	1.4
(n = 12,631)	Hypertension & Musculoskeletal Problem & Obesity	374	0.8
	Anxiety or Depression & Cancer & Musculoskeletal Problem	365	0.8
	Anxiety or Depression & Musculoskeletal Problem & Obesity	286	0.6
	Anxiety or Depression & Hypertension & Obesity	264	0.6
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	180	0.4
(n = 7,494)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	176	0.4
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	140	0.3
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	111	0.2
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	106	0.2
≥ 5	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or	58	0.1
(n = 8,088)	Rheumatoid Arthritis		
	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	52	0.1
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	49	0.1
	Anxiety or Depression & Cancer & Hypertension & Musculoskeletal Problem & Obesity	49	0.1
	Cancer & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	44	0.1

* Combinations listed in alphabetical order

Table 5.15 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 18 – 34 years with multimorbidity (n = 5,565)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 18 – 34 Years
2	Anxiety or Depression & Musculoskeletal Problem	443	8.0
(n = 3,478)	Anxiety or Depression & Obesity	397	7.1
	Musculoskeletal Problem & Obesity	253	4.5
	Anxiety or Depression & Cancer	243	4.4
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma	166	3.0
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	157	2.8
(n = 1,387)	Anxiety or Depression & Cancer & Obesity	67	1.2
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem	61	1.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem	59	1.1
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Obesity	55	1.0
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	36	0.6
(n = 501)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	28	0.5
	Anxiety or Depression & Colon Problem & Musculoskeletal Problem & Obesity	18	0.3
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Thyroid Problem	15	0.3
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Urinary Problem	15	0.3
≥ 5	Anxiety or Depression & Cancer & Chronic Obstructive Pulmonary Disease or Asthma &	8	0.1
(n = 199)	Musculoskeletal Problem & Obesity		
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity & Urinary Problem	6	0.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Thyroid Problem	5	0.1
	Anxiety or Depression & Cancer & Colon Problem & Musculoskeletal Problem & Obesity	5	0.1
	Results Supressed (<5 Patients)		

* Combinations listed in alphabetical order

Table 5.16 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 35 – 44 years with multimorbidity (n = 6,747)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 35 – 44 Years
2	Anxiety or Depression & Musculoskeletal Problem	497	7.4
(n = 3,624)	Anxiety or Depression & Obesity	333	4.9
	Musculoskeletal Problem & Obesity	330	4.9
	Anxiety or Depression & Cancer	206	3.1
	Cancer & Musculoskeletal Problem	180	2.7
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	203	3.0
(n = 1,859)	Anxiety or Depression & Cancer & Musculoskeletal Problem	115	1.7
	Cancer & Musculoskeletal Problem & Obesity	76	1.1
	Anxiety or Depression & Cancer & Obesity	70	1.0
	Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	51	0.8
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	50	0.7
(n = 792)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	38	0.6
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	31	0.5
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Thyroid Problem	30	0.4
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Urinary Problem	22	0.3
≥ 5	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Thyroid Problem	13	0.2
(n = 472)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Hypertension & Musculoskeletal Problem & Obesity	11	0.2
	Anxiety or Depression & Cancer & Colon Problem & Musculoskeletal Problem & Obesity	9	0.1
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity & Thyroid Problem	8	0.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Stomach Problem	8	0.1

* Combinations listed in alphabetical order

Table 5.17 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 45 – 64 years with multimorbidity (n = 18,426)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 45 – 64 Years
2	Anxiety or Depression & Musculoskeletal Problem	674	3.7
(n = 7,516)	Musculoskeletal Problem & Obesity	472	2.6
	Cancer & Musculoskeletal Problem	404	2.2
	Anxiety or Depression & Obesity	404	2.2
	Hypertension & Obesity	345	1.9
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	291	1.6
(n = 5,171)	Hypertension & Musculoskeletal Problem & Obesity	205	1.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem	162	0.9
	Cancer & Musculoskeletal Problem & Obesity	132	0.7
	Anxiety or Depression & Hypertension & Obesity	131	0.7
4	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	88	0.5
(n = 2,981)	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	84	0.5
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	68	0.4
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	66	0.4
	Anxiety or Depression & Hyperlipidemia & Musculoskeletal Problem & Obesity	54	0.3
≥ 5	Anxiety or Depression & Cancer & Hypertension & Musculoskeletal Problem & Obesity	28	0.2
(n = 2,758)	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	27	0.1
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	24	0.1
	Anxiety or Depression & Diabetes & Hypertension & Musculoskeletal Problem & Obesity	22	0.1
	Cancer & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	20	0.1

* Combinations listed in alphabetical order

Table 5.18 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 65 – 84 years with multimorbidity (n = 12,819)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 65 – 84 Years
2	Hypertension & Obesity	323	2.5
(n = 3,467)	Hyperlipidemia & Hypertension	158	1.2
	Cancer & Hypertension	147	1.1
	Hypertension & Musculoskeletal Problem	141	1.1
	Hypertension & Osteoarthritis or Rheumatoid Arthritis	123	1.0
3	Diabetes & Hypertension & Obesity	129	1.0
(n = 3,257)	Hypertension & Musculoskeletal Problem & Obesity	100	0.8
	Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	97	0.8
	Hyperlipidemia & Hypertension & Obesity	95	0.7
	Cancer & Hypertension & Obesity	81	0.6
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	73	0.6
(n = 2,527)	Diabetes & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	39	0.3
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	39	0.3
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	35	0.3
	Anxiety or Depression & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	33	0.3
≥ 5	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or	32	0.2
(n = 3,568)	Rheumatoid Arthritis		
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	28	0.2
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	24	0.2
	Cancer & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	21	0.2
	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	20	0.2

* Combinations listed in alphabetical order

Table 5.19 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 85 years and older with multimorbidity (n = 3,824)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, ≥ 85 Years
2	Dementia & Hypertension	76	2.0
(n = 1,083)	Cardiovascular Disease & Hypertension	69	1.8
	Hypertension & Obesity	63	1.6
	Hypertension & Osteoarthritis or Rheumatoid Arthritis	54	1.4
	Hypertension & Musculoskeletal Problem	49	1.3
3	Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	31	0.8
(n = 957)	Hypertension & Musculoskeletal Problem & Obesity	26	0.7
	Cardiovascular Disease & Hypertension & Musculoskeletal Problem	21	0.5
	Hypertension & Musculoskeletal Problem & Osteoarthritis or Rheumatoid Arthritis	19	0.5
	Cancer & Hypertension & Obesity	19	0.5
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	17	0.4
(n = 693)	Anxiety or Depression & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	14	0.4
	Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Osteoarthritis or Rheumatoid Arthritis	11	0.3
	Cancer & Hypertension & Musculoskeletal Problem & Obesity	11	0.3
	Cardiovascular Disease & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	9	0.2
≥ 5	Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	8	0.2
(n = 1,091)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	7	0.2
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis & Osteoporosis	6	0.2
	Anxiety or Depression & Cardiovascular Disease & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	6	0.2
	Dementia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	5	0.1

* Combinations listed in alphabetical order

Most Frequently Occurring Combinations Among Male Patients

The most frequently occurring combinations were explored according to patient age and total number of chronic diseases among male patients. These results include only those chronic diseases that had at least one-day elapsing between the associated dates of diagnoses. Among adult male patients of all ages (n = 30,478 patients), the most common combination of chronic diseases was Musculoskeletal Problem and Obesity (1,073 patients). This meant that 1,073 male patients were either diagnosed with Musculoskeletal Problem and then Obesity, or first with Obesity and then Musculoskeletal Problem. This was followed by a combination of Hypertension and Obesity (895 patients) and Anxiety or Depression and Musculoskeletal Problem (882 patients). Among male patients with three chronic diseases, the most common combination was Hypertension, Musculoskeletal Problem and Obesity (364 patients). For patients with four chronic disease diagnoses, the most frequently occurring combination was Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity (153 patients). Lastly, for male patients living with five or more chronic diseases, the most frequently occurring combination was present in 66 patients and consisted of Diabetes, Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity. These results are presented in **Table 5.20**.

Among the youngest group of male patients aged 18 to 34 years (n = 2,624 patients), the most commonly occurring combination was Anxiety or Depression and Musculoskeletal Problem (313 patients), which was similar to the most common combination among female patients aged 18 to 34 years. This was followed by a combination of Musculoskeletal Problem and Obesity (219 patients). Among those patients with three chronic diseases, the most frequently occurring combination was Anxiety or Depression, Musculoskeletal Problem and Obesity among 69 patients (again, similar to the findings among females aged 18 to 34 years).

For male patients with four chronic disease diagnoses, the most common combinations were Anxiety or Depression, Chronic Obstructive Pulmonary Disease or Asthma, Musculoskeletal Problem and Obesity, which was present among 8 patients. For male patients aged 18 to 34 years who were living with five or more chronic diseases, the combinations that were detected were only present in fewer than five patients indicating increasingly unique clinical profiles in these young, yet complex male patients. These results are presented in **Table 5.21**.

Among male patients aged 35 to 44 years (n = 3,583 patients), the most commonly occurring combination was Musculoskeletal Problem and Obesity (299 patients). This was followed by a combination of Anxiety or Depression and Musculoskeletal Problem (263 patients) and Anxiety or Depression and Obesity (175 patients). Among those male patients with three chronic diseases, the most frequently occurring combinations were Anxiety or Depression, Musculoskeletal Problem and Obesity (99 patients) and Cancer, Musculoskeletal Problem and Obesity (50 patients). For patients with four chronic disease diagnoses, the most common combination was Anxiety or Depression, Cancer, Musculoskeletal Problem and Obesity among 16 patients. Lastly, for male patients aged 35 to 44 years who were living with five or more chronic diseases, the combinations that were detected were only present among fewer than five patients, once again indicating unique clinical profiles among male patients aged 35 to 44 years with five or more chronic diseases. These results are presented in **Table 5.22**.

For male patients aged 45 to 64 years (n = 12,372 patients), the most commonly occurring combinations were Musculoskeletal Problem and Obesity (483 patients) and Hypertension and Obesity (441 patients). Among those male patients with three chronic diseases, the most frequently occurring combinations were Hypertension, Musculoskeletal Problem and Obesity (201 patients) and Hyperlipidemia, Hypertension and Obesity (193

patients). For patients with four chronic disease diagnoses, the most common combination was Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity, which was present among 100 patients. For male patients aged 45 to 64 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Diabetes, Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity (34 patients). These results are presented in **Table 5.23**.

Among male patients aged 65 to 84 years (n = 9,652 patients), the most commonly occurring combination was Hypertension and Obesity (280 patients). This was followed by the combinations of Diabetes and Obesity (176 patients) and Hyperlipidemia and Hypertension (124 patients). Among those male patients with three chronic diseases, the most frequently occurring combinations were Diabetes, Hypertension and Obesity (147 patients) and Hyperlipidemia, Hypertension and Obesity (106 patients). For patients with four chronic disease diagnoses, the most common combination was Diabetes, Hyperlipidemia, Hypertension and Obesity (52 patients). For male patients aged 65 to 84 years who were living with five or more chronic diseases, the most common combination was a diagnosis of Diabetes, Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity, which was present among 28 patients. These results are presented in **Table 5.24**.

Finally, among male patients aged 85 years and older (n = 2,247 patients), the most commonly occurring combination was Cancer and Hypertension (42 patients). This was followed by the combinations of Hypertension and Obesity (41 patients) and Cardiovascular Disease and Hypertension (36 patients). Among those older male patients with three chronic diseases, the most frequently occurring combinations were Diabetes, Hypertension and Obesity (29 patients) and Cardiovascular Disease, Hypertension and Obesity (19 patients). For male

patients with four chronic disease diagnoses, the most common combination was Hypertension, Musculoskeletal Problem, Obesity and Osteoarthritis or Rheumatoid Arthritis (13 patients). For male patients aged 85 years and older who were living with five or more chronic diseases, the most common combinations were among less than five male patients, indicating an elderly and uniquely complex set of patients. These results are presented in **Table 5.25**.

Once again, it is important to note that all unique combinations found among male patients constituted mutually exclusive groups. For example, among all male patients, the 364 patients with Hypertension, Musculoskeletal Problem and Obesity (three chronic diseases) or the Hyperlipidemia, Hypertension, Musculoskeletal Problem and Obesity (four chronic diseases) are not subsets of the 1,073 patients with only Musculoskeletal Problem and Obesity (two chronic diseases). This ensured that all clusters represented unique, unordered clinical profiles among male patients with multimorbidity.

Table 5.20 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among all eligible male patients with multimorbidity (n = 30,478)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, All Ages
2	Musculoskeletal Problem & Obesity	1,073	3.5
(n = 12,557)	Hypertension & Obesity	895	2.9
	Anxiety or Depression & Musculoskeletal Problem	882	2.9
	Anxiety or Depression & Obesity	622	2.0
	Diabetes & Obesity	467	1.5
3	Hypertension & Musculoskeletal Problem & Obesity	364	1.2
(n = 8,158)	Diabetes & Hypertension & Obesity	343	1.1
	Anxiety or Depression & Musculoskeletal Problem & Obesity	340	1.1
	Hyperlipidemia & Hypertension & Obesity	326	1.1
	Hyperlipidemia & Musculoskeletal Problem & Obesity	238	0.8
4	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	153	0.5
(n = 4,190)	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	120	0.4
	Diabetes & Hyperlipidemia & Hypertension & Obesity	101	0.3
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	92	0.3
	Cancer & Hypertension & Musculoskeletal Problem & Obesity	91	0.3
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	66	0.2
(n = 4,853)	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	41	0.1
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	39	0.1
	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	39	0.1
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	38	0.1

* Combinations listed in alphabetical order

Table 5.21 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 18 – 34 years with multimorbidity (n = 2,624)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 18 – 34 Years
2	Anxiety or Depression & Musculoskeletal Problem	313	11.9
(n = 1,878)	Musculoskeletal Problem & Obesity	219	8.3
	Anxiety or Depression & Obesity	189	7.2
	Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem	88	3.4
	Cancer & Musculoskeletal Problem	80	3.0
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	69	2.6
(n = 573)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem	35	1.3
	Cancer & Musculoskeletal Problem & Obesity	31	1.2
	Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	26	1.0
	Anxiety or Depression & Cancer & Musculoskeletal Problem	22	0.8
4	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	8	0.3
(n = 135)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	6	0.2
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	5	0.2
	Anxiety or Depression & Colon Problem & Musculoskeletal Problem & Obesity	5	0.2
	Cancer & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	5	0.2
≥ 5			
(n = 38)			
	Results Supressed (<5 Patients)		

* Combinations listed in alphabetical order

Table 5.22 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 35 – 44 years with multimorbidity (n = 3,583)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 35 – 44 Years
2	Musculoskeletal Problem & Obesity	299	8.3
(n = 2,139)	Anxiety or Depression & Musculoskeletal Problem	263	7.3
	Anxiety or Depression & Obesity	175	4.9
	Hypertension & Obesity	103	2.9
	Cancer & Musculoskeletal Problem	77	2.1
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	99	2.8
(n = 945)	Cancer & Musculoskeletal Problem & Obesity	50	1.4
	Hypertension & Musculoskeletal Problem & Obesity	41	1.1
	Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	32	0.9
	Anxiety or Depression & Hypertension & Obesity	31	0.9
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	16	0.4
(n = 352)	Anxiety or Depression & Hyperlipidemia & Musculoskeletal Problem & Obesity	12	0.3
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	11	0.3
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	11	0.3
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Stomach Problem	10	0.3
≥ 5			
(n = 147)			
	Results Supressed (<5 Patients)		

* Combinations listed in alphabetical order

Table 5.23 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 45 – 64 years with multimorbidity (n = 12,372)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 45 – 64 Years
2	Musculoskeletal Problem & Obesity	483	3.9
(n = 5,237)	Hypertension & Obesity	441	3.6
	Anxiety or Depression & Musculoskeletal Problem	268	2.2
	Hyperlipidemia & Musculoskeletal Problem	247	2.0
	Hypertension & Musculoskeletal Problem	243	2.0
3	Hypertension & Musculoskeletal Problem & Obesity	201	1.6
(n = 3,644)	Hyperlipidemia & Hypertension & Obesity	193	1.6
	Hyperlipidemia & Musculoskeletal Problem & Obesity	173	1.4
	Anxiety or Depression & Musculoskeletal Problem & Obesity	154	1.2
	Diabetes & Hypertension & Obesity	147	1.2
4	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	100	0.8
(n = 1,992)	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	65	0.5
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	51	0.4
	Cancer & Hypertension & Musculoskeletal Problem & Obesity	40	0.3
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	39	0.3
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	34	0.3
(n = 1,499)	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	24	0.2
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	16	0.1
	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	14	0.1
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	13	0.1

* Combinations listed in alphabetical order

Table 5.24 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 65 – 84 years with multimorbidity (n = 9,652)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 65 – 84 Years
2	Hypertension & Obesity	280	2.9
(n = 2,696)	Diabetes & Obesity	176	1.8
	Hyperlipidemia & Hypertension	124	1.3
	Cancer & Hypertension	115	1.2
	Diabetes & Hypertension	113	1.2
3	Diabetes & Hypertension & Obesity	147	1.5
(n = 2,460)	Hyperlipidemia & Hypertension & Obesity	106	1.1
	Hypertension & Musculoskeletal Problem & Obesity	95	1.0
	Cancer & Hypertension & Obesity	81	0.8
	Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	80	0.8
4	Diabetes & Hyperlipidemia & Hypertension & Obesity	52	0.5
(n = 1,995)	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	48	0.5
	Cardiovascular Disease & Diabetes & Hypertension & Obesity	41	0.4
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	40	0.4
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	38	0.4
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	28	0.3
(n = 2,501)	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	23	0.2
	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	23	0.2
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	22	0.2
	Diabetes & Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Obesity	16	0.2

* Combinations listed in alphabetical order

Table 5.25 Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 85 years and older with multimorbidity (n = 2,247)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, ≥ 85 Years
2	Cancer & Hypertension	42	1.9
(n = 607)	Hypertension & Obesity	41	1.8
	Cardiovascular Disease & Hypertension	36	1.6
	Diabetes & Hypertension	26	1.2
	Hypertension & Osteoarthritis or Rheumatoid Arthritis	20	0.9
3	Diabetes & Hypertension & Obesity	29	1.3
(n = 536)	Cardiovascular Disease & Hypertension & Obesity	19	0.8
	Hypertension & Musculoskeletal Problem & Obesity	12	0.5
	Cancer & Hypertension & Obesity	10	0.4
	Cancer & Cardiovascular Disease & Hypertension	10	0.4
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	13	0.6
(n = 436)	Cancer & Hypertension & Musculoskeletal Problem & Obesity	7	0.3
	Cardiovascular Disease & Diabetes & Hypertension & Obesity	7	0.3
	Cardiovascular Disease & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	6	0.3
	Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Obesity	6	0.3
≥ 5			
(n = 668)			
	Results Supressed (<5 Patients)		

* Combinations listed in alphabetical order

Most Frequent Permutations of Multimorbidity

Total Number of Permutations

The total numbers of permutations among patients with multimorbidity are presented in **Table 5.26**. After stratifying the results by patient age, patient sex and total number of chronic diseases, a large number of permutations were detected in each group. As described in **Section 4.8.2**, only those patients with at least one chronic disease and with at least one day elapsing between chronic disease diagnoses were included in this analysis. A permutation is an ordered cluster of multiple chronic diseases where the specific sequence in which the chronic disease diagnoses occurred is assessed. These are not simply co-occurring chronic diseases, but instead indicate a sequence of events over time. Overall, a total of 14,911 permutations were found among female patients of all ages with multimorbidity (n = 47,381) and a total of 9,736 permutations were found among male patients of all ages with multimorbidity (n = 30,478). While these results may indicate a mean of 3.2 female patients and 3.1 male patients who had the same permutation of multiple chronic diseases, the spread of patients across permutation type was not normally distributed.

Among patients aged 18 to 34 years, there were 1,288 permutations found among females and approximately half the number (610) of permutations found among males. A more comparative number of permutations were detected among females and males who were 35 to 44 years of age, with 1,917 and 1,026 permutations identified, respectively. For patients aged 45 to 64 years, there were 6,351 permutations found among females and 4,076 permutations found among males. Similar to the total number of combinations, the largest number of permutations were detected among patients aged 65 to 84 years; 7,019 permutations were found among females and 5,149 permutations were found among males. For female and male patients aged 85

years and older, a total of 2,532 permutations and 1,633 permutations were identified, respectively. While the total number of permutations decreased among patients aged 85 years and older, these permutations represented increasingly unique clusters.

As seen in **Table 5.26**, for both female and male patients, the total number of permutations stratified by age category does not add up to the total number of permutations among all ages. For example, male patients of all ages could be grouped into the same permutation, which would reduce the amount of potential permutations occurring among males of all patients. In contrast, more permutations were observed when stratified by patient age category due to the categorization by patient age and permutation type. Therefore, there were a total of only 14,911 permutations and 9,736 permutations detected among female and male patients, respectively. Finally, to assess the differences that occurred when excluding cases in which the time elapsing between diagnoses was zero days, the same computational analysis was conducted for all patients and for all data points (that is, even when time elapsing between chronic disease diagnoses was equal to zero). These results are included in **Appendix W** to **Appendix AH**. While there were differences in the total number of permutations found among the stratified groups, a large number of permutations (as well as similar patterns of permutation types among females and males, stratified by patient age category) were detected among all patients with multimorbidity.

Table 5.26 Total number of permutations, stratified by patient age and patient sex, among patients with multimorbidity

Patient Sex	Patient Age Category	n	Total Number of Permutations*
Females	All Ages	47,381	14,911
	18 – 34 Years	5,565	1,288
	35 – 44 Years	6,747	1,917
	45 – 64 Years	18,426	6,351
	65 – 84 Years	12,819	7,019
	≥ 85 Years	3,824	2,532
Males	All Ages	30,478	9,736
	18 – 34 Years	2,624	610
	35 – 44 Years	3,583	1,026
	45 – 64 Years	12,372	4,076
	65 – 84 Years	9,652	5,149
	≥ 85 Years	2,247	1,633

* The total number of permutations, stratified by age category among female and male patients, will not add to the total number of permutations among female and male patients of all ages

Most Frequently Occurring Permutations Among Female Patients

The most frequently occurring permutations were explored according to patient age and total number of chronic diseases among female patients. These results include only those chronic diseases that had at least one day elapsing between the associated dates of diagnoses. Among adult female patients of all ages (n = 47,381 patients), the most common permutation of chronic diseases was Anxiety or Depression, and then Obesity (1,160 patients). This meant that 1,160 female patients were first diagnosed with Anxiety or Depression and then with Obesity. This was followed by a permutation of Musculoskeletal Problem, and then Obesity (1,094 patients) and Anxiety or Depression, and then Musculoskeletal Problem (909 patients). Among patients with three chronic diseases, the most common permutation was Anxiety or Depression, then Obesity, and then Musculoskeletal Problem (177 patients). For patients with four chronic

disease diagnoses, the most frequently occurring permutation was Hypertension, then Obesity, then Musculoskeletal Problem, and then Anxiety or Depression (24 patients). Lastly, for female patients living with five or more chronic diseases, the most frequently occurring permutations were only present among fewer than five patients. These results are presented in **Table 5.27**.

Among the youngest group of female patients aged 18 to 34 years (n = 5,565 patients), the most commonly occurring permutation was again Anxiety or Depression, and then Obesity (388 patients). Likewise, the next two commonly occurring permutations were Anxiety or Depression, and then Musculoskeletal Problem (249 patients) and Musculoskeletal Problem, and then Obesity (245 patients). Among those female patients with three chronic diseases, the most frequently occurring permutation was Musculoskeletal Problem, then Obesity, and then Anxiety or Depression (41 patients). For female patients with four chronic disease diagnoses, the most common permutation was the diagnoses of Thyroid Problem, then Anxiety or Depression, then Obesity, and then Musculoskeletal Problem, which was present among 5 patients. For female patients aged 18 to 34 years who were living with five or more chronic diseases, the permutations that were detected were only present among fewer than five patients. These results are presented in **Table 5.28**.

Among female patients aged 35 to 44 years (n = 6,747 patients), the most commonly occurring permutation was again Anxiety or Depression, and then Obesity (327 patients). This was followed by the permutations of Musculoskeletal Problem, and then Obesity (318 patients) and Anxiety or Depression, and then Musculoskeletal Problem (256 patients). Among those female patients with three chronic diseases, the most frequently occurring permutation was Anxiety or Depression, then Musculoskeletal Problem, and then Obesity (57 patients). For patients with four chronic disease diagnoses, the most common permutation was Anxiety or

Depression, then Musculoskeletal Problem, then Obesity, and then Cancer, which was present in 10 patients. Lastly, for female patients aged 35 to 44 years who were living with five or more chronic diseases, the most common permutations were once again present in fewer than five patients. These results are presented in **Table 5.29**.

For female patients aged 45 to 64 years (n = 18,426 patients), the most commonly occurring permutation was Musculoskeletal Problem, and then Obesity (456 patients). This was followed by a permutation of Anxiety or Depression, and then Obesity (400 patients) and Anxiety or Depression, and then Musculoskeletal Problem (365 patients). Among those female patients with three chronic diseases, the most frequently occurring permutation was Hypertension, then Obesity, and then Musculoskeletal Problem, which was present among 87 patients. For patients with four chronic disease diagnoses, the most common permutation was Hypertension, then Obesity, then Musculoskeletal Problem, and then Anxiety or Depression (14 patients). Similar to the previous age groups, for female patients aged 45 to 64 years who were living with five or more chronic diseases, the most frequent permutations were present among less than five patients. These results are presented in **Table 5.30**.

Among female patients aged 65 to 84 years (n = 12,819 patients), the most commonly occurring permutation was Hypertension, and then Obesity (322 patients). This was followed by the permutation of Hypertension, and then Musculoskeletal Problem (102 patients) and Hypertension, and then Hyperlipidemia (98 patients). Among those female patients with three chronic diseases, the most frequently occurring permutations were Hypertension, then Obesity, and then Hyperlipidemia (48 patients) and Hypertension, then Obesity, and then Musculoskeletal Problem (46 patients). For patients with four chronic disease diagnoses, the most common permutation was Hypertension, then Obesity, then Musculoskeletal Problem, and then

Osteoarthritis or Rheumatoid Arthritis, which occurred in 9 patients. For female patients aged 65 to 84 years who were also living with five or more chronic diseases, the most frequent permutations were present in fewer than five patients. These results are presented in **Table 5.31**.

Finally, among female patients aged 85 years and older (n = 3,824 patients), the most commonly occurring permutation was Hypertension, and then Obesity (62 patients). This was followed by the permutations of Hypertension, and then Dementia (53 patients) and Hypertension, and then Cardiovascular Disease (44 patients). Among those older female patients with three chronic diseases, the most frequently occurring permutations were Hypertension, then Obesity, and then Osteoarthritis or Rheumatoid Arthritis (15 patients) and Hypertension, then Obesity, and then Cancer (14 patients). For female patients aged 85 years and older who were living with four and five or more chronic diseases, the most frequent permutations were present among less than five female patients. These results are presented in **Table 5.32**.

All unique permutations found among female patients constituted mutually exclusive groups as the results were stratified by the total number of chronic diseases. For example, among all female patients, the 177 female patients who were diagnosed with Anxiety or Depression, then Obesity, and then Musculoskeletal Problem (three chronic diseases) were not a subset of the 1,160 female patients with only Anxiety or Depression, and then Obesity (two chronic diseases) or the 1,094 female patients with only Musculoskeletal Problem, and then Obesity (two chronic diseases). This ensured that all clusters represented unique, ordered clinical profiles among female patients with multimorbidity. Likewise, patients diagnosed first with Obesity, and then with Anxiety or Depression represent a distinct clinical profile from those patients who were diagnosed first with Anxiety or Depression, and then with Obesity. This ensured that all clusters were unique, ordered clinical profiles of multimorbidity.

Table 5.27 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among all eligible female patients with multimorbidity (n = 47,381)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, All Ages
2	Anxiety or Depression >> Obesity	1,160	2.4
(n = 19,168)	Musculoskeletal Problem >> Obesity	1,094	2.3
	Anxiety or Depression >> Musculoskeletal Problem	909	1.9
	Hypertension >> Obesity	836	1.8
	Musculoskeletal Problem >> Anxiety or Depression	785	1.7
3	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	177	0.4
(n = 12,631)	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	176	0.4
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	161	0.3
	Hypertension >> Obesity >> Musculoskeletal Problem	159	0.3
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	149	0.3
4	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	24	0.1
(n = 7,494)	Hypertension >> Obesity >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	18	0.0
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	18	0.0
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	18	0.0
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity >> Cancer	18	0.0
≥ 5			
(n = 8,088)			
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Table 5.28 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 18 – 34 years with multimorbidity (n = 5,565)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 18 – 34 Years
2	Anxiety or Depression >> Obesity	388	7.0
(n = 3,478)	Anxiety or Depression >> Musculoskeletal Problem	249	4.5
	Musculoskeletal Problem >> Obesity	245	4.4
	Musculoskeletal Problem >> Anxiety or Depression	194	3.5
	Anxiety or Depression >> Cancer	131	2.4
3	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	41	0.7
(n = 1,387)	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	41	0.7
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	37	0.7
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	35	0.6
	Anxiety or Depression >> Obesity >> Cancer	22	0.4
4	Thyroid Problem >> Anxiety or Depression >> Obesity >> Musculoskeletal Problem	5	0.1
(n = 501)			
≥ 5	*Results Supressed (<5 Patients)*		
(n = 199)			

* Permutations listed in sequential order

Table 5.29 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 35 – 44 years with multimorbidity (n = 6,747)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 35 – 44 Years
2 (n = 3,624)	Anxiety or Depression >> Obesity	327	4.8
	Musculoskeletal Problem >> Obesity	318	4.7
	Anxiety or Depression >> Musculoskeletal Problem	256	3.8
	Musculoskeletal Problem >> Anxiety or Depression	241	3.6
	Cancer >> Obesity	161	2.4
3 (n = 1,859)	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	57	0.8
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	51	0.8
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	48	0.7
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	43	0.6
	Anxiety or Depression >> Obesity >> Cancer	25	0.4
4 (n = 792)	Anxiety or Depression >> Musculoskeletal Problem >> Obesity >> Cancer	10	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	6	0.1
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem >> Cancer	6	0.1
	Anxiety or Depression >> Obesity >> Cancer >> Musculoskeletal Problem	6	0.1
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression >> Cancer	5	0.1
≥ 5 (n = 472)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.30 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 45 – 64 years with multimorbidity (n = 18,426)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 45 – 64 Years
2 (n = 7,516)	Musculoskeletal Problem >> Obesity	456	2.5
	Anxiety or Depression >> Obesity	400	2.2
	Anxiety or Depression >> Musculoskeletal Problem	365	2.0
	Hypertension >> Obesity	340	1.8
	Musculoskeletal Problem >> Anxiety or Depression	309	1.7
3 (n = 5,171)	Hypertension >> Obesity >> Musculoskeletal Problem	87	0.5
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	80	0.4
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	78	0.4
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	65	0.4
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	63	0.3
4 (n = 2,981)	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	14	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	10	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	10	0.1
	Musculoskeletal Problem >> Obesity >> Hypertension >> Anxiety or Depression	9	0.0
	Musculoskeletal Problem >> Obesity >> Osteoarthritis or Rheumatoid Arthritis >> Anxiety or Depression	9	0.0
≥ 5 (n = 2,758)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.31 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 65 – 84 years with multimorbidity (n = 12,819)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 65 – 84 Years
2 (n = 3,467)	Hypertension >> Obesity	322	2.5
	Hypertension >> Musculoskeletal Problem	102	0.8
	Hypertension >> Hyperlipidemia	98	0.8
	Hypertension >> Cancer	97	0.8
	Diabetes >> Obesity	97	0.8
3 (n = 3,257)	Hypertension >> Obesity >> Hyperlipidemia	48	0.4
	Hypertension >> Obesity >> Musculoskeletal Problem	46	0.4
	Diabetes >> Obesity >> Hypertension	42	0.3
	Hypertension >> Obesity >> Cancer	38	0.3
	Hypertension >> Obesity >> Osteoarthritis or Rheumatoid Arthritis	34	0.3
4 (n = 2,527)	Hypertension >> Obesity >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	9	0.1
	Hypertension >> Obesity >> Osteoarthritis or Rheumatoid Arthritis >> Musculoskeletal Problem	8	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	8	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Cancer	7	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Osteoarthritis or Rheumatoid Arthritis	7	0.1
≥ 5 (n = 3,568)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.32 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible female patients aged 85 years and older with multimorbidity (n = 3,824)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, ≥ 85 Years
2 (n = 1,083)	Hypertension >> Obesity	62	1.6
	Hypertension >> Dementia	53	1.4
	Hypertension >> Cardiovascular Disease	44	1.2
	Hypertension >> Cancer	37	1.0
	Hypertension >> Osteoarthritis or Rheumatoid Arthritis	33	0.9
3 (n = 957)	Hypertension >> Obesity >> Osteoarthritis or Rheumatoid Arthritis	15	0.4
	Hypertension >> Obesity >> Cancer	14	0.4
	Hypertension >> Obesity >> Musculoskeletal Problem	12	0.3
	Hypertension >> Osteoarthritis or Rheumatoid Arthritis >> Obesity	9	0.2
	Hypertension >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	8	0.2
4 (n = 693)			
≥ 5 (n = 1,091)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Most Frequently Occurring Permutations Among Male Patients

The most frequently occurring permutations were explored according to patient age and total number of chronic diseases among male patients. These results include only those chronic diseases that had at least one day elapsing between the associated dates of diagnoses. Among adult male patients of all ages (n = 30,478 patients), the most common permutation of chronic diseases was Musculoskeletal Problem, and then Obesity (1,051 patients). This meant that 1,051 male patients were first diagnosed with Musculoskeletal Problem, and then Obesity and with that specific sequence. This was followed by a permutation of Hypertension, and then Obesity (880 patients) and Anxiety or Depression, and then Obesity (618 patients). Among patients with three chronic diseases, the most common permutation was Hypertension, then Obesity, and then Hyperlipidemia (162 patients). For patients with four chronic disease diagnoses, the most frequently occurring permutation was Hypertension, then Obesity, then Hyperlipidemia, and then Musculoskeletal Problem (19 patients). Lastly, for male patients living with five or more chronic diseases, the common permutations were present among less than five male patients. These results are presented in **Table 5.33**.

Among the youngest group of male patients aged 18 to 34 years (n = 2,624 patients), the most commonly occurring permutation was again Musculoskeletal Problem, and then Obesity, which was present among 216 patients. The next two commonly occurring permutations were Anxiety or Depression, and then Obesity (187 patients) and Anxiety or Depression, and then Musculoskeletal Problem (161 patients). Among those male patients with three chronic diseases, the most frequently occurring permutation was Anxiety or Depression, then Obesity, and then Musculoskeletal Problem (22 patients). For male patients aged 18 to 34 years who were living with four and five or more chronic diseases, the most common permutations were detected in

fewer than five patients, indicating increasingly unique clinical profiles in these young, yet complex male patients. These results are presented in **Table 5.34**.

Among male patients aged 35 to 44 years (n = 3,583 patients), the most commonly occurring permutation was Musculoskeletal Problem, and then Obesity (291 patients). This was followed by the permutation of Anxiety or Depression, and then Obesity (174 patients) and Musculoskeletal Problem, and then Anxiety or Depression (135 patients). Among those male patients with three chronic diseases, the most frequently occurring permutation was Anxiety or Depression, then Obesity, and then Musculoskeletal Problem (31 patients). Lastly, for male patients aged 35 to 44 years who were living with four and five or more chronic diseases, the permutations that were detected were only present among less than five patients. These results are presented in **Table 5.35**.

For male patients aged 45 to 64 years (n = 12,372 patients), the most commonly occurring permutation was Musculoskeletal Problem, and then Obesity (473 patients). This was followed by a permutation of Hypertension, and then Obesity (432 patients) and Anxiety or Depression, and then Obesity (228 patients). Among those male patients with three chronic diseases, the most frequently occurring permutation was Hypertension, then Obesity, and then Hyperlipidemia, which occurred among 94 patients. For these middle-aged male patients with four chronic disease diagnoses, the most common permutations were Hypertension, then Obesity, then Hyperlipidemia, and then Musculoskeletal Problem (10 patients) and Musculoskeletal Problem, then Obesity, then Hypertension, and then Hyperlipidemia (10 patients). For male patients aged 45 to 64 years who were living with five or more chronic diseases, the most frequent permutations were detected in less than five patients and these results were supressed. These results are presented in **Table 5.36**.

Among male patients aged 65 to 84 years (n = 9,652 patients), the most commonly occurring permutation was Hypertension, and then Obesity (278 patients). This was followed by the permutation of Diabetes, and then Obesity (175 patients) and Hypertension, and then Hyperlipidemia (79 patients). Among those male patients with three chronic diseases, the most frequently occurring permutations were Diabetes, then Obesity, and then Hypertension (56 patients) and Hypertension, then Obesity, and then Musculoskeletal Problem (55 patients). For patients with four chronic disease diagnoses, the most common permutations were Hypertension, then Obesity, then Musculoskeletal Problem, and then Cancer, which occurred among 9 male patients. For male patients aged 65 to 84 years who were living with five or more chronic diseases, there were a number of permutations that were present among groups of fewer than five male patients. These results are presented in **Table 5.37**.

Finally, among male patients aged 85 years and older (n = 2,247 patients), the most commonly occurring permutation was Hypertension, and then Obesity (41 patients). This was followed by the permutations of Hypertension, and then Cancer (30 patients) and Hypertension, and then Cardiovascular Disease (22 patients). Among those older male patients with three chronic diseases, the most frequently occurring permutations were Diabetes, then Obesity, and then Hypertension (12 patients) and Hypertension, then Obesity, and then Musculoskeletal Problem (9 patients). For male patients aged 85 years and older who were living with four and five or more chronic diseases, the most common permutations occurred among fewer than five patients. These results are presented in **Table 5.38**.

Similar to the combination analysis, all unique permutations found among male patients constituted mutually exclusive groups as the results were stratified by the total number of chronic diseases a patient had by the end of the observation period. For example, among male patients of

all ages, the 162 patients who were diagnosed with Hypertension, then Obesity, and then Hyperlipidemia (three chronic diseases) or the 132 patients who were diagnosed with Hypertension, then Obesity, and then Musculoskeletal Problem (three chronic diseases) were not a subset of the 880 patients who were diagnosed first with Hypertension, and then with Obesity. Likewise, patients diagnosed first with Obesity, and then with Hypertension represent a distinct clinical profile from those patients who were diagnosed first with Hypertension, and then with Obesity. This ensured that all clusters represented unique, ordered clinical profiles among male patients with multimorbidity.

Table 5.33 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among all eligible male patients with multimorbidity (n = 30,478)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, All Ages
2 (n = 12,557)	Musculoskeletal Problem >> Obesity	1,051	3.4
	Hypertension >> Obesity	880	2.9
	Anxiety or Depression >> Obesity	618	2.0
	Diabetes >> Obesity	458	1.5
	Musculoskeletal Problem >> Anxiety or Depression	451	1.5
3 (n = 8,158)	Hypertension >> Obesity >> Hyperlipidemia	162	0.5
	Hypertension >> Obesity >> Musculoskeletal Problem	132	0.4
	Diabetes >> Obesity >> Hypertension	110	0.4
	Musculoskeletal Problem >> Obesity >> Hypertension	103	0.3
	Hypertension >> Obesity >> Diabetes	97	0.3
4 (n = 4,190)	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	19	0.1
	Diabetes >> Obesity >> Musculoskeletal Problem >> Hypertension	15	0.0
	Hypertension >> Obesity >> Musculoskeletal Problem >> Cancer	14	0.0
	Hypertension >> Obesity >> Hyperlipidemia >> Diabetes	14	0.0
	Hypertension >> Obesity >> Diabetes >> Musculoskeletal Problem	13	0.0
≥ 5 (n = 4,853)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.34 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 18 – 34 years with multimorbidity (n = 2,624)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 18 – 34 Years
2 (n = 1,878)	Musculoskeletal Problem >> Obesity	216	8.2
	Anxiety or Depression >> Obesity	187	7.1
	Anxiety or Depression >> Musculoskeletal Problem	161	6.1
	Musculoskeletal Problem >> Anxiety or Depression	152	5.8
	Chronic Obstructive Pulmonary Disease or Asthma >> Obesity	62	2.4
3 (n = 573)	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	22	0.8
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	17	0.6
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	16	0.6
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	14	0.5
	Chronic Obstructive Pulmonary Disease or Asthma >> Musculoskeletal Problem >> Anxiety or Depression	11	0.4
4 (n = 135)			
≥ 5 (n = 38)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Table 5.35 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 35 – 44 years with multimorbidity (n = 3,583)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 35 – 44 Years
2 (n = 2,139)	Musculoskeletal Problem >> Obesity	291	8.1
	Anxiety or Depression >> Obesity	174	4.9
	Musculoskeletal Problem >> Anxiety or Depression	135	3.8
	Anxiety or Depression >> Musculoskeletal Problem	128	3.6
	Hypertension >> Obesity	99	2.8
3 (n = 945)	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	31	0.9
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	27	0.8
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	24	0.7
	Musculoskeletal Problem >> Obesity >> Cancer	21	0.6
	Musculoskeletal Problem >> Obesity >> Hypertension	17	0.5
4 (n = 352)			
≥ 5 (n = 147)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Table 5.36 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 45 – 64 years with multimorbidity (n = 12,372)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 45 – 64 Years
2 (n = 5,237)	Musculoskeletal Problem >> Obesity	473	3.8
	Hypertension >> Obesity	432	3.5
	Anxiety or Depression >> Obesity	228	1.8
	Diabetes >> Obesity	201	1.6
	Hyperlipidemia >> Obesity	184	1.5
3 (n = 3,644)	Hypertension >> Obesity >> Hyperlipidemia	94	0.8
	Musculoskeletal Problem >> Obesity >> Hyperlipidemia	69	0.6
	Musculoskeletal Problem >> Obesity >> Hypertension	67	0.5
	Hypertension >> Obesity >> Musculoskeletal Problem	58	0.5
	Hypertension >> Obesity >> Diabetes	52	0.4
4 (n = 1,992)	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	10	0.1
	Musculoskeletal Problem >> Obesity >> Hypertension >> Hyperlipidemia	10	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	8	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Diabetes	7	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	7	0.1
≥ 5 (n = 1,499)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.37 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 65 – 84 years with multimorbidity (n = 9,652)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 65 – 84 Years
2 (n = 2,696)	Hypertension >> Obesity	278	2.9
	Diabetes >> Obesity	175	1.8
	Hypertension >> Hyperlipidemia	79	0.8
	Hypertension >> Cancer	78	0.8
	Cardiovascular Disease >> Obesity	67	0.7
3 (n = 2,460)	Diabetes >> Obesity >> Hypertension	56	0.6
	Hypertension >> Obesity >> Musculoskeletal Problem	55	0.6
	Hypertension >> Obesity >> Hyperlipidemia	54	0.6
	Hypertension >> Obesity >> Cancer	37	0.4
	Hypertension >> Obesity >> Osteoarthritis or Rheumatoid Arthritis	36	0.4
4 (n = 1,995)	Hypertension >> Obesity >> Musculoskeletal Problem >> Cancer	9	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	8	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Urinary Problem	8	0.1
	Hypertension >> Diabetes >> Hyperlipidemia >> Obesity	8	0.1
	Diabetes >> Obesity >> Hypertension >> Musculoskeletal Problem	8	0.1
≥ 5 (n = 2,501)			

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Table 5.38 Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among eligible male patients aged 85 years and older with multimorbidity (n = 2,247)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, ≥ 85 Years
2 (n = 607)	Hypertension >> Obesity	41	1.8
	Hypertension >> Cancer	30	1.3
	Hypertension >> Cardiovascular Disease	22	1.0
	Diabetes >> Obesity	17	0.8
	Hypertension >> Osteoarthritis or Rheumatoid Arthritis	14	0.6
3 (n = 536)	Diabetes >> Obesity >> Hypertension	12	0.5
	Hypertension >> Obesity >> Musculoskeletal Problem	9	0.4
	Hypertension >> Obesity >> Cancer	8	0.4
	Diabetes >> Hypertension >> Obesity	8	0.4
	Hypertension >> Obesity >> Dementia	7	0.3
4 (n = 436)			
≥ 5 (n = 668)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

5.2 Objective Two

The results for Objective Two describe the time elapsing between chronic disease diagnoses among patients with at least one chronic disease. These results will describe the mean time until subsequent chronic disease diagnosis, an assessment of whether this mean time decreases as the number of chronic disease diagnoses increases, and whether other factors (e.g., patient age, patient sex, patient residential location, patient median household income, total number of chronic diseases, provider age, provider sex, practice EMR type and practice location) influence the mean time until subsequent chronic disease diagnosis.

5.2.1 Patient Sample Characteristics

The characteristics of patients with one or more chronic disease diagnoses (n = 286,998 patients) and two or more chronic disease diagnoses (n = 195,838 patients) are presented in **Table 5.39** to **Table 5.41**. For Research Question 1 and Research Question 3, the sample was derived from all adult patients with at least one chronic disease diagnoses as of September 30, 2013. However, for Research Question 2, the sample was focused on those adult patients with at least two chronic disease diagnoses. As described previously in the Methodology Chapter, all analyses for Objective Two were conducted using those chronic diseases (or data points) that had at least one day elapsing between diagnoses.

Overall, the patients with one or more chronic diseases were a mean age of 55.3 years (SD: 17.8 years), with a range from 18 to 114 years. The majority of patients were female (57.5%) and were between the ages of 45 and 64 years (39.2%). Slightly more than half of these patients (51.4%) were living in an urban setting and the median of the median household income was found to be $60,310 per year (Canadian dollars), ranging from as low as $22,457 to as much

as $181,454 per year. Approximately one-third of patients did not have data recorded for their residential postal code, and therefore their median household income could not be determined. The mean number of chronic diseases these patients were living with was 2.6 (SD: 1.6) with a range from those patients living with one chronic disease to fourteen chronic diseases. These characteristics can be seen in **Table 5.39**.

The characteristics of patients with two or more chronic diseases were previously presented for Objective One and are presented again in **Table 5.39**. These patients had a mean age of 59.0 years (SD: 17.0 years), with a range between 18 and 114 years. The majority of patients were female (57.8%) and were between 45 and 64 years of age (40.6%). Approximately 52% of these patients were living in an urban setting and the median of the median household income was found to be $60,952 per year (Canadian dollars). Once again, approximately one-third of patients did not have data recorded for their residential postal code, and therefore their median household income could not be determined. The mean number of chronic diseases these patients were living with was 3.3 (SD: 1.5) with a range from those patients living with two chronic diseases to fourteen chronic diseases.

The demographic characteristics of the PHC providers who were caring for these two patient groups are presented in **Table 5.40**. For patients with one or more chronic diseases, about one-quarter (25.3%) were being cared for by PHC providers who were aged 45 to 64 years. These PHC providers had a mean age of 50.8 years (SD: 10.3 years). About 28.9% of patients with one or more chronic diseases were being cared for by male PHC providers. For patients with two or more chronic diseases, about 25.5% were being cared for by PHC providers who were aged 45 to 64 years, these PHC providers had a mean age of 51.2 years (SD: 10.2 years)

and about 29.8% of patients with two or more chronic diseases were being cared for by male PHC providers.

Table 5.39 Patient-level characteristics of the two groups of adult patients (those with one or more and two or more chronic diseases) for Objective Two

Patient-Level Variable	Patients with One or More Chronic Diseases (n = 286,998)	Patients with Two or More Chronic Diseases (n = 195,838)
Age (Years), n (%)		
Mean (SD)	55.3 Years (17.8 Years)	59.0 Years (17.0 Years)
Range (Minimum – Maximum)	18 Years – 114 Years	18 Years – 114 Years
18 – 34	41,980 (14.6%)	17,466 (8.9%)
35 – 44	43,450 (15.1%)	23,855 (12.2%)
45 – 64	112,354 (39.2%)	79,571 (40.6%)
65 – 84	71,808 (25.0%)	60,696 (31.0%)
≥ 85	17,406 (6.1%)	14,250 (7.3%)
Sex, n (%)		
Female	165,111 (57.5%)	113,209 (57.8%)
Male	121,870 (42.5%)	82,622 (42.2%)
Residential Location, n (%)		
Rural	44,741 (15.6%)	32,607 (16.7%)
Urban	147,501 (51.4%)	102,151 (52.2%)
Missing	94,756 (33.0%)	61,080 (31.2%)
Median Household Income (Canadian Dollars)		
Median (IQR)	$60,310 ($$12,497)	$60,952 ($12,497)
Range (Minimum – Maximum)	$22,457 – $181,454	$22,457 – $181,454
Missing (%)	95,092 (33.1%)	61,263 (31.3%)
Total Number of Chronic Diseases		
Mean (SD)	2.6 (1.6)	3.3 (1.5)
Range (Minimum – Maximum)	1 – 14	2 – 14

* SD = Standard deviation, CI = Confidence interval, IQR = Interquartile range

Table 5.40 Characteristics of PHC providers caring for the two groups of adult patients (those with one or more and two or more chronic diseases) for Objective Two

Provider-Level Variable	Patients with One or More Chronic Diseases (n = 286,998)	Patients with Two or More Chronic Diseases (n = 195,838)
Age (Years), n (%)		
Mean (SD)	50.8 Years (10.3 Years)	51.2 Years (10.2 Years)
Range (Minimum – Maximum)	27 Years – 72 Years	27 Years – 72 Years
25 – 44	35,020 (12.2%)	22,402 (11.4%)
45 – 64	72,662 (25.3%)	49,871 (25.5%)
≥ 65	10,681 (3.7%)	7,730 (4.0%)
Missing	168,635 (58.8%)	115,835 (59.2%)
Sex, n (%)		
Female	61,082 (21.3%)	39,517 (20.2%)
Male	83,017 (28.9%)	58,364 (29.8%)
Missing	142,899 (49.8%)	97,957 (50.0%)

* SD = Standard deviation, CI = Confidence interval

The characteristics of the PHC practices where these two patient groups were cared for are presented in **Table 5.41**. Among adult patients with one or more chronic diseases, 25.6% came from PHC practices that were using the Nightingale EMR software. This was followed by clinical data recorded using the Wolf (9.0%), Accuro (8.5%) and Bell (7.4%) EMR software programs. The majority of these patients (57.2%) received care from urban PHC practices, according to the first three letters of the practices' postal code. The largest proportion of patients belonged to Network 4 (21.4%) and Network 5 (24.4%), which were located in Central Ontario and Eastern Ontario, respectively. While all adult PHC patients were allocated to one of the ten CPCSSN Networks, approximately one-third of patients were missing data for both the EMR software type and practice location variables.

Table 5.41 Characteristics of PHC practices caring for the two groups of adult patients (those with one or more and two or more chronic diseases) for Objective Two

Practice-Level Variable	Patients with One or More Chronic Diseases (n = 286,998)	Patients with Two or More Chronic Diseases (n = 195,838)
EMR Type, n (%)		
Accuro	24,324 (8.5%)	16,001 (8.2%)
Bell	21,247 (7.4%)	15,601 (8.0%)
DaVinci	824 (0.3%)	376 (0.2%)
Jonoke	16,399 (5.7%)	12,953 (6.6%)
Med Access	8,676 (3.0%)	6,437 (3.3%)
Nightingale	73,328 (25.6%)	50,998 (26.0%)
Oscar	11,177 (3.9%)	6,208 (3.2%)
Practice Solutions	14,111 (4.9%)	8,723 (4.5%)
Wolf	25,713 (9.0%)	18,732 (9.6%)
Xwave	680 (0.2%)	528 (0.3%)
Missing	90,519 (31.5%)	59,281 (30.3%)
Practice Location, n (%)		
Rural	26,450 (9.2%)	19,471 (9.9%)
Urban	164,048 (57.2%)	113,120 (57.8%)
Missing	96,500 (33.6%)	63,247 (32.3%)
CPCSSN Network, n (%)		
1	30,128 (10.5%)	21,060 (10.8%)
2	15,344 (5.4%)	11,081 (5.7%)
3	5,897 (2.1%)	4,801 (2.5%)
4	61,403 (21.4%)	38,797 (19.8%)
5	70,098 (24.4%)	47,986 (24.5%)
6	1,900 (0.7%)	814 (0.4%)
7	25,883 (9.0%)	17,218 (8.8%)
8	27,278 (9.5%)	20,374 (10.4%)
9	40,003 (13.9%)	27,656 (14.1%)
10	9,064 (3.2%)	6,051 (3.1%)

* SD = Standard deviation, CI = Confidence interval

5.2.2 Objective Two, Research Question 1 – Time Until Multimorbidity

To address Research Question 1, the median and mean time until the second chronic disease diagnoses were explored for all adult patients with at least one chronic disease as of September 30, 2013. As described previously in the Methodology Chapter, this included only those chronic diseases in which at least one day elapsed between diagnoses. As such, the data points that reported zero days elapsing between diagnoses were removed. A descriptive analysis was conducted to determine the time elapsing (in days) between the first (X1) and second (X2) chronic diseases. This time from morbidity to multimorbidity or "Time Until Multimorbidity" is presented in **Table 5.42** and has been stratified by patient age and patient sex.

These results indicate that the time elapsing until the onset of multimorbidity decreased between the youngest and oldest age groups: a decrease of 200 days among female patients and a decrease of 150 days among male patients. For example, among female patients aged 18 to 34 years, the median time elapsing between the first and second chronic disease diagnoses was 301.7 days, as compared to a median time of 97.4 days among female patients aged 85 years and older. Similarly, among male patients aged 18 to 34 years, the median time until the onset of multimorbidity was 249.0 days, while among male patients aged 85 years and older the median time was only 93.0 days. For patients aged 35 to 44 years, the median time elapsing until the second chronic disease diagnosis was 308.3 days among females and 244.0 days among males. For patients aged 45 to 64 years, the median time elapsing between the first and second chronic disease diagnoses was 224.3 days among females and 149.8 days among males. Finally, among patients aged 65 to 84 years, the median time elapsing until the second chronic disease was 114.6 days among females and 83.0 days among males. Interestingly, the median time elapsing until

multimorbidity was 10 days shorter among males aged 65 to 84 years, as compared to males aged 85 years and older.

The "Time Until Multimorbidity" was also explored by the first or index chronic disease type, and these results were stratified by patient age and patient sex. **Table 5.43** presents the index chronic disease types that led to the quickest and slowest accumulation of the next chronic disease. For patients aged 18 to 34 years, both female and male patients progressed most quickly to the second chronic disease when they were first diagnosed with Diabetes (median of 131.0 days and 30.8 days, respectively). In comparison, female patients aged 35 to 44 years progressed most quickly to the next chronic disease when they were first diagnosed with Stroke or Transient Ischemic Attack (median of 79.3 days) and male patients aged 35 to 44 years progressed quickly when they first experienced Heart Failure (median of 69.6 days). Progression to the second chronic disease occurred the quickest after first being diagnosed with Diabetes for female patients aged 45 to 64 years (median of 50.1 days), 65 to 84 years (median of 39.5 days) and 85 years and older (median of 46.5 days). A similar quick progression was seen among male patients aged 45 to 64 years and 65 to 84 years who were first diagnosed with Diabetes (median of 44.4 days and 32.0 days, respectively). Finally, among male patients aged 85 years and older, the quickest accumulation occurred for those patients who were first diagnosed with Stroke or Transient Ischemic Attack (median of 18.5 days).

The index chronic disease types that led to the slowest accumulation of the second chronic disease diagnosis was also explored in **Table 5.43**. For patients aged 18 to 34 years, the longest median time until multimorbidity was observed among female patients who were first diagnosed with Osteoporosis (median time of 921.4 days) and male patients who were first diagnosed with Stroke or Transient Ischemic Attack (median of 1,993.1 days). For patients aged

35 to 44 years, the slowest accumulation to the second chronic disease was seen among female patients who were first diagnosed with Heart Failure (median time of 935.0 days) and male patients who were first diagnosed with Liver Disease (median of 627.0 days). Among patients aged 45 to 64 years, both female and male patients had the longest median time until multimorbidity when they were first diagnosed with Dementia (median time of 603.3 days and 369.0 days, respectively). Progression to the second chronic disease occurred the slowest after first being diagnosed with Kidney Disease or Failure for female patients aged 65 to 84 years and 85 years and older (median time of 680.4 days and 449.7 days, respectively). Male patients aged 65 to 74 years experienced the longest time until multimorbidity when they were first diagnosed with Dementia (266.0 days). Male patients aged 85 years and older had the longest median time (260.5 days) until the second chronic disease after first being diagnosed with Osteoporosis.

To assess the differences that occur when excluding data points in which the time elapsing between diagnoses was zero days, the same analysis was conducted for all patients and for all data points (that is, when time elapsing between chronic disease diagnoses was equal to zero days). These results are included in **Appendix AI**. After including these data points, the same patterns of time elapsing until multimorbidity were observed, while the median and mean time elapsing between chronic disease diagnoses were notably lower as compared to the estimates presented in **Table 5.42**. For example, within the sensitivity analysis, male patients aged 18 to 34 years had a median time of only 87.0 days (mean of 424.1 days) until the second chronic disease, as compared a median time of 249.0 days (mean of 534.1 days) in the original analysis. A similar pattern was observed for all remaining patient categories, indicating the impact of removing those data points where the time elapsing between diagnoses was equal to zero days.

Table 5.42 Time (in days) until subsequent chronic disease diagnosis, stratified by patient age category (years), patient sex and total number of chronic diseases

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
T1 → T2	301.7	308.3	224. 3	114.6	97.4	249.0	244.0	149.8	83.0	93.0
(n = 238,237)	537.1	569.7	521.6	407.2	366.4	534.1	525.2	473.5	387.9	363.4
	(635.4)	(688.9)	(707.0)	(677.4)	(638.6)	(692.1)	(694.2)	(695.4)	(682.3)	(646.7)
T2 → T3	377.9	396.0	342.0	238.5	202.4	364.8	365.0	321.0	239.0	211.0
(n = 141,684)	561.1	606.0	562.3	466.6	398.1	565.7	577.2	544.0	473.8	406.0
	(598.8)	(667.1)	(667.1)	(617.6)	(519.3)	(667.3)	(680.7)	(661.3)	(649.3)	(542.0)
T3 → T4	343.2	357.0	304.1	248.0	238.1	340.0	326.9	311.0	252.0	236.5
(n = 82,373)	488.8	522.4	473.0	408.6	398.9	524.2	508.2	484.3	421.8	389.0
	(486.7)	(533.4)	(506.7)	(460.3)	(453.1)	(556.2)	(547.6)	(530.1)	(490.7)	(443.6)
T4 → T5	292.0	360.0	294.0	260.0	245.9	349.2	301.4	320.0	278.0	251.4
(n = 44,255)	439.1	514.0	454.7	402.1	392.4	458.8	489.4	469.9	424.1	406.1
	(462.6)	(516.2)	(485.3)	(435.4)	(427.2)	(430.0)	(529.1)	(487.3)	(466.2)	(462.6)
T5 → T6	283.0	358.1	289.8	266.7	274.5	276.9	316.5	301.0	275.1	259.7
(n = 22,035)	395.5	496.7	433.9	398.6	417.5	441.4	461.2	451.8	417.2	398.4
	(388.5)	(477.7)	(451.3)	(424.6)	(445.4)	(492.3)	(472.4)	(485.5)	(444.8)	(446.5)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red

Table 5.43 Time (in days) until multimorbidity, stratified by patient age category (years), patient sex and index chronic disease

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Hypertension → T2	184.8	193.0	102.0	68.8	70.0	127.1	76.7	57.8	44.0	62.6
	448.2	442.6	368.8	304.5	278.8	474.8	386.4	348.4	286.2	292.6
	(591.1)	(583.2)	(616.2)	(582.9)	(551.4)	(709.8)	(635.0)	(607.8)	(582.9)	(581.7)
Obesity → T2	165.0	169.0	132.5	50.6	133.6	268.8	163.5	175.7	123.3	Results
	280.4	383.9	370.8	274.8	184.3	571.6	437.7	410.2	182.2	Suppresse
	(371.1)	(499.5)	(536.9)	(479.4)	(203.9)	(791.3)	(669.1)	(540.9)	(235.3)	d
Diabetes → T2	131.0	196.5	50.1	39.5	46.5	30.8	75.0	44.4	32.0	59.1
	437.8	488.4	321.3	316.8	327.8	284.6	362.9	319.6	258.6	306.5
	(677.8)	(694.8)	(574.5)	(653.5)	(639.6)	(551.8)	(608.0)	(580.8)	(542.2)	(610.2)
Chronic Obstructive Pulmonary	216.5	286.0	219.9	153.2	91.7	154.7	218.1	193.5	130.1	109.3
Disease or Asthma → T2	433.1	526.5	496.5	410.6	415.4	390.0	474.6	500.0	475.7	309.2
	(566.3)	(646.8)	(732.1)	(650.0)	(692.3)	(558.6)	(631.6)	(742.8)	(809.4)	(517.4)
Hyperlipidemia → T2	238.6	209.6	178.6	103.1	47.3	126.1	150.0	99.0	62.6	88.0
	580.6	483.6	459.3	344.0	254.8	372.5	414.0	404.7	325.6	280.9
	(766.0)	(614.6)	(675.2)	(540.3)	(526.4)	(559.9)	(577.1)	(629.7)	(573.0)	(427.6)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

Table 5.43 Time (in days) until multimorbidity, stratified by patient age category (years), patient sex and index chronic disease, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Cancer → T2	321.5	350.8	311.9	168.6	107.0	217.5	238.0	183.4	100.5	103.7
	525.5	601.8	579.5	484.3	389.9	509.6	528.0	496.9	446.6	423.9
	(617.8)	(689.6)	(724.5)	(761.1)	(630.1)	(692.2)	(691.9)	(693.8)	(731.2)	(749.3)
Cardiovascular Disease → T2	429.5	336.5	354.6	175.0	139.7	275.7	398.0	239.5	111.9	83.5
	613.3	635.9	642.2	492.3	449.0	579.6	546.9	591.8	492.4	391.7
	(672.2)	(722.5)	(757.0)	(715.3)	(725.4)	(759.7)	(607.6)	(778.3)	(813.4)	(675.4)
Heart Failure → T2	201.5	935.0	259.0	65.0	152.0	141.9	69.6	116.6	189.0	87.6
	298.1	820.7	581.0	391.0	372.6	561.3	140.5	524.8	433.9	332.1
	(363.2)	(306.8)	(982.8)	(672.8)	(565.4)	(1,010.2)	(201.3)	(842.2)	(636.2)	(542.7)
Anxiety or Depression → T2	278.4	281.3	240.0	174.3	118.9	237.7	244.0	167.6	134.1	207.7
	534.6	548.8	540.7	476.7	446.2	518.4	533.5	481.0	507.0	520.7
	(640.9)	(675.5)	(692.0)	(746.1)	(777.5)	(662.0)	(713.4)	(684.1)	(757.4)	(690.3)
Osteoarthritis or Rheumatoid	249.3	428.0	328.6	219.6	201.6	349.4	305.5	301.4	199.7	254.6
Arthritis → T2	523.3	618.5	640.4	555.9	569.0	667.6	616.4	634.7	600.7	571.6
	(612.2)	(684.4)	(785.7)	(798.2)	(775.7)	(799.0)	(767.7)	(799.4)	(875.7)	(831.2)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

Table 5.43 Time (in days) until multimorbidity, stratified by patient age category (years), patient sex and index chronic disease, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Stroke or Transient Ischemic Attack → T2	*Results Supressed*	79.3 155.4 (219.4)	220.5 764.8 (949.8)	347.4 784.9 (931.4)	399.5 662.5 (842.5)	1,993.1 1,569.4 (1,406.2)	*Results Supressed*	153.4 421.0 (555.5)	124.8 371.0 (544.5)	18.5 291.4 (689.2)
Thyroid Problem → T2	218.8 448.6 (580.3)	189.0 448.2 (611.6)	154.0 438.8 (644.3)	96.5 349.1 (604.2)	71.0 344.5 (671.5)	153.5 392.9 (636.7)	110.4 353.3 (616.7)	104.8 440.6 (701.5)	153.6 382.7 (524.4)	81.0 429.6 (739.6)
Kidney Disease or Failure → T2	325.0 325.0 (321.5)	263.0 464.3 (552.0)	134.6 230.2 (243.1)	680.4 1,049.3 (1,182.4)	449.7 860.7 (1,039.57)	31.8 73.4 (106.9)	157.5 143.4 (95.7)	239.6 683.2 (893.1)	97.5 595.5 (934.2)	20.2 154.9 (308.1)
Osteoporosis → T2	921.4 1,041.3 (901.2)	354.0 590.4 (660.6)	258.2 508.5 (641.3)	151.4 392.3 (524.2)	100.0 313.8 (495.5)	55.9 119.5 (165.3)	274.2 274.2 (383.6)	187.3 388.1 (502.2)	96.3 288.7 (404.9)	260.5 361.4 (364.2)
Dementia → T2	669.7 757.6 (454.0)	143.4 406.6 (777.2)	503.3 681.5 (835.6)	125.3 497.8 (806.4)	128.0 371.9 (585.5)	1,002.0 888.9 (683.0)	574.0 769.7 (650.4)	369.0 633.6 (734.7)	266.0 528.1 (675.8)	115.8 346.7 (579.0)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

** Results were supressed when < 5 patients were included in the category

Table 5.43 Time (in days) until multimorbidity, stratified by patient age category (years), patient sex and index chronic disease, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Musculoskeletal Problem → T2	378.3	371.8	312.0	208.6	165.6	354.2	337.9	274.3	189.0	146.0
	609.7	652.1	602.3	504.6	458.0	631.2	612.7	580.6	514.0	477.2
	(676.0)	(739.6)	(748.8)	(724.3)	(680.9)	(753.2)	(736.5)	(755.8)	(752.6)	(735.9)
Stomach Problem → T2	294.0	275.0	326.7	185.2	111.3	263.3	298.0	278.6	205.3	160.6
	467.8	542.9	539.5	432.7	226.7	536.6	559.6	534.8	488.4	353.7
	(497.0)	(690.5)	(655.4)	(629.5)	(319.2)	(656.6)	(700.7)	(694.1)	(749.2)	(529.5)
Colon Problem → T2	371.0	287.5	229.5	211.5	119.0	298.5	255.0	195.4	206.0	221.0
	575.8	542.8	511.2	496.9	287.1	527.9	453.4	475.5	472.0	478.5
	(629.3)	(708.3)	(657.9)	(712.7)	(450.8)	(636.1)	(537.0)	(667.5)	(649.2)	(633.9)
Liver Disease → T2	573.9	175.5	135.0	223.1	367.7	681.7	627.0	239.1	46.1	*Results Supressed*
	523.5	175.5	349.0	506.9	367.7	807.8	956.5	472.4	333.0	
	(423.5)	(73.8)	(531.2)	(646.1)	(519.4)	(600.1)	(966.8)	(620.2)	(550.0)	
Urinary Problem → T2	430.6	494.0	439.3	286.4	122.5	364.2	334.7	254.1	122.3	123.0
	638.3	722.5	713.1	600.2	407.2	637.8	602.9	582.3	466.8	342.9
	(657.5)	(772.7)	(814.6)	(834.5)	(680.4)	(750.6)	(751.2)	(754.3)	(746.8)	(633.0)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

** Results were supressed when < 5 patients were included in the category

5.2.3 Objective Two, Research Question 2 – Time Until Advancing Multimorbidity

To address Research Question 2, the "Time Until Advancing Multimorbidity" was assessed by determining the median and mean time until subsequent chronic disease diagnoses after the second chronic disease (as seen in **Table 5.42**). This was conducted for adult patients with at least two chronic diseases as of September 30, 2013 and only those chronic diseases with at least one-day elapsing between diagnoses were included in the analysis. The results presented in **Table 5.42** were stratified by both patient age and patient sex. These results indicate that generally, the time elapsing until advancing multimorbidity was indeed the slowest from the second to third chronic disease diagnoses. For example, among patients aged 18 to 34 years, the median time from the second to third chronic disease was 377.9 days for females and 364.8 days for males. For female patients aged 35 to 44 years and 45 to 64 years, the median time until the third chronic disease diagnoses was 396.0 days and 342.0 days, respectively. For male patients aged 35 to 44 years and 45 to 64 years, the median time until the third chronic disease diagnoses was 365.0 days and 321.0 days, respectively. Interestingly, for female and male patients aged 65 to 84 years and over 85 years, the longest time until the subsequent chronic disease was observed from the fifth to sixth diagnoses. More specifically, for females, the median time until the sixth chronic disease diagnoses was 266.7 days and 274.5 days among patients aged 65 to 84 years and 85 years and older, respectively. For males, the median time until the sixth chronic disease diagnoses was 279.1 days and 259.7 days among patients aged 65 to 84 years and 85 years and older, respectively. These results demonstrate that the time until advancing multimorbidity is the slowest from the second to third chronic disease among female and male patients aged 18 to 64 years, whereas the longest time was observed from the fifth to sixth chronic disease among female and male patients aged 65 years and older.

Similar to Research Question 1, in order to assess the differences that occurred when excluding data points in which the time elapsing between diagnoses was zero days, the same analysis was conducted for all patients and for all data points (that is, when time elapsing between chronic disease diagnoses was equal to zero days). These results are included in **Appendix AI**. While the same patterns were observed within this sensitivity analyses, the median and mean time elapsing between chronic disease diagnoses was again notably lower as compared to the estimates presented in **Table 5.42**. However, the data points that were equal to zero days did not have as much of an impact on the median and mean time elapsing between diagnoses when examining the time until advancing multimorbidity (that is, among patients with more than two chronic diseases), as compared to the time elapsing until multimorbidity (that is, among patients transitioning from the first to second chronic disease). Nonetheless, the time elapsing between chronic diseases diagnoses still decreased within the sensitivity analysis. For example, among male patients aged 18 to 34 years, the median time until the third chronic disease was 340.7 days (mean of 577.1 days) when data points that were equal to zero days were included in the analysis. This estimate was only slightly lower than the median time elapsing until the third chronic disease in the original analysis, which was 364.8 days (mean of 565.7 days). As well, among female patients aged 85 years and older, the median time until the third chronic disease diagnoses was only 5.2 days (mean of 224.4 days) when data points that were equal to zero days were maintained in the analyses, as compared to a median time of 97.4 days (mean of 366.4 days) when these data points were removed from the analysis.

5.2.4 Objective Two, Research Question 3 – Examining Patient-, Provider- and Practice-Level Predictors of Time Until Subsequent Chronic Disease

To address Research Question 3, univariate and bivariate analyses were first conducted for both continuous and categorical predictors, and the results from these analyses are presented in **Table 5.44**. This was conducted for adult PHC patients with at least one chronic disease as of September 30, 2013 and only those chronic diseases with at least one-day elapsing between diagnoses were included in the analysis. As described in the Methodology Chapter, a total of nine predictors were included in the multilevel, recurrent event survival analysis. Among the patient-level predictors, all five independent variables were statistically significantly related to the dependent variable (p-value < 0.001). Similarly, among the provider- and practice-level predictors, all four independent variables were statistically significantly related to the dependent variable of time until subsequent chronic disease diagnosis (p-value < 0.001). Consequently, a statistically significant correlation between each of the nine independent variables and the continuous dependent variable (that is, time until subsequent chronic disease) was observed. These graphs indicate that the majority of time elapsing until subsequent chronic disease was under 5.5 years (or 2,000 days) for both female and male patient groups. This broad pattern was observed among both female and male patients, regardless of patient age category. The unadjusted Kaplan–Meier failure curves for female and male patients can also be seen in **Figure 5.8** and **Figure 5.9**, and displays the event rate among those patients with one or more chronic disease diagnoses and stratified by patient age category.

The results from the multilevel, recurrent event survival analysis are presented in **Table 5.45** and demonstrate the relationship between each independent variable and dependent variable, controlling for all other variables in the final model. This table also presents the

variance contributed by clustering of events at the provider- and practice-level. After conducting the bivariate analyses, each of the nine predictor variables were independently entered into the basic survival analysis model. Following this initial assessment, all nine predictor variables were included in the multilevel, recurrent event survival analysis among patients with at least one chronic disease diagnosis. Among the patient-level variables, patient age, patient sex, median household income and the total number of chronic diseases were all significantly related to time until subsequent chronic disease, after controlling for all other variables in the model (p-value < 0.05). While patient sex and total number of chronic diseases demonstrated more notable effect sizes, the effects of patient age, residential location and median household income were negligible, despite being found statistically significant. From the hazard ratios reported in the adjusted model, female patients experienced a 19% decrease in the rate until the next chronic disease diagnosis, as compared to male patients and controlling for all other variables in the model (p-value < 0.001). Similarly, as the number of chronic diseases increased by one unit, and with all other variables held constant, there was a 33% increase in the rate until the next chronic disease diagnosis (p-value < 0.001).

Among the provider-level variables, provider age and provider sex were both found to be statistically significant (p-value < 0.05). While the increasing age of a PHC provider created only a 2% decrease in the rate until the next chronic disease (p-value < 0.001), the patients who received care from a female PHC provider experienced an 8% decrease in the rate until their next chronic disease diagnosis (p-value < 0.05).

Finally, among the practice-level variables, both the EMR type and the location of the PHC practice were found to have a statistically significant relationship with the outcome, holding all other variables in the model constant. More specifically, adult patients who were receiving

care from an urban-based PHC practices experienced a 26% decrease in the rate until their subsequent chronic disease diagnosis (p-value < 0.001). Multiple EMR software types were also significantly related to the outcome of interest, and as compared to the Accuro EMR software (reference category). For example, those patients who were receiving care from a PHC practice that utilized the Bell EMR software type had a 46% increase in rate until the subsequent chronic disease, as compared to those patients receiving care from a PHC practice that utilized the Accuro EMR software (p-value < 0.001). Likewise, those patients who were receiving care from a PHC practice that used the Oscar EMR software had a 62% increase in the rate until subsequent chronic disease diagnosis, as compared to the Accuro EMR software and holding all other variables in the model constant (p-value < 0.001). Those patients who received care from a PHC practice using the Practice Solutions and Wolf EMR software programs experienced a decreased rate until their next chronic disease diagnosis. For example, those patients whose data were recorded using the Practice Solutions EMR software had a 57% decrease in the rate until their next chronic disease diagnosis (p-value < 0.001), whereas those patients whose data were recorded using the Wolf EMR software had a 27% decrease in the rate until their next chronic disease diagnosis (p-value < 0.001). Both of these hazard ratios were calculated as compared to the Accuro EMR software and holding all other variables in the final model constant. As highlighted further in the Discussion Chapter, these results could potentially be due to coding artefacts within the EMR data based or due to true differences in the accumulation of multiple chronic diseases among the patients within the sample.

When examining the potential for an interaction between patient age and patient sex, the interaction term was found to be statistically significant (p-value < 0.001), but the hazard ratio indicated a negligible effect size on the dependent variable and was not interpreted any further.

The multilevel survival analysis also determined the variance contributed by clustering of events at each level, that is within PHC providers and within PHC practices. In the results presented in **Table 5.45**, almost 10.0% of variance was contributed by provider-level clustering. There was no notable variance contributed by the practice-level clustering (0.18%). The associated likelihood ratio test was statistically significant (p-value < 0.001) indicating the suitability of a multilevel survival analysis. An exploration of the multilevel, single event survival analysis, stratified by the total number of chronic diseases, was also conducted and the results are presented in **Appendix AJ**. These additional analyses produced similar results when the multilevel survival analyses was conducted for recurrent or single events.

Table 5.44 Results of univariate and bivariate analyses between independent variables and dependent variable (time until subsequent chronic disease diagnosis) among adult patients with one or more chronic diseases (n = 238,237)

Independent Variable	Univariate Analysis	Bivariate Analysis (p-value)
Patient-Level		
Age (Years)		
Mean (SD)	54.5 Years (17.7 Years)	
Median (IQR)	54.0 Years (26.0 Years)	<0.001
Range (Minimum – Maximum)	18 Years – 114 Years	
Sex, n (%)		
Female	137,587 (57.8%)	<0.001
Male	100,650 (42.2%)	
Residential Location, n (%)		
Rural	37,424 (15.7%)	
Urban	112,072 (47.0%)	<0.001
Missing	88,741 (37.3%)	
Median Household Income (Canadian Dollars)		
Median (IQR)	$61,221 ($12,497)	<0.001
Range (Minimum – Maximum)	$22,457 – $181,454	
Total Number of Chronic Diseases		
Mean (SD)	2.5 (1.6)	
Median (IQR)	2.0 (2.0)	<0.001
Range (Minimum – Maximum)	1 – 13	

* SD = Standard deviation, IQR = Interquartile range

Table 5.44 Results of univariate and bivariate analyses between independent variables and dependent variable (time until subsequent chronic disease diagnosis) among adult patients with one or more chronic diseases (n = 238,237), *Continued*

Independent Variable	Univariate Analysis	Bivariate Analysis (p-value)
Provider-Level		
Age (Years)		
Mean (SD)	50.7 Years (10.3 Years)	
Median	50.0 Years	<0.001
Range (Minimum – Maximum)	27 Years – 72 Years	
Sex, n (%)		
Female	63,494 (26.7%)	
Male	45,231 (19.0%)	<0.001
Missing	129,512 (54.4%)	
Practice-Level Variable		
EMR Type, n (%)		
Accuro	20,318 (8.5%)	
Bell	18,952 (8.0%)	
DaVinci	678 (0.3%)	
Jonoke	13,572 (5.7%)	
Med Access	6,583 (2.8%)	
Nightingale	53,319 (22.4%)	<0.001
Oscar	9,624 (4.0%)	
Practice Solutions	9,446 (4.0%)	
Wolf	19,118 (8.0%)	
Xwave	597 (0.3%)	
Missing	86,030 (36.1%)	
Practice Location, n (%)		
Rural	22,692 (9.5%)	
Urban	124,682 (52.3%)	<0.001
Missing	90,863 (38.1%)	

* SD = Standard deviation

Figure 5.8 Kaplan-Meier curves indicating time (in days) until subsequent chronic disease diagnosis (event) among female patients, stratified by patient age category

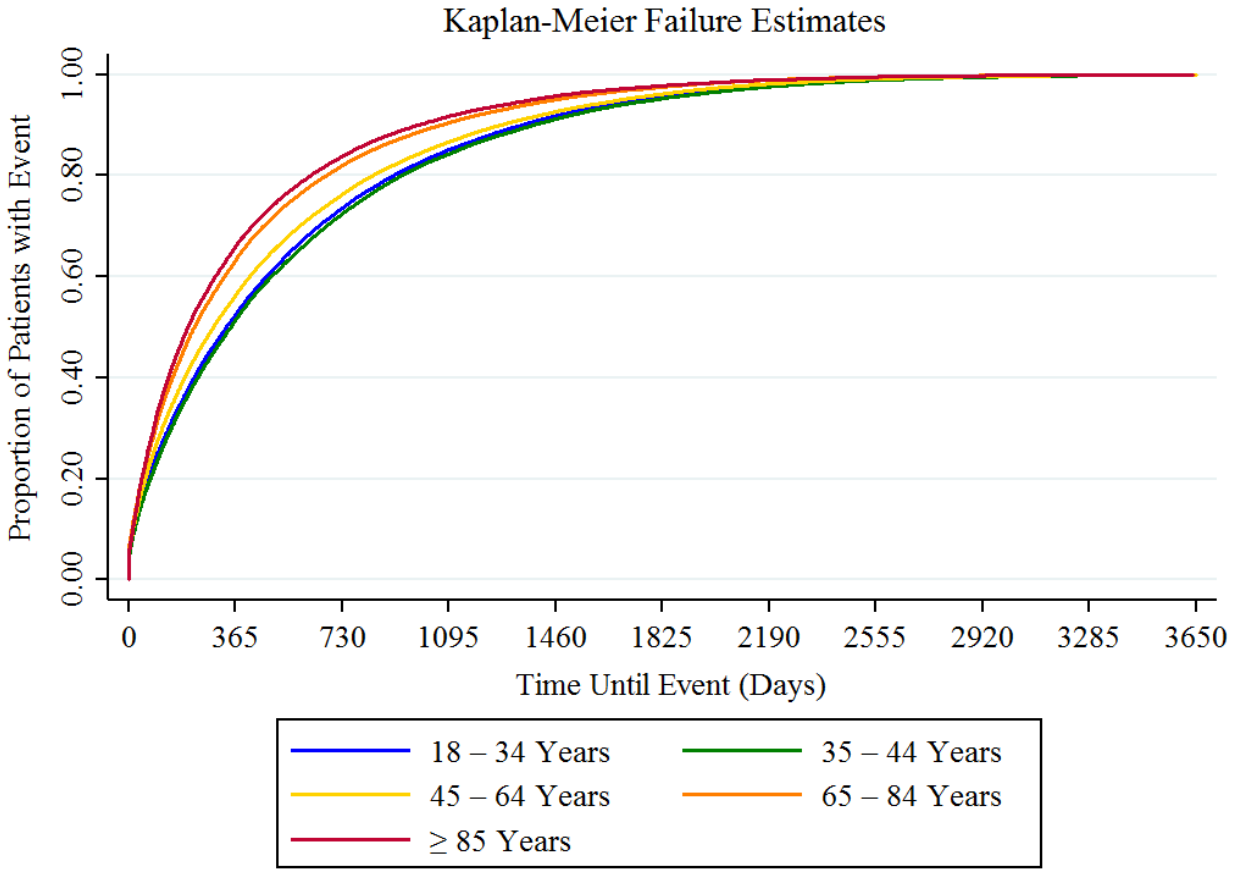


Figure 5.9 Kaplan-Meier curves indicating time (in days) until subsequent chronic disease diagnosis (event) among male patients, stratified by patient age category

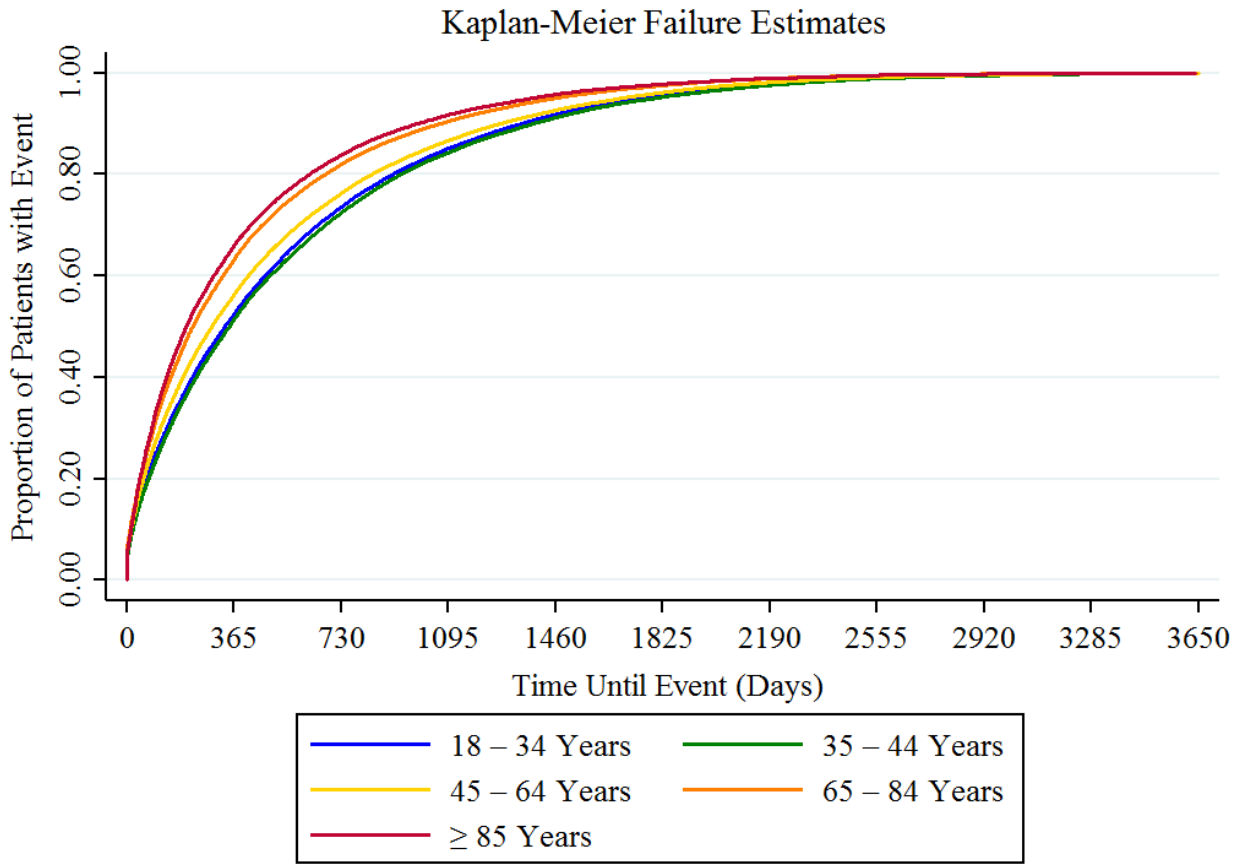


Table 5.45 Results of multilevel, recurrent event survival analyses for time until subsequent chronic disease diagnosis among adult patients with one or more chronic diseases (n = 238,237)

Independent Variable	Hazard Ratio (95% CI) *	p-value
Patient-Level		
Age	1.002 (1.001 – 1.003)	<0.001
Sex (Female)	0.81 (0.78 – 0.85)	<0.001
Residential Location (Urban)	0.99 (0.97 – 1.01)	0.410
Median Household Income	1.000001 (1.00 – 1.000001)	0.018
Total Number of Chronic Diseases	1.33 (1.33 – 1.34)	<0.001
Provider-Level		
Age	0.98 (0.98 – 0.99)	<0.001
Sex (Female)	0.92 (0.85 – 0.99)	0.029
Practice-Level		
EMR Type		
Accuro	*Reference*	
Bell	1.46 (1.23 – 1.72)	<0.001
DaVinci	0.98 (0.90 – 1.08)	0.067
Jonoke	1.08 (0.96 – 1.14)	0.093
Med Access	0.87 (0.74 – 1.01)	0.083
Nightingale	0.95 (0.85 – 1.06)	0.332
Oscar	1.62 (1.40 – 1.88)	<0.001
Practice Solutions	0.43 (0.37 – 0.50)	<0.001
Wolf	0.73 (0.64 – 0.84)	<0.001
Xwave	1.98 (0.82 – 4.73)	0.127
Practice Location (Urban)	0.74 (0.67 – 0.83)	<0.001
Interaction Term		
Patient Age & Patient Sex	1.002 (1.001 – 1.002)	<0.001
% Variance (95% CI) Contributed by Each Level		
Within Provider	9.51 (95% CI: 6.99 – 12.41)	
Within Site	0.18 (95% CI: 0.00 – 0.20)	

*CI = Confidence interval; Extra decimal places added where necessary

Chapter 6

6 Discussion

This chapter will highlight the key results presented in the previous chapter with further discussion and interpretation. This discussion will be supplemented by a highlight of this research work's strengths, limitations and implications within the broader clinical, policy and research contexts.

6.1 Summary of Key Findings from Objective One

6.1.1 Prevalence and Characteristics of Patients with Multimorbidity

Overall, this research identified that about one in two adult PHC patients (or 53.3%) within the CPCSSN database were living with two or more chronic diseases as of September 30, 2013. About one in three adult PHC patients (or 33.1%) within the CPCSSN database were living with three or more chronic diseases as of September 30, 2013. These estimates were compared to literature where a similar definition of multimorbidity was used, as well as those studies that were conducted in a Canadian context and a PHC context.

Among those studies that were conducted in Canada, the prevalence of individuals with two or more chronic diseases ranged from as low as 12.9% in a general adult population sample (Roberts et al., 2015), to as high as 89.3% in an adult PHC patient sample (Fortin et al., 2005). While the sample size of the study conducted by Roberts et al. (2015) was almost ten times smaller than the sample size of the study conducted by Fortin et al. (2005), the prevalence of multimorbidity was considerably lower as this was a health survey of the general adult population in Canada and the measurement of multimorbidity only included nine, self-reported diseases. In comparison, the study conducted by Fortin et al. (2005) collected data from

consecutive visits of adult PHC patients and any diagnosed conditions were included in the multimorbidity measurement. This study represented the collection of data from adults who were seeking care from their health care provider and a full health record review was conducted for each consenting patient. While this study provided the first Canadian prevalence estimate for multimorbidity in the adult population, the prevalence of multimorbidity was found to be notably higher than the prevalence estimate detected in the current study. Although both studies aimed to capture the occurrence of multiple "chronic" health problems within a patient, the lists of chronic diseases used in the two studies differed. A study conducted by Stewart et al. (2013) took place in a Canadian setting and reported the most comparable prevalence estimate of multimorbidity in the literature. This study included almost 3,000 adult PHC patients whose data were collected in the Deliver Primary Health Care Information (DELPHI) database (also a regional network of the CPCSSN database). Using a list of 98 chronic disease categories from the International Classification of Primary Care (ICPC) system, this study found a prevalence of 34.0% adult PHC patients living with two or more chronic diseases. This prevalence estimate was still approximately 20% lower than the estimate reported in the current study (53.3%), but this may have been due to the variation in the definition of multimorbidity or the process of identification of chronic disease diagnoses within the EMR data between the two studies.

The prevalence of individuals with three or more chronic diseases, within a Canadian setting, ranged from as low as 3.9% among a general adult population (Roberts et al., 2015) to as high as 75.6% among an adult PHC sample (Fortin et al., 2005). Once again, the study conducted by Roberts et al. (2015) utilized self-reported data from just over 100,000 adults in the Canadian Community Health Survey. This definition of multimorbidity included only nine chronic diseases, and respondents were asked whether or not they had received a diagnosis for

any of the diseases in the past. The study conducted by Fortin et al. (2005) found a high prevalence of adult PHC patients diagnosed with any condition and who had three or more chronic diseases, using a similar methodology to identifying patients with two or more chronic disease diagnoses. The Canadian study conducted by Pefoyo et al. (2015) reported the most comparable prevalence estimate of multimorbidity in the literature. This study utilized a large population-based cohort and an administrative database from the province of Ontario. With a list of sixteen chronic disease categories in the measurement of multimorbidity, this study reported a prevalence estimate of 13.6% of residents who were living with three or more chronic diseases. Again, this prevalence estimate was still approximately 20% lower than the estimate reported in the current study (33.1%), but this may have been because the study by Pefoyo et al. (2015) used a population-level approach, as compared to examining individuals specifically seeking care from a PHC provider.

When compared to the international literature within the context of primary health care, the prevalence estimate of adult patients living with two or more chronic diseases was most comparable with three recently published studies: a sample of randomly selected PHC patients in a retrospective cohort study in the United Kingdom, which reported a prevalence of 58.0% among almost 100,000 adult patients over 182 PHC practices (Salisbury et al., 2011); a cross-sectional sample of adult PHC patients in the United States, which reported a prevalence of 45.3% using a list of 24 chronic diseases within their definition of multimorbidity (Ornstein et al., 2013); and a sample of randomly selected PHC patients within a prospective cohort study in Australia, which reported a prevalence of 43.7% using health charts to capture multimorbidity (Harrison et al., 2014). The prevalence of PHC adults with three or more chronic diseases was most comparable with two recently published studies. As previously described, the study by

Harrison et al. (2014) included a prospective sample of adult PHC patients and detected a prevalence estimate of 27.4% of patients with three or more chronic diseases, which was comparable to the prevalence estimate detected in the current study (33.1%). A retrospective study by Prados-Torres et al. (2012) in Spain among more than 275,000 patients and including chronic diseases with at least a 1% prevalence level in the population, reported that 20.2% of their patients were living with three or more chronic diseases. Similar to the high prevalence estimates detected by Fortin et al. (2005), a study conducted in Portugal by Prazeres et al. (2015) detected a notably higher prevalence of adult PHC patients living with two or more and three or more chronic diseases (72.7% and 57.2%, respectively). This study investigated a large list of 147 chronic health problems and included clinical data that were collected from three data sources for each patient: provider knowledge of a patient's history, patient self-reported information and medical records. The high prevalence estimates detected by Fortin et al. (2005) and Prazeres et al. (2015) may be due to the wide breadth of information that was collected for each patient included in the sample. As a result, these studies may demonstrate the influence of the data collection approach on the eventual estimates of multimorbidity.

Among our sample of patients with two or more chronic diseases, the mean age was 59.0 years (SD: 17.0) and 57.8% were female. Slightly more than half of these patients were living in an urban setting (52.2%) and the median of the median household income was about $60,950 per year (Canadian dollars). Similar characteristics were observed for patients with three or more chronic diseases: the mean age of these patients was 62.7 years (SD: 15.9), the majority were female (58.5%), the majority were living in an urban setting (53.4%) and the median of their median of household incomes was $61,175 per year (Canadian dollars). The descriptive analysis indicated that the mean age of patients increased as the number of chronic diseases diagnosed

also increased. In fact, the mean age difference between those patients with no chronic disease diagnoses and five or more chronic disease diagnoses was 26.6 years. The association between multimorbidity and whether a patient is older or female has been consistently reported in the existing literature (Harrison et al., 2013; Barnett et al., 2012; Salisbury et al., 2011; Britt et al., 2008; Uijen et al., 2008; Fortin et al., 2005; van den Akker et al., 1998). However, while the prevalence of multimorbidity increased as patient age increased, the largest proportion of patients living with multimorbidity was between the ages of 45 to 64 years (about 25.0% of adult PHC patients) and the majority of patients with multimorbidity were under the age of 65 years. More specifically, 61.7% of patients with two or more chronic diseases were under the age of 65 years, while 53.4% of patients with three or more chronic diseases were under the age of 65 years. This finding is consistent with previous literature that has highlighted the growing burden of multimorbidity among younger cohorts of individuals. Indeed, multimorbidity is no longer an issue of the oldest patients and it must be appropriately managed among younger and younger patients (Barnett et al., 2012; Taylor et al., 2010; Mercer et al., 2009).

The highest prevalence of multimorbidity was also explored amongst the most commonly reported demographic characteristics: age and sex. This study found that the highest prevalence of multimorbidity (defined as two or more chronic diseases) was among those patients aged 45 to 64 years (40.6%) and those patients who were female (57.8%). Much of the published multimorbidity research conducted in the Canadian and international context has reported the highest prevalence among those who are 65 years of age and older (Jovic et al., 2016; Pefoyo et al., 2015; Pati et al., 2015; Prazeres et al., 2015; Roberts et al., 2015; Wang et al., 2015; Harrison et al., 2014; Orueta et al., 2014; Rocca et al., 2014; Ornstein et al., 2013; Stewart et al., 2013; Ward et al., 2013; Agborsangaya et al., 2012; Barnett et al., 2012; Prados-Torres et al., 2012;

Rizza et al., 2012; van Oostrom et al., 2012; Salisbury et al., 2011; Fortin et al., 2005; van den Akker et al., 1998). The published multimorbidity research is still demonstrating split findings in whether the prevalence of multimorbidity is more notable among female or male individuals, but the majority of studies seem to indicate a slightly higher prevalence among females (Roberts et al., 2015; Wang et al., 2015; Pati et al., 2015; Orueta et al., 2014; Barnett et al., 2012; Prados-Torres et al., 2012; van Oostrom et al., 2012; van den Akker et al., 1998). An exception was observed in Portugal, in which the study conducted by Prazeres et al. (2015) found that male patients had the highest prevalence of two or more chronic diseases (75.9%), as compared to female patients.

Comparing the demographic characteristics with the literature that defined multimorbidity as three or more chronic diseases is more difficult because these studies report patient characteristics in less detail. While the current study found that the prevalence of three or more chronic diseases was highest among those patients who were 45 to 64 years and who were female (39.6% and 58.5%, respectively), the majority of the literature found the highest prevalence of three or more chronic diseases among the oldest age group of patients (e.g., those patients who are aged 65 and older or 85 years and older). The literature also showed mixed findings in that some studies reported females with the higher prevalence of three or more chronic diseases, ranging from 4.5% by Roberts et al. (2015) to 77.4% by Fortin et al. (2005). However, two additional studies reported that males experienced the highest prevalence of three or more chronic diseases, ranging from 7.6% by Rizza et al. (2012) to 61.6% by Prazeres et al. (2015). These inconsistent findings indicate a need to further explore and understand the characteristics of those patients who are living with advancing multimorbidity, as well as more comprehensive reporting of research findings (Stewart et al., 2013).

Overall, the estimates of multimorbidity detected within the current study fall on the higher end of the prevalence spectrum (e.g., ranging from 0% to 100% prevalence), as compared to the estimates that have been reported to date. The characteristics of those adult patients who were living with multimorbidity (regardless of definition) were somewhat comparable with the existing literature, but again, notable variation was observed in the distinct patterns of characteristics. These differences may be a result of interrelated causes. For example, these differences may indicate true and distinct differences between populations, in that perhaps the burden of multimorbidity is higher in Portugal than in Canada. However, these differences also may be due to methodological differences in data collection, sample recruitment and inclusion criteria for disease within the multimorbidity definition. For example, the lack of comparable findings between population-level surveys and clinical chart reviews may be an artefact of the data collection approach. Or, these potential causes may be interrelated and more convoluted. As such, comparisons between studies should be made cautiously as long as these differences in research methodology continue to prevail.

6.1.2 Most Frequently Occurring Clusters of Multimorbidity

Before examining the discrete clusters of multiple chronic diseases, the prevalence of individual chronic diseases, stratified by patient age and patient sex, were explored. This analysis detected a changing distribution of individual chronic diseases as patient age increased. For example, those patients who were between the ages of 18 and 34 years had the highest prevalence of diagnoses for Obesity, Anxiety or Depression and Musculoskeletal Problem. Among patients aged between 65 and 84 years, the most prevalent individual chronic diseases were Hypertension and Obesity. Those patients who were 85 years of age and older had the

highest prevalence of diagnoses for Hypertension, followed by diagnoses of Obesity, Diabetes and Cardiovascular Disease. The changing prevalence of individual chronic diseases by patient age group may be reflecting the changing characteristics of an aging patient. For example, PHC providers may be more sensitive or attuned to the mental health challenges experienced by young adults, creating a higher prevalence of diagnoses for Anxiety or Depression in this age group, particularly due to increased media and policy attention for this important issue. Or perhaps those young patients who are experiencing Anxiety or Depression or a Musculoskeletal Problem require a diagnosis and a clinical note if work or school absences are required (e.g., missing an examination due to chronic anxiety or requiring time off work due to chronic back pain). While those patients who were aged 85 years and older were most likely to be diagnosed with Hypertension and Obesity, the prevalence of the remaining chronic diseases was much more evenly distributed. This pattern was observed for both female and male patients and may indicate that older patients who are living with multiple chronic diseases are more likely to live with a wide range of chronic diseases or those chronic diseases that have a less direct link with mortality. As will be confirmed shortly, these older patients also represent increasingly complex clinical profiles and are managing more unique clusters of multiple chronic disease diagnoses.

A high prevalence of obesity was found in a Canadian study using the Health Quality Council of Alberta 2012 Patient Experience Survey that found an obesity prevalence of 28.1% (Agborsangaya et al., 2013). However, a study conducted in the United States by Ornstein et al. (2013) among 148 practices with more than 650,000 adult patients found a prevalence of obesity of 11.9% using only ICD-9-CM codes. A study conducted in Sweden by Rizza et al. (2012) using the ICPC-2 classification system found a very small prevalence of obesity, that of less than 3.0% among adult PHC patients. Likewise, a study conducted in Germany by Schafer et al.

(2012) found a small prevalence of diagnosed obesity of 4.8% among adult PHC patients. Hypertension is a consistently measured and highly prevalent chronic disease, particularly among those with at least one chronic disease or older populations. Likewise, psychological chronic diseases (including anxiety and depression) were prominent in many of the multimorbidity studies. The study conducted by Prazeres et al. (2015) found a staggeringly high prevalence of both hypertension and depressive disorder within their sample of patients. The prevalence of hypertension among female and male patients with multimorbidity was about 94.0%, whereas the prevalence of depressive disorder among female patients with multimorbidity was as high as 88.4% (Prazeres et al., 2015). In comparison, the study conducted in Australia determined the prevalence of psychological or mental and behavioural disorders ranged from 22.2% to 21.9% among adult PHC patients using the ICPC-2 and ICD-10 classification systems, respectively (Harrison et al., 2014). Although anxiety was not measured, the studies conducted by Roberts et al. (2015) and Ornstein et al. (2013) reported a prevalence of depression ranging from 11.2% among community-dwelling adults in Canada to almost 20.0% among care-seeking adults in the United States. Finally, a high prevalence of chronic musculoskeletal problems (e.g., chronic low back pain) were also reported in the multimorbidity literature. A study conducted in Australia found a prevalence of 26.3% and 26.0% among adult PHC patients, as measured using the ICPC-2 and ICD-10 classification systems, respectively (Harrison et al., 2014). A higher prevalence was detected in sample of adult PHC patients in Germany, in which at least 50.0% of the sample were living with chronic pain impacting function (Schafer et al., 2012). Overall, the most prevalent individual chronic diseases were Obesity, Hypertension, Musculoskeletal Problem and Anxiety or Depression, which demonstrated consistency with the multimorbidity literature.

The computational cluster analysis that was conducted using the Multimorbidity Cluster Analysis Tool detected many unique combinations and permutations, and indicated that patients with multimorbidity represent increasingly complex clinical profiles. A similar computational cluster analysis has not been published in the multimorbidity literature to date. Instead, varying techniques to identify co-occurring clusters of multiple chronic diseases have been reported, including exploratory factor analysis, cluster analysis and latent class growth analysis (Prados-Torres et al., 2014; Violán et al., 2014; Garin et al., 2014; Strauss et al., 2014; van Oostrom et al., 2014; Ornstein et al., 2013; Prados-Torres et al., 2012; Newcomer et al., 2011; Schafer et al., 2010; Cornell et al., 2007). In the current study, approximately 5,000 unique combinations were detected for female and male patients living with multimorbidity, while almost 10,000 and 15,000 unique permutations were found for female and male patients living with multimorbidity, respectively. Due to these large numbers of mutually exclusive clusters, this analysis indicates that the top twenty most frequently occurring combinations and permutations among all female and male patients represented only about 20.0% of adult patients with multimorbidity. This means that even the most frequently occurring clusters represent a comparatively small proportion of adult patients with multimorbidity.

Among female patients of all ages, the most frequently occurring combinations were Anxiety or Depression and Musculoskeletal Problem (1,694 or 3.6% of all female patients); Anxiety or Depression and Obesity (1,179 or 2.5% of all female patients); and Musculoskeletal Problem and Obesity (1,132 or 2.4% of all female patients). These three commonly occurring combinations remained the most common among female patients aged 18 to 34 years and 35 to 44 years. For female patients aged 45 to 64 years, the most common combination was Anxiety or Depression and Musculoskeletal Problem (674 or 3.7% of female patients aged 45 to 64 years.

The diagnosis of Hypertension was frequent in the top combinations among female patients aged 65 years and older and the most common combinations were Hypertension and Obesity (323 or 2.5% of female patients aged 65 to 84 years) and Dementia and Hypertension (76 or 2.0% of female patients aged 85 years and older). Similar to the common combinations among female patients of all ages, the most common permutations were Anxiety or Depression then Obesity (1,160 or 2.4% of all female patients); Musculoskeletal Problem then Obesity (1,094 or 2.3% of all female patients); and Anxiety or Depression then Musculoskeletal Problem (909 or 1.9% of all female patients). These three commonly occurring permutations remained the most common among female patients aged 18 to 34 years, 35 to 44 years and 45 to 64 years. A shift occurred among female patients aged 65 years and older, in which the permutation of Hypertension then Obesity became the most commonly occurring permutation among patients aged 65 to 84 years (322 or 2.5% of female patients aged 65 to 84 years) and 85 years and older (62 or 1.6% of female patients aged 85 years and older).

Among male patients of all ages, the most frequently occurring combinations were Hypertension and Obesity (3,866 or 4.7% of all male patients); Musculoskeletal Problem and Obesity (3,580 or 4.3% of all male patients); and Anxiety or Depression and Obesity (2,431 or 2.9% of all male patients). These three commonly occurring combinations were persistent among male patients aged 18 to 34 years, 35 to 44 years and 45 to 64 years. For male patients aged 65 years and older, the diagnosis of Obesity was present in the most common combinations and the most frequent combination was Hypertension and Obesity (1,092 or 4.0% of male patients aged 65 to 84 years). Similar to the common combinations among all male patients, the most common permutations were Obesity then Hypertension (2,201 or 2.7% of all male patients); Obesity then Musculoskeletal Problem (2,138 or 2.6% of all male patients); and

Hypertension then Obesity (1,665 or 2.0% of all male patients). For all age groups of male patients, Obesity was involved in the most frequent permutations. Among male patients aged 18 to 34 years, the most common permutation was Obesity then Anxiety or Depression (437 or 7.3% of male patients aged 18 to 34 years); for male patients aged 35 to 44 years, the most common permutation was Obesity then Musculoskeletal Problem (532 or 5.8% of male patients aged 35 to 44 years); and for patients aged 45 years and older, the most common permutation was Obesity then Hypertension (1,167 or 3.3% of male patients aged 45 to 64 years; 584 or 2.1% of male patients aged 65 to 84 years; and 68 or 1.3% of male patients aged 85 years and older.

While to our knowledge, no published literature to date has examined the sequence of multiple chronic disease diagnoses, a recent systematic review of the clusters or patterns of multimorbidity identified three most prevalent patterns: cardiovascular and metabolic disorders, mental health problems and musculoskeletal disorders (Prados-Torres et al., 2014). The cardiovascular and metabolic disorder pattern described by Prados-Torres et al. (2014) was composed of diseases that are consistent with what is commonly known as the metabolic syndrome, such as hyperlipidemia, hypertension, heart disease, diabetes and obesity. The second group of patterns included at least one mental health problem, such as depression and anxiety, which co-occurred with thyroid disease, pain, asthma and obesity. The third group of patterns included at least one musculoskeletal problem, such as back or neck pain (Prados-Torres et al., 2014). Another systematic review of patterns of multimorbidity in primary health care found similar commonly occurring patterns in that cardiovascular and metabolic disorders, mental health disorders and musculoskeletal pain were the most frequent patterns among females and males (Newcomer et al., 2011). Finally, a systematic review conducted by Sinnige et al. (2015) found that among older adult populations, depression was the disease that most commonly

clustered with other disease diagnoses and was specifically paired with eight other diseases (hypertension, arthritis, diabetes mellitus, asthma or chronic obstructive pulmonary disease, stroke, cancer, heart failure and heart disease).

The patterns found in the above systematic reviews were also detected in the current study of adult PHC patients. While the three chronic disease categories of Obesity, Musculoskeletal Problem and Anxiety or Depression were the most prevalent individual chronic diseases in our sample of adult patients, these diagnoses indicated an interesting clustering with less prevalent chronic diseases (e.g., Dementia, Cancer). Distinct patterns were also seen based on whether these chronic disease categories occurred in a combination (no specific sequence) or a permutation (specific sequence). For example, for female patients who were 85 years and older, one of the most commonly occurring combination was that of Dementia and Hypertension (76 or 2.0% of female patients aged 85 years and older). However, if the specific sequence of chronic disease diagnoses mattered, the more commonly occurring combination was actually Hypertension then Obesity (62 or 1.6% of female patients aged 85 years and older).

Importantly, the aim of this computational cluster analysis was not to determine a causal link between disease diagnoses. While the temporality of diagnoses was accounted for in the permutation or ordered cluster analysis, this does not necessarily indicate a pathophysiological link between one chronic disease diagnosis and the following chronic disease diagnoses. Indeed, a robust life course approach would be necessary to determine substantial causal links between multiple chronic disease occurrence (Wister et al., 2016; Pavela and Latham, 2015; van den Akker et al., 2015; Vos et al., 2015; Strauss et al., 2014). This approach, combined with the information provided from objective cluster analysis, could be used to inform single-disease, basic science research to investigate the biology of co-occurring diseases and potentially

exploring pathophysiological pathways to these clustered diseases. For example, a study conducted by Lappenschaar et al. (2013) determined that among individuals with both hyperlipidemia and hypertension at baseline, the probability of having coexisting ischemic heart disease and heart failure was greater than the product of their individual rates. The conclusion that hyperlipidemia and hypertension interact synergistically to effect risk of ischemic heart disease and heart failure is important for guiding combined prevention efforts, such as population interventions to reduce fast-food intake (Prados-Torres et al., 2014).

From the current study, the synergistic relationship between Hypertension and Obesity, as well as the potentially synergistic effects of lifestyle behaviours between Musculoskeletal Problem and Obesity, could be explored in more detail. Even further, these relationships could be explored among less concordant diseases, such as the co-occurrence of Hypertension and Cancer or the specific sequence of patients who were first diagnosed with Anxiety or Depression and then a Musculoskeletal Problem. While these clusters demonstrate less obvious pathophysiological pathways, clinical insight might help to inform why these patterns co-exist. Moving beyond these investigations to more broad implications, the results from the cluster analysis could be used to suggest new (physiological, clinical or behavioural) interaction hypotheses that could be used in the design and implementation of more pragmatic and personalized intervention or prevention programs for patient with multimorbidity. Making these interventions more personalized to the unique clusters of patients with multimorbidity will also make them more actionable.

However, these findings should be used cautiously to inform clinical care or intervention programs. While this information may be used to inform more creative approaches to clinical care and pragmatic interventions, these quantitative results importantly lack the voice and

perspective of the individuals who are living with multimorbidity. Using a large population-based database, this research provides empirical evidence of the increasingly unique clinical profiles among adult PHC patients with multimorbidity. While the patients could be grouped into the same clusters (based on sequence of diagnosis or not), these clusters do not completely capture or depict the same experience among all patients. Instead, it is crucial to recognize the individuality of each patient who has been diagnosed with and is now managing multimorbidity, as well as their changing needs over time (Gill et al., 2014; Noël et al., 2007; Fortin et al., 2007; Noël et al., 2005).

Ultimately, this research further supports the need for a patient-centered approach to delivering comprehensive and effective care for this important patient population. Although several models of patient-centeredness have been suggested, essential components of a patient-centered consultation for patients with multimorbidity was presented by Stewart and Fortin in the "ABC of Multimorbidity" textbook (Mercer et al., 2014). These four components are interrelated and are meant to be guides for the patient-provider relationship. Over time, the provider will weave back and forth between the four components: exploring diseases and illness experience; understanding the whole person; finding common ground; and enhancing the patient-provider relationship. Stewart and Fortin state that the main justification for a patient-centered approach, particularly for those with multimorbidity, is that this is the "moral imperative" or the "right approach to take". Moreover, this approach can alleviate common pitfalls encountered with complex patients and enable the PHC provider to deliver more comprehensive, effective, continuous and responsive health care to their patients over time.

6.2 Summary of Key Findings from Objective Two

6.2.1 Time Until Multimorbidity

In exploring the "Time Until Multimorbidity", that is the accumulation of a second chronic disease diagnosis, patterns of the shortest and longest amount of time elapsing between diagnoses were stratified by patient age and patient sex. Among all male patients, the quickest accumulation of a subsequent chronic disease occurred between the first and second chronic disease, regardless of age group. For example, the median time until the second chronic disease ranged from 249.0 days among male patients aged 18 to 34 years to only 93.0 days among male patients aged 85 years and older. In fact, the fastest median time until the second chronic disease diagnosis occurred among male patients aged 65 to 84 years. In comparison, all female patients who were 35 years and older and living with at least one chronic disease received their second chronic disease the quickest, as compared to diagnoses that occurred after the second chronic disease. The median time until the second chronic disease ranged from 308.3 days among female patients aged 35 to 44 years to only 97.4 days among female patients aged 85 years and older. The exception to this pattern was female patients aged 18 to 34 years, who experienced the quickest median time (283.0 days) until the subsequent chronic disease diagnosis between the fifth and sixth chronic disease.

The "Time Until Multimorbidity" was also explored when stratified by patient age, patient sex and index chronic disease type. This descriptive analysis indicated that among female and male patients, the quickest accumulation until the second chronic disease occurred most often when the index chronic disease type was Diabetes. For example, the median time elapsing between the diagnosis of Diabetes until the second chronic disease for female patients aged 18 to 34 years was 131.0 days. Those female patients aged 65 to 84 years who were first

diagnosed with Diabetes received their second chronic disease diagnosis in a median time of 46.5 days. Likewise, among male patients aged 18 to 34 years who were first diagnosed with Diabetes, the second chronic disease diagnosis was made in only 30.8 days. Among male patients aged 65 to 84 years, those patients who were first diagnosed with Diabetes were diagnosed with their second chronic disease in a median time of 32.0 days. Further exploration of the data (to potentially describe the very short time elapsing after a diagnosis of Diabetes) showed that the large majority of patients (regardless of patient age and patient sex) who were first diagnosed with Diabetes were subsequently diagnosed with either Hypertension or Obesity following their Diabetes diagnosis. This may indicate the pathophysiological link between diagnoses, but again, the causal associations between chronic diseases were not explored in this current research.

The longest median time until second chronic disease diagnosis did not demonstrate a clear pattern. For example, among patients aged 18 to 34 years, the longest median time until the second chronic disease elapsed when female patients were first diagnosed with Osteoporosis (921.4 days) and when male patients were first diagnosed with Stroke or Transient Ischemic Attack (1,993.1 days). Those female and male patients aged 45 to 64 years who were first diagnosed with Dementia experienced the longest time until their second chronic disease with a median time of 503.3 days and 369.0 days, respectively. Finally, among female and male patients who were 85 years and older, the longest median time until their second chronic disease occurred when these patients were first diagnosed with Kidney Disease or Failure (449.7 days) and Osteoporosis (260.5 days), respectively. Further exploration of the data also did not show consistent patterns in subsequent chronic disease type for these index chronic disease diagnoses.

6.2.2 Time Until Advancing Multimorbidity

The "Time Until Advancing Multimorbidity" exploration, that is the accumulation of more than two chronic diseases, indicated two distinct patterns. First, among both female and male patients who were younger than 65 years of age, the longest median time elapsed between their second and third diagnoses (as compared to all other diagnoses and regardless of disease type). Second, among both female and male patients who were 65 years of age and older, the longest median time elapsed between their fifth and sixth diagnoses (as compared to all other diagnoses and regardless of disease type). It could be hypothesized that patients accumulate subsequent chronic diseases quicker as the number of chronic disease diagnoses increases, due to an increased exposure to health care services (and therefore higher potential to receive a new diagnosis) and an increased potential susceptibility to further pathology (Fabbri et al., 2015; Hsu, 2015; Vos et al., 2015; Strauss et al., 2014; van den Akker et al., 2006). This in fact was not observed in our sample of adult patients with multimorbidity. Two studies that examined the trajectory of multimorbidity determined specific groups of low risk of multimorbidity, specific risk of a cluster and risk of multiple clusters of chronic diseases (Hsu, 2015; Strauss et al., 2014).

More specifically, Strauss et al. (2014) detected five groups of individuals who represented different trajectories: those who had no recorded chronic diseases (40.0% of sample); those who developed their first chronic disease in a 3-year observation period (10.0% of sample); those who progressed into multimorbidity (37.0% of sample); those with advancing multimorbidity (12.0% of sample); and those patients who started with multimorbidity and further developed more chronic diseases during the observation period (1.0% of sample). A study conducted by Hsu (2015) used a group-based trajectories approach to identify four trajectory groups of multimorbidity: low risk (55.5% of sample); cardiovascular disease risk only

(15.6% of sample); gastrointestinal disease and lung disease risk (20.2% of sample); and multiple risks (8.7% of sample). These two studies indicate a differentiation between the onset of multimorbidity and the progression of multimorbidity, which was was also detected in the current study. More specifically, the potential or risk for a subsequent chronic disease diagnosis (after existing morbidity) changes over time. However, this study explored risk using the measurement of time (that is, the time-to-event risk that will be presented in the next section). In fact, comparing methodologies in this broad life course approach to multimorbidity, based on risk profiles and time-to-event risk, would be a very interesting next step for the complex field of longitudinal multimorbidity research.

To date, extensive research has been conducted to examine and delineate the life course epidemiology of individual chronic diseases (Bijker et al., 2016; Oliveira et al., 2016; Ben-Shlomo et al., 2016; Pavela and Latham, 2015; Viner et al., 2015; Duijts et al., 2014; Kelishadi et al., 2014; Power et al., 2013; Godfrey et al., 2010; White et al., 2009; Batty et al., 2007; Lynch and Smith, 2005; Barker, 2004). However, further research is required to move beyond the focus on individual chronic disease epidemiology across the life course. This will help to determine how and why individuals accumulate multiple diseases over a lifetime, using both social and biological pathways (Ben-Shlomo et al., 2016). This information can encourage PHC providers to proactively offset the risk of their patients developing multimorbidity based on their influential role in society (Mercer et al., 2014; McWhinney and Freeman, 2009; Starfield et al., 2005). Ideally, this information will also support the need for more comprehensive health promotion across the life course. These resources must be made available to individuals regardless of life circumstances, such as early childhood disease or socioeconomic disadvantage. Finally, this information will enable the collaborative work of primary health care and public

health systems in the prevention of individual chronic diseases and multiple chronic diseases as populations continue to age over time.

6.2.3 Predicting Time Until Subsequent Chronic Disease

In the multilevel, recurrent event survival analysis, the relevant patient-level predictors of time until subsequent chronic disease included patient age, patient sex, patient residential location, median household income and the total number of chronic diseases diagnosed. The provider- and practice-level predictors of time until subsequent chronic disease were provider age, patient sex, EMR software type and practice location. Among the patient-level independent variables, patient sex and total number of chronic diseases were found to be significantly related to the time until subsequent chronic disease diagnosis, controlling for all other variables in the final model. Female patients were found to experience a 19% decrease in the rate until the next chronic disease diagnosis, as compared to male patients and controlling for all other variables in the model. Similarly, as the number of chronic diseases increased by one unit, and with all other variables held constant, there was a 33% increase in the rate until the next chronic disease diagnosis. Hsu (2015) and Strauss et al. (2014) also found that patient age and patient sex were factors in the trajectory of multimorbidity over time among patients who were 50 years of age and older. More generally, the association between multimorbidity, patient age and patient sex has been demonstrated in more descriptive findings (Barnett et al., 2012; Salisbury et al., 2011; Harrison et al., 2013; Britt et al., 2008; Uijen et al., 2008; Fortin et al., 2005).

Among the provider-level independent variables, provider age and provider sex were both found to be significantly related to the time until subsequent chronic disease diagnosis, controlling for all other variables in the final model. More specifically, while the increasing age

of a PHC provider demonstrated only a 2% decrease in the rate until the next chronic disease diagnosis, the patients who received care from a female PHC provider experienced an 8% decrease in the rate until their next chronic disease diagnosis. For practice-level independent variables, adult patients who were receiving care from urban-based PHC practices experienced a 26% decrease in the rate until their subsequent chronic disease diagnosis. Multiple EMR software types were also significantly related to the time until subsequent chronic disease diagnosis, as compared to the Accuro EMR software (reference category).

As described in the Methodology Chapter, provider-level characteristics (including provider age and provider sex) may influence diagnostic behaviours and whether a provider prefers to use an interventionist or "wait and see" approach (Hajjaj et al., 2010; Forrest et al., 2006; Tracy et al., 2005; Franks and Bertakis, 2003; Bertakis et al., 2003; McKinlay et al., 2002). Likewise, practice-level influences can include characteristics of the practice organization, such as geographic location of the practice and availability of health resources (Iverson et al., 2005; McKinlay et al., 1996). Consequently, the patient-, provider- and practice-level domains were relevant layers to capture and explore in this time-to-event analysis.

Finally, within this multilevel survival analysis, the variation in the time until subsequent chronic disease diagnosis was assessed at both the level of the PHC provider and the PHC practice. The amount of variation in the outcome contributed at the provider-level was 10.0% (95% CI: 8.4 – 11.9), while the amount of variation contributed at the site-level was less than 1.0% (that is, 0.18%, 95% CI: 0.0 – 2.0). Although it was important to examine the effect of clustering of events (or diagnoses) within PHC practices and within PHC providers, this analysis indicated reasonably minimal impact (< 10%) of these clusters.

6.3 Strengths and Limitations

6.3.1 Strengths of Research

There are three notable strengths of this research. Firstly, the findings of this work provide necessary insight into the prevalence, patterns and progression of multimorbidity among adult patients in the Canadian PHC context. While the multimorbidity literature continues to become much more mature and robust, national estimates of multimorbidity in Canada are still missing. While this research represents a small piece of the "multimorbidity puzzle", it may help to guide future multimorbidity research and it will contribute to the international evidence base.

Secondly, the CPCSSN EMR database represents an important and unique resource for researchers who are interested in the combined fields of PHC and multimorbidity. The longitudinal nature of the CPCSSN EMR data allowed for estimates of multimorbidity prevalence among adult PHC patients and the examination of the progression of multimorbidity over time. This longitudinal analysis included information that spanned many years (in some cases, ten or more years) for a large cohort of patients. As such, this rich source of longitudinal, clinical data provides a PHC-specific picture of how patients progress from living with one chronic disease to multiple chronic diseases. Building on these findings, health care providers and health care policy makers could utilize longitudinal data to inform prevention and management practices for patients who are most at-risk of developing a subsequent chronic disease. Ideally, these interventions would aim to prevent patient progression into complex clinical profiles, and to help a patient maintain or improve upon their current health status.

Thirdly, the methodology used in this research provided a solution to addressing a number of challenges in the EMR database and the study of the complex issue of multimorbidity. The challenges encountered in using the EMR database included detecting singular chronic

disease diagnoses, as well as clusters of chronic disease diagnoses. Another challenge was the appropriate analyses of the complex longitudinal data. While the approaches utilized for the current research must be compared and contrasted with other approaches, the methodology outlined in the work may help to inform future research in similar areas or facing similar methodological or data-related challenges. Finally, this methodology has been published and has been made accessible to external researchers to encourage its replication and comparison of the eventual findings (Nicholson et al., 2015).

6.3.2 Limitations of Research

This research has three important limitations to consider. Firstly, this research used a simplified approach to operationalize the definition of multimorbidity by strictly counting chronic disease diagnoses and incident ICD-9 codes within the EMR database. This approach allowed for the identification of the first occurrence of ICD-9 diagnoses throughout the patient's longitudinal electronic record. However, this approach does not account for the severity of disease or symptom burden on the patient, which may be very valuable information when examining progression into more complex clinical profiles. While examining the occurrence of combinations and permutations of multiple chronic diseases created an understanding of the multidimensional characteristics of multimorbidity, another potentially important dimension would be the severity of chronic disease. For example, although this research was able to detect that specific combinations and permutations were most frequent in the sample of adult PHC patients, these findings were not stratified by disease severity. In a similar sense, the identification of combinations and permutations did not indicate a causal relationship between diseases. Indeed, this would be an area for extensive further study.

Secondly, the use of EMR data may have introduced the potential for misclassification of chronic disease occurrence and, therefore, a biased estimate of multimorbidity prevalence. This potential for misclassification is not only specific to EMRs, but to medical records in general. For example, if a patient was truly living with one of the twenty chronic diseases included in the measurement of multimorbidity, this patient may not have been detected in the EMR database because: 1) the patient did not present pathophysiological indications for the PHC provider to examine further through laboratory tests or examinations that would confirm a diagnosis; 2) the patient did present pathophysiological indications that were diagnosed as one of the twenty chronic diseases by the PHC provider, but this diagnosis was not recorded within the patient's EMR; or 3) the patient did present pathophysiological indications that were diagnosed as one of the twenty chronic diseases by the PHC provider, but this diagnosis was not recorded in an area of the patient's EMR that was extracted into the CPCSSN EMR database. Each of these factors may have resulted in a patient being misclassified as not living with a chronic disease, when in fact this patient was living with one or more chronic diseases. Alternatively, patient diagnoses may have been entered incorrectly into the EMR or with an incorrect date of diagnoses. A related limitation of the EMR data is that potentially modifiable risk factors that were not available in the CPCSSN EMR database (e.g., socioeconomic status, lifestyle behaviours or levels of self-efficacy to improving lifestyle behaviours) would be meaningful to explore in terms of their potential impact on the occurrence or progression of multimorbidity among adult PHC patients. The impact of socioeconomic status on multimorbidity has been identified in previous literature (Roberts et al., 2015; Payne et al., 2013; Agborsangaya et al., 2012; Mercer et al., 2012; Barnett et al., 2012), and indicates an important area of improvement within the CPCSSN EMR database.

Finally, the time elapsing between chronic diseases (explored in Objective Two) was potentially impacted by the recording behaviours of the providers within an electronic medical record. For example, providers are expected to record the diagnostic codes when a diagnosis follows patient visit and presentation of related symptoms. To adequately examine the time elapsing between diagnoses, providers are also expected to record the diagnostic codes at first detection or confirmation of a disease within a patient. While the original intent of Objective Two was to report and describe the natural history of multimorbidity over time, the measure of "time" could not differentiate between the recording behaviours of the PHC provider and the true progression of multimorbidity over time. For example, the observation that approximately 20% of patients received multiple chronic disease diagnoses at the same encounter may have indicated an artefact of the EMR data. However, this is not completely clear as a patient may have been truly diagnosed with multiple chronic diseases at a single encounter because: 1) the PHC provider may have received awaited results from multiple laboratory tests and/or examinations; 2) the patient may have been a new patient to the PHC provider and already living with multiple chronic diseases, which would then be recorded at a single encounter; or 3) the PHC provider may have entered the diagnostic information or associated dates incorrectly.

6.4 Implications

6.4.1 Clinical and Policy Implications

The findings from this research could be used in the clinical context to inform training for future health care providers, as well as in the policy context to guide intervention efforts. For example, the cluster information could be used to create "multimorbidity-based patient vignettes" of either the most common or most uncommon clusters of chronic diseases occurring

within subsets of patients. These could be used for educational purposes by introducing and orienting future health care professionals with the realities and complexities of multimorbidity. In fact, these vignettes can prime current medical students and health care providers with commonly co-occurring issues among PHC patients in Canada. This information could be used to tailor educational modules programs around questions like: "When is the patient most susceptible to acquire another chronic disease?" or "How can this progression into a subsequent chronic disease be avoided, based on the patient's preferences and goals?" These are complex, clinical questions to answer in any context. However, it may be important to start asking these questions now within our educational programs. This approach could be nested within the enhanced training environments in which multidisciplinary health care professionals can be trained together to provide more integrated and patient-centered health care.

The implications for the purposes of health policy should be somewhat conservative, due to the observed complex nature of this patient group. However, the time elapsing between multiple chronic disease diagnoses information that was derived from Objective Two could be used strategically in the design and implementation of chronic disease prevention and management programs. The point of transition from living with one chronic disease to living with multimorbidity (defined as two or more chronic diseases) indicates a period of time in which the health care team must deliver its most effective care. This is particularly important to avoid a negative evolution into poorer and poorer health by the patient, especially as the patient continues to age. While the exact trajectory of an individual patient cannot be completely predicted, the longitudinal data collected over time from millions of adult PHC patients could be used to inform more proactive delivery of care. As stated previously, the time to event findings could be carefully used to identify at-risk patients for specific and pragmatic interventions within

a PHC setting. These more adaptive and proactive interventions could be a new focus for health policy makers who are looking to alleviate the growing burden of multimorbidity.

6.4.2 Research Implications

The completion of this work indicates three main areas in which future multimorbidity research will be particularly important. Firstly, measures and definitions of multimorbidity that are used in research should be more systematically compared and contrasted between study settings. This would include the replication of the definition and operationalization of multimorbidity from the current study in other populations in Canada and abroad. A more consistent methodological approach would allow the international research community to establish a more robust understanding of the true burden of multimorbidity among community and clinical populations. Secondly, future research should more clearly define what factors make a patient most susceptible to developing multiple chronic diseases. In other words, the sociodemographic and socioeconomic risk factors to becoming a patient with complex chronic disease profile should be explored further. While our research accounted for a number of patient-, provider- and practice-level factors that may influence the time until another chronic disease diagnosis is received, more substantial and potentially modifiable risk factors (e.g., family history, lifestyle habits or patient resiliency) should be examined. Finally, future research should work to understand the impact of these patients with multimorbidity on the health care system, and more importantly, where additional resources and supports are needed for both patients and their caregivers to improve health-related outcomes. More specifically, research should continue to identify and focus on the most successful approaches to delivering individualized, adaptive and patient-centered care for this significant and growing population of

patients. Indeed, this research will be one of the keys to ensuring that those patients living with multimorbidity are receiving the highest quality of care from their multidisciplinary health care team.

6.5 Future Directions

Overall, the results from this doctoral research indicate that the burden of multimorbidity among adult PHC in Canada is substantial as approximately 50% of adult PHC patients in our sample were living with multimorbidity, defined as two or more chronic diseases. Moreover, the complexity of these patients with multimorbidity was detected. These results indicate that even among a large cohort of adult PHC patients in Canada, patients with multimorbidity were living with increasingly unique and increasing complex clinical profiles, indicating the importance of an individualized and patient-centered approach to delivering effective and responsive care. The time elapsing between chronic disease diagnoses indicated that there were certain patient profiles that resulted in a much quicker accumulation of another chronic disease diagnoses, as well as relevant patient-, provider- and practice-level factors influencing this progression. These findings should be carefully assessed in further research in order to confirm whether these patterns exist in other patient populations, beyond the pan-Canadian CPCSSN EMR database. The results of this research, however, provide empirical evidence that there will not be a singular solution to the challenge of multimorbidity. As such, the international research community must continue to work collaboratively together to put the elusive "multimorbidity puzzle" together.

Chapter 7

7 Conclusion

Broadly, this thesis provided insight into the prevalence, patterns and natural progression of multimorbidity among adult PHC patients in Canada. The prevalence of multimorbidity, defined either as "two or more chronic diseases" or "three or more chronic diseases" was found to be 53.3% or 33.1% among adult PHC patients in the CPCSSN EMR database, respectively. While common combinations and permutations of multiple chronic diseases were explored by both patient age and patient sex, the findings from the computational cluster analysis suggested that patients with multimorbidity represent increasingly unique clinical profiles. This has been somewhat supported in the growing "associative multimorbidity" literature, but this research is distinct as it provides empirical evidence that multimorbidity patients are indeed unique and cannot be easily clumped together. The longitudinal CPCSSN database allowed for the exploration of the natural progression of multimorbidity over time. From this analysis, independent predictors of progressing multimorbidity were detected, particularly at the patient-level. This requires further exploration, and further delineation of relevant and modifiable risk factors. Most importantly, however, is the voice and perspective of the patients and caregivers who are living with these "unique and complex clinical profiles" of multimorbidity. The multidimensional and far-reaching impact that multimorbidity has on patient's life cannot be underestimated or underexplored. As such, the conduct of both large-scale, quantitative analyses, as presented here in this thesis, and small-scale, qualitative analyses should be encouraged and facilitated into the future. This multidisciplinary combination of research will provide the complete picture and understanding of multimorbidity – something for which we are continuing to strive towards.

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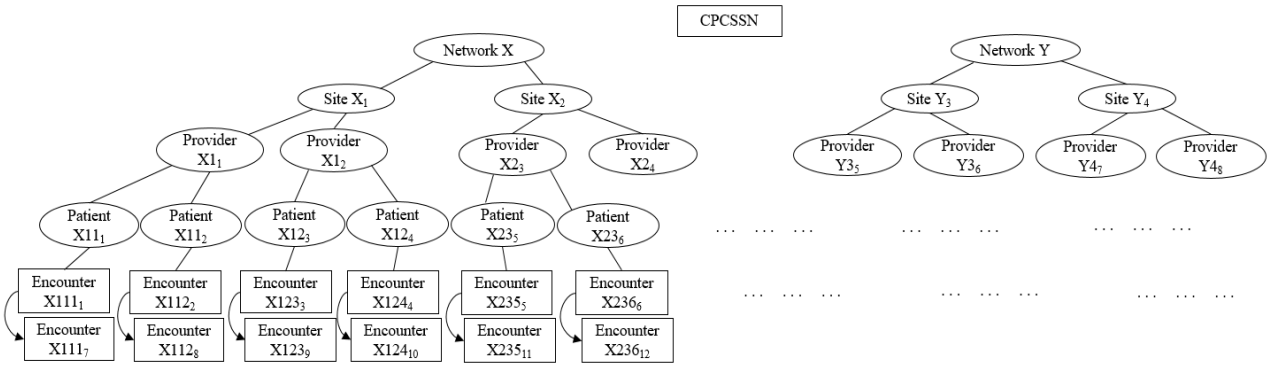
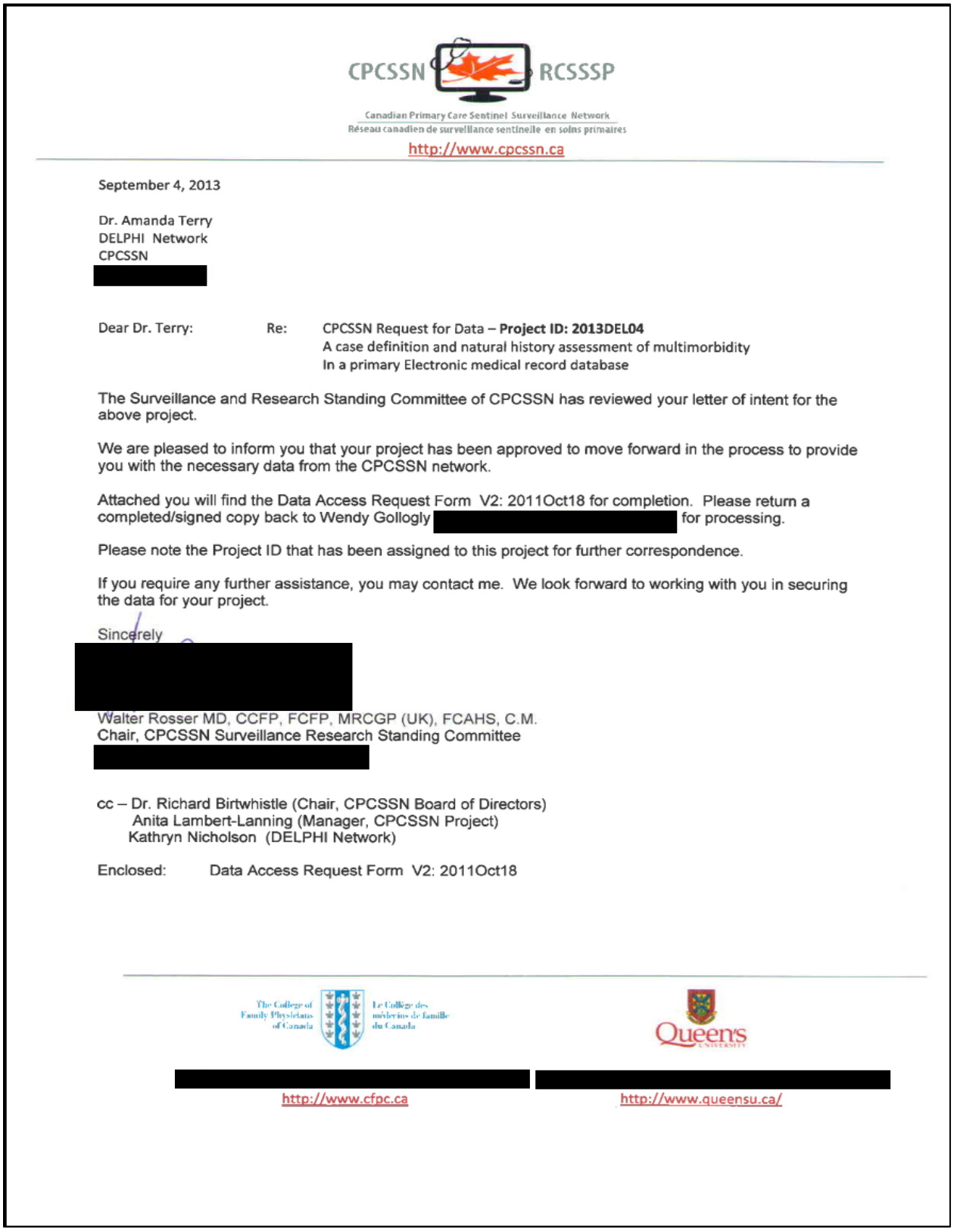
Appendices

Appendix A. Multilevel structure of the CPCSSN data and relevant CPCSSN data elements



Group Data Element	Detailed Data Elements
Network_ID	NetworkName
Practice_ID	LocationType, LocationFSA, Province, EMRName, StartDate
Provider_ID	BirthYear, Sex
Patient_ID	BirthYear, Sex, OptedOut, PatientStatus_orig, PatientStatus_calc, Occupation, HighestEducation, HousingStatus, Language, Ethnicity, DeceasedYear, ResidenceFSA, DateCreated
Encounter_ID	EncounterDate, Reason_orig, Reason_calc, EncounterType, DiagnosisText_orig, DiagnosisText_calc, DiagnosisCodeType_orig, DiagnosisCodeType_calc, DiagnosisCode_orig, DiagnosisCode_calc, DateCreated
Billing_ID	ServiceDate, ServiceCode, DiagnosisText_orig, DiagnosisText_calc, DiagnosisCodeType_orig, DiagnosisCodeType_calc, DiagnosisCode_orig, DiagnosisCode_calc, DateCreated

Appendix B. CPCSSN Letter of Permission for secondary data source access



CPCSSN RCSSSP

Canadian Primary Care Sentinel Surveillance Network
Réseau canadien de surveillance sentinelle en soins primaires

http://www.cpcssn.ca

September 4, 2013

Dr. Amanda Terry
DELPHI Network
CPCSSN
[redacted]

Dear Dr. Terry: Re: CPCSSN Request for Data – **Project ID: 2013DEL04**
A case definition and natural history assessment of multimorbidity
In a primary Electronic medical record database

The Surveillance and Research Standing Committee of CPCSSN has reviewed your letter of intent for the above project.

We are pleased to inform you that your project has been approved to move forward in the process to provide you with the necessary data from the CPCSSN network.

Attached you will find the Data Access Request Form V2: 2011Oct18 for completion. Please return a completed/signed copy back to Wendy Gollogly [redacted] for processing.

Please note the Project ID that has been assigned to this project for further correspondence.

If you require any further assistance, you may contact me. We look forward to working with you in securing the data for your project.

Sincerely

[redacted]

Walter Rosser MD, CCFP, FCFP, MRCGP (UK), FCAHS, C.M.
Chair, CPCSSN Surveillance Research Standing Committee
[redacted]

cc – Dr. Richard Birtwhistle (Chair, CPCSSN Board of Directors)
Anita Lambert-Lanning (Manager, CPCSSN Project)
Kathryn Nicholson (DELPHI Network)

Enclosed: Data Access Request Form V2: 2011Oct18

The College of Family Physicians of Canada | Le Collège des médecins de famille du Canada

Queen's University

[redacted] [redacted]

http://www.cfpc.ca http://www.queensu.ca/

Appendix C. Ethics approval notice from research ethics board (#104705)

Western Research

Research Ethics

Use of Human Participants - Initial Ethics Approval Notice

Principal Investigator: Dr. Amardeep Thind
File Number:104705
Review Level: Delegated
Protocol Title: Multimorbidity in Primary Care: Identifying and Understanding Complex Patients with Electronic Medical Records
Department & Institution: Schulich School of Medicine and Dentistry\Epidemiology & Biostatistics,Western University
Sponsor:
Ethics Approval Date: December 05, 2013 **Expiry Date:**December 31, 2016
Documents Reviewed & Approved & Documents Received for Information:

Document Name	Comments	Version Date
Western University Protocol		
Recommendations Form		2013/12/05

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced revision(s) or amendment(s) on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the University of Western Ontario Updated Approval Request Form.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

The Chair of the HSREB is Dr. Joseph Gilbert. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

[redacted]

Signature

Ethics Officer to Contact for Further Information

Erika Basile	✓ Grace Kelly	Mina Mekhail	Vikki Tran

[redacted]

This is an official document. Please retain the original in your files.

[redacted]

Appendix D. Data dictionary of original and *created* CPCSSN data elements

Data Element	Description
Cycle_ID	Name of the cycle
Network_ID	Unique identifier for each network
NetworkName	Name of CPCSSN network
Site_ID	Unique identifier for each site
Site_LocationType	Type of site practice
Site_LocationFSA	First three digits of the postal code of the site location
Site_Province	Unique two-character province name of the site location
Site_EMRName	Name of the EMR used by the participating site
Site_EMRStartDate	Date the site implemented the EMR
Provider_ID	Unique identifier for each provider in the database
Provider_BirthYear	Birth year of provider
Provider_Sex	Sex of provider
Patient_ID	Unique identifier for each patient in the database
Patient_BirthYear	Birth year of patient
Patient_Sex	Sex of patient
Patient_OptedOut	If the patient has opted out in any extraction
PatientStatus_orig	Status of patient (original)
PatientStatus_calc	CPCSSN re-coding of patient status into consistent text (data cleaning)
Patient_Occupation	Occupation of patient
Patient_HighestEducation	Highest education achieved by patient
Patient_HousingStatus	Housing status of patient
Patient_Language	Primary language of patient
Patient_Ethnicity	Ethnicity of patient
Patient_DeceasedYear	Deceased year of patient
Patient_ResidenceFSA	First three digits of the patient residential postal code
Patient_DateCreated	EMR date stamp of when the original record was created
Encounter_ID	Unique identifier for each encounter
EncounterDate	Date the encounter occurred
EncounterReason_orig	Reason for the encounter exactly as it appears in the EMR (original)
EncounterReason_calc	CPCSSN re-coding of the reason for the encounter as it appears in the EMR (data cleaning)
EncounterType	How or where the encounter occurred
DiagnosisText_orig	Diagnosis text exactly as it appears in the EMR (original)
EncounterDiagnosisText_calc	CPCSSN re-coding of the diagnosis text into consistent text (data cleaning)
EncounterDiagnosisCodeType_orig	Diagnosis code type associated with the encounter exactly as it appears in the EMR (original)
EncounterDiagnosisCodeType_calc	CPCSSN re-coding of diagnosis code type into consistent text (data cleaning)
EncounterDiagnosisCode_orig	Diagnosis code associated with the encounter exactly as it appears in the EMR (original)
EncounterDiagnosisCode_calc	CPCSSN re-coding diagnosis code into consistent text (data cleaning)
Encouner_DateCreated	EMR date stamp of when the original record was created
Billing_ID	Unique identifier for each billing entry
ServiceDate	Date the billing was performed/submitted
Billing_ServiceCode	Service code associated with the billing
BillingDiagnosisText_orig	Diagnosis text exactly as it appears in the EMR (original)

BillingDiagnosisText_calc	CPCSSN re-coding of diagnosis into consistent text (data cleaning)
BillingDiagnosisCodeType_orig	Diagnosis code type associated with the billing exactly as it appears in the EMR (original)
BillingDiagnosisCodeType_calc	CPCSSN re-coding of diagnosis code type into consistent text (data cleaning)
BillingDiagnosisCode_orig	Diagnosis code associated with the billing exactly as it appears in the EMR (original)
BillingDiagnosisCode_calc	CPCSSN re-coding of diagnosis code into consistent text (data cleaning)
Billing_DateCreated	EMR date stamp of when the original record was created
Patient_Age	*Calculated as of September 30, 2013 with the recorded Patient_BirthYear*
Residential_Location	*Re-coding based on the second character of Patient_ResidenceFSA*
Provider_Age	*Calculated as of September 30, 2013 with the recorded Provider_BirthYear*
Practice_Location	*Re-coding based on the second character of Site_LocationFSA*
Chronic_Disease	*Identified in the EMR using list of twenty chronic disease categories and associated ICD-9 disease codes*
Time_BetweenDisease	*Time elapsing (in days) between chronic disease diagnoses*
Total_ChronicDisease	*Total number of "first occurrence" chronic disease diagnoses recorded in the EMR using list of twenty chronic disease categories and associated ICD-9 disease codes*

Appendix E. Example data entries of patient-level socioeconomic characteristics

Occupation Data Entry Examples			
admin manager	engineering	machinist (self-employed)	RETAIL MANAGER
Airport attendant	Family Caregiver	manufacturing manager	Retired
assistant to disabled	financial management	multiple jobs	Revenue Canada
bank teller	FREELANCE WRITER	nanny	Roofer, full time
bookkeeper	Government analyst	Nurse	sales coordinator
Cake decorator	hairdresser	nutritionist	secretarial
Cashier	Home Care Worker	Office Work	self employed mechanic
Client Service Officer	homemaker	Owner/Operator	Social work
consulting business	HOUSECLEANER	Part-time in sales	technician
delivery driver	interior designer	Project Co-ordinator	truck driver
Director of Marketing	Lawyer	Public Health Nurse	Work, Full-time - Bookkeeper
Employed	LIBRARY ASSISTANT	Realtor	works as chef
Highest Education Data Entry Examples			
CEGEP	Professional Degree	Technical College	Unfinished studies
College	Secondary	Trade School	University
High School			
Housing Status Data Entry Examples			
Common-law spouse	Lives alone	Separated	Widow(er)
Common-law - x 8 years	Married	Single	With spouse
Divorced	New spouse - 1 year	Single - lives with mother	With spouse - since 2001
Ethnicity Data Entry Examples			
ABORIGINAL	CAMBODIAN	ENGLISH/SCOTTISH	JEWISH
AFRICAN	CANADIAN	ETHIOPIAN	KOREAN
ASIAN	CANTONESE	FILIPINO	MEXICAN
AUSTRALIAN	CAUCASIAN	FIRST NATIONS	NATIVE
BHUTAN	CHINESE	FRANCOPHONE	PAKISTAN
BLACK/CAUCASIAN	CHINESE/ CAUCASIAN	FRENCH CANADIAN	PHILIPPINO
BLACK/NATIVE/SPANISH/CAUCASIAN	COLUMBIAN	GERMAN	PORTUGUESE
BRAZILIAN	CZECH	IRISH	SRI LANKAN
BURMESE	EAST INDIAN	ITALIAN	UKRANIAN
Belgian	EL SALVADOR	JAPANESE	Undetermined
Language Data Entry Examples			
English	Italian	Portuguese	Undetermined
French	Other language not specified	Some English	

Appendix F. First character of forward sortation area and corresponding province, territory or major region

Alphabetic Character	Province, Territory or Region
A	Newfoundland and Labrador
B	Nova Scotia
C	Prince Edward Island
E	New Brunswick
G	Québec East
H	Montréal
J	Québec West
K	Eastern Ontario
L	Central Ontario
M	Toronto
N	Southwestern Ontario
P	Northern Ontario
R	Manitoba
S	Saskatchewan
T	Alberta
V	British Columbia
X	Northwest Territories and Nunavut
Y	Yukon Territory

Appendix G. Complete list of chronic disease categories and corresponding International Classification of Disease, 9th Revision (ICD-9) disease codes, for the identification of adult primary health care patients with multimorbidity*

ICD-9 Code	ICD-9 Description
1. Hypertension	
401-405	Hypertensive disease
401	Essential hypertension
401	Malignant essential hypertension
401.1	Benign essential hypertension
401.9	Unspecified essential hypertension
405	Secondary hypertension
405	Malignant secondary hypertension
405.01	Malignant renovascular hypertension
405.09	Other malignant secondary hypertension
405.1	Benign secondary hypertension
405.11	Benign renovascular hypertension
405.19	Other benign secondary hypertension
405.9	Unspecified secondary hypertension
405.91	Unspecified renovascular hypertension
405.99	Other unspecified secondary hypertension
2. Obesity	
278	Overweight and obesity
278	Obesity, unspecified
278.01	Morbid obesity
≥30	Body mass index
3. Diabetes – 51 ICD-9 Codes	
250	Diabetes mellitus
250	Diabetes mellitus without mention of complication
250	Diabetes mellitus without mention of complication, type II or unspecified type, not stated as uncontrolled
250.01	Diabetes mellitus without mention of complication, type I [juvenile type], not stated as uncontrolled
250.02	Diabetes mellitus without mention of complication, type II or unspecified type, uncontrolled
250.03	Diabetes mellitus without mention of complication, type I [juvenile type], uncontrolled
250.1	Diabetes with ketoacidosis
250.1	Diabetes with ketoacidosis, type II or unspecified type, not stated as uncontrolled
250.11	Diabetes with ketoacidosis, type I [juvenile type], not stated as uncontrolled
250.12	Diabetes with ketoacidosis, type II or unspecified type, uncontrolled
250.13	Diabetes with ketoacidosis, type I [juvenile type], uncontrolled
250.2	Diabetes with hyperosmolarity
250.2	Diabetes with hyperosmolarity, type II or unspecified type, not stated as uncontrolled
250.21	Diabetes with hyperosmolarity, type I [juvenile type], not stated as uncontrolled
250.22	Diabetes with hyperosmolarity, type II or unspecified type, uncontrolled
250.23	Diabetes with hyperosmolarity, type I [juvenile type], uncontrolled

250.3 Diabetes with other coma
250.3 Diabetes with other coma, type II or unspecified type, not stated as uncontrolled
250.31 Diabetes with other coma, type I [juvenile type], not stated as uncontrolled
250.32 Diabetes with other coma, type II or unspecified type, uncontrolled
250.33 Diabetes with other coma, type I [juvenile type], uncontrolled
250.4 Diabetes with renal manifestations
250.4 Diabetes with renal manifestations, type II or unspecified type, not stated as uncontrolled
250.41 Diabetes with renal manifestations, type I [juvenile type], not stated as uncontrolled
250.42 Diabetes with renal manifestations, type II or unspecified type, uncontrolled
250.43 Diabetes with renal manifestations, type I [juvenile type], uncontrolled
250.5 Diabetes with ophthalmic manifestations
250.5 Diabetes with ophthalmic manifestations, type II or unspecified type, not stated as uncontrolled
250.51 Diabetes with ophthalmic manifestations, type I [juvenile type], not stated as uncontrolled
250.52 Diabetes with ophthalmic manifestations, type II or unspecified type, uncontrolled
250.53 Diabetes with ophthalmic manifestations, type I [juvenile type], uncontrolled
250.6 Diabetes with neurological manifestations
250.6 Diabetes with neurological manifestations, type II or unspecified type, not stated as uncontrolled
250.61 Diabetes with neurological manifestations, type I [juvenile type], not stated as uncontrolled
250.62 Diabetes with neurological manifestations, type II or unspecified type, uncontrolled
250.63 Diabetes with neurological manifestations, type I [juvenile type], uncontrolled
250.7 Diabetes with peripheral circulatory disorders
250.7 Diabetes with peripheral circulatory disorders, type II or unspecified type, not stated as uncontrolled
250.71 Diabetes with peripheral circulatory disorders, type I [juvenile type], not stated as uncontrolled
250.72 Diabetes with peripheral circulatory disorders, type II or unspecified type, uncontrolled
250.73 Diabetes with peripheral circulatory disorders, type I [juvenile type], uncontrolled
250.8 Diabetes with other specified manifestations
250.8 Diabetes with other specified manifestations, type II or unspecified type, not stated as uncontrolled
250.81 Diabetes with other specified manifestations, type I [juvenile type], not stated as uncontrolled
250.82 Diabetes with other specified manifestations, type II or unspecified type, uncontrolled
250.83 Diabetes with other specified manifestations, type I [juvenile type], uncontrolled
250.9 Diabetes with unspecified complication
250.9 Diabetes with unspecified complication, type II or unspecified type, not stated as uncontrolled
250.91 Diabetes with unspecified complication, type I [juvenile type], not stated as uncontrolled
250.92 Diabetes with unspecified complication, type II or unspecified type, uncontrolled
250.93 Diabetes with unspecified complication, type I [juvenile type], uncontrolled

4. Chronic Obstructive Pulmonary Disease or Asthma

491 Chronic bronchitis
491 Simple chronic bronchitis
491.1 Mucopurulent chronic bronchitis
491.2 Obstructive chronic bronchitis
491.2 Obstructive chronic bronchitis without exacerbation
491.21 Obstructive chronic bronchitis with (acute) exacerbation
491.22 Obstructive chronic bronchitis with acute bronchitis
491.8 Other chronic bronchitis
491.9 Unspecified chronic bronchitis
492 Emphysema
492 Emphysematous bleb
492.8 Other emphysema

493	Asthma
493	Extrinsic asthma
493	Extrinsic asthma, unspecified
493.01	Extrinsic asthma with status asthmaticus
493.02	Extrinsic asthma with (acute) exacerbation
493.1	Intrinsic asthma
493.1	Intrinsic asthma, unspecified
493.11	Intrinsic asthma with status asthmaticus
493.12	Intrinsic asthma with (acute) exacerbation
493.2	Chronic obstructive asthma
493.2	Chronic obstructive asthma, unspecified
493.21	Chronic obstructive asthma with status asthmaticus
493.22	Chronic obstructive asthma with (acute) exacerbation
493.8	Other forms of asthma
493.81	Exercise induced bronchospasm
493.82	Cough variant asthma
493.9	Asthma unspecified
493.9	Asthma, unspecified type, unspecified
493.91	Asthma, unspecified type, with status asthmaticus
493.92	Asthma, unspecified type, with (acute) exacerbation
496	Chronic airway obstruction, not elsewhere classified

5. Hyperlipidemia

272	Disorders of lipoid metabolism
272	Pure hypercholesterolemia
272.1	Pure hyperglyceridemia
272.2	Mixed hyperlipidemia
272.3	Hyperchylomicronemia
272.4	Other and unspecified hyperlipidemia

6. Cancer

140-239	Neoplasms
140-149	Malignant Neoplasm Of Lip, Oral Cavity and Pharynx
150-159	Malignant Neoplasm Of Digestive Organs And Peritoneum
160-165	Malignant Neoplasm Of Respiratory And Intrathoracic Organs
170-176	Malignant Neoplasm Of Bone, Connective Tissue, Skin and Breast
179-189	Malignant Neoplasm Of Genitourinary Organs
190-199	Malignant Neoplasm Of Other And Unspecified Sites
200-209	Malignant Neoplasm Of Lymphatic And Hematopoietic Tissue

7. Cardiovascular Disease

412	Old myocardial infarction
413	Angina pectoris
413	Angina decubitus
413.1	Prinzmetal angina
413.2	Other and unspecified angina pectoris
440-449	Diseases Of Arteries, Arterioles and Capillaries
427	Cardiac dysrhythmias
427.3	Atrial fibrillation and flutter

427.31	Atrial fibrillation
417.32	Atrial flutter

8. Heart Failure

428	Heart failure
394	Diseases of mitral valve
394	Mitral stenosis
394.1	Rheumatic mitral insufficiency
394.2	Mitral stenosis with insufficiency
395	Diseases of aortic valve
395.1	Rheumatic aortic insufficiency
395.2	Rheumatic aortic stenosis with insufficiency
395.9	Other and unspecified rheumatic aortic diseases

9. Anxiety or Depression

296	Episodic mood disorders
296.2	Major depressive disorder single episode
296.2	Major depressive affective disorder, single episode, unspecified
296.21	Major depressive affective disorder, single episode, mild
296.22	Major depressive affective disorder, single episode, moderate
296.23	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior
296.24	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior
296.25	Major depressive affective disorder, single episode, in partial or unspecified remission
296.26	Major depressive affective disorder, single episode, in full remission
296.3	Major depressive disorder recurrent episode
296.3	Major depressive affective disorder, recurrent episode, unspecified
296.31	Major depressive affective disorder, recurrent episode, mild
296.32	Major depressive affective disorder, recurrent episode, moderate
296.33	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior
296.34	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior
296.35	Major depressive affective disorder, recurrent episode, in partial or unspecified remission
296.36	Major depressive affective disorder, recurrent episode, in full remission
300	Anxiety, dissociative and somatoform disorders
300	Anxiety states
300	Anxiety state, unspecified
300.01	Panic disorder without agoraphobia
300.02	Generalized anxiety disorder
300.09	Other anxiety states

10. Osteoarthritis or Rheumatoid Arthritis

714	Rheumatoid arthritis and other inflammatory polyarthropathies
714	Rheumatoid arthritis
714.1	Felty's syndrome
714.2	Other rheumatoid arthritis with visceral or systemic involvement
714.3	Juvenile chronic polyarthritis
715	Osteoarthrosis and allied disorders
715	Osteoarthrosis generalized
715.1	Osteoarthrosis localized primary
715.2	Osteoarthrosis localized secondary

715.3	Osteoarthrosis localized not specified whether primary or secondary
715.8	Osteoarthrosis involving or with mention of more than one site but not specified as generalized
715.9	Osteoarthrosis unspecified whether generalized or localized

11. Stroke or Transient Ischemic Attack

434	Occlusion of cerebral arteries
434	Cerebral thrombosis
434	Cerebral thrombosis without mention of cerebral infarction
434.01	Cerebral thrombosis with cerebral infarction
434.1	Cerebral embolism
434.1	Cerebral embolism without mention of cerebral infarction
434.11	Cerebral embolism with cerebral infarction
433.9	Cerebral artery occlusion unspecified
434.9	Cerebral artery occlusion, unspecified without mention of cerebral infarction
434.91	Cerebral artery occlusion, unspecified with cerebral infarction
435	Transient cerebral ischemia
435	Basilar artery syndrome
435.1	Vertebral artery syndrome
435.2	Subclavian steal syndrome
435.3	Vertebrobasilar artery syndrome
435.8	Other specified transient cerebral ischemias
435.9	Unspecified transient cerebral ischemia

12. Thyroid Problem

240-246	Disorders Of Thyroid Gland
240	Goiter, simple not otherwise specified
241	Nontoxic nodular goiter
242	Thyrotoxicosis
243	Congenital hypothyroidism
244	Acquired hypothyroidism
245	Thyroiditis
246	Other disorders of the thyroid

13. Kidney Disease or Failure

585	Chronic kidney disease
585.1	Chronic kidney disease, Stage I
585.2	Chronic kidney disease, Stage II (mild)
585.3	Chronic kidney disease, Stage III (moderate)
585.4	Chronic kidney disease, Stage IV (severe)
585.5	Chronic kidney disease, Stage V
585.6	End stage renal disease
585.9	Chronic kidney disease, unspecified

14. Osteoporosis

733	Osteoporosis
733	Osteoporosis, unspecified
733.01	Senile osteoporosis
733.02	Idiopathic osteoporosis
733.03	Disuse osteoporosis

733.09 Other osteoporosis

15. Dementia

290 Dementias
290 Senile dementia, uncomplicated
290.1 Presenile dementia
290.1 Presenile dementia, uncomplicated
290.11 Presenile dementia with delirium
290.12 Presenile dementia with delusional features
290.13 Presenile dementia with depressive features
290.2 Senile dementia with delusional or depressive features
290.2 Senile dementia with delusional features
290.21 Senile dementia with depressive features
290.3 Senile dementia with delirium
290.4 Vascular dementia
294 Persistent mental disorders due to conditions classified elsewhere
294.1 Dementia in conditions classified elsewhere
294.2 Dementia, unspecified

16. Musculoskeletal Problem

723 Other disorders of cervical region
723.1 Cervicalgia
724 Other and unspecified disorders of back
724.1 Pain in thoracic spine
724.2 Lumbago
724.3 Sciatica
724.4 Thoracic or lumbosacral neuritis or radiculitis, unspecified
724.5 Backache, unspecified
725 Polymyalgia rheumatica
726 Peripheral enthesopathies and allied syndromes
726 Adhesive capsulitis of shoulder
726.1 Rotator cuff syndrome of shoulder and allied disorders
726.2 Other affections of shoulder region, not elsewhere classified
726.3 Enthesopathy of elbow region
726.3 Enthesopathy of elbow, unspecified
726.31 Medial epicondylitis
726.32 Lateral epicondylitis
726.33 Olecranon bursitis
726.39 Other enthesopathy of elbow region
726.4 Enthesopathy of wrist and carpus
726.5 Enthesopathy of hip region
726.6 Enthesopathy of knee
726.6 Enthesopathy of knee, unspecified
726.61 Pes anserinus tendinitis or bursitis
726.62 Tibial collateral ligament bursitis
726.63 Fibular collateral ligament bursitis
726.64 Patellar tendinitis
726.65 Prepatellar bursitis
726.69 Other enthesopathy of knee

726.7	Enthesopathy of ankle and tarsus
726.7	Enthesopathy of ankle and tarsus, unspecified
726.71	Achilles bursitis or tendinitis
726.72	Tibialis tendinitis
726.73	Calcaneal spur
726.79	Other enthesopathy of ankle and tarsus
726.9	Unspecified enthesopathy
726.9	Enthesopathy of unspecified site
726.91	Exostosis of unspecified site
727	Other disorders of synovium tendon and bursa
727	Synovitis and tenosynovitis
727	Synovitis and tenosynovitis, unspecified
727.01	Synovitis and tenosynovitis in diseases classified elsewhere
727.03	Trigger finger (acquired)
727.04	Radial styloid tenosynovitis
727.05	Other tenosynovitis of hand and wrist
727.06	Tenosynovitis of foot and ankle
727.09	Other synovitis and tenosynovitis
727.2	Specific bursitides often of occupational origin
727.3	Other bursitis
729	Other disorders of soft tissues
729	Rheumatism, unspecified and fibrositis
729.1	Myalgia and myositis, unspecified
729.2	Neuralgia, neuritis and radiculitis, unspecified
729.4	Fasciitis, unspecified
729.5	Pain in limb

17. Stomach Problem

530	Diseases of esophagus
530.81	Esophageal reflux
531	Gastric ulcer
531.4	Chronic or unspecified gastric ulcer with hemorrhage
531.4	Chronic or unspecified gastric ulcer with hemorrhage, without mention of obstruction
531.41	Chronic or unspecified gastric ulcer with hemorrhage, with obstruction
531.5	Chronic or unspecified gastric ulcer with perforation
531.5	Chronic or unspecified gastric ulcer with perforation, without mention of obstruction
531.51	Chronic or unspecified gastric ulcer with perforation, with obstruction
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation
531.6	Chronic or unspecified gastric ulcer with hemorrhage and perforation, without mention of obstruction
531.61	Chronic or unspecified gastric ulcer with hemorrhage and perforation, with obstruction
531.7	Chronic gastric ulcer without mention of hemorrhage or perforation
531.7	Chronic gastric ulcer without mention of hemorrhage or perforation, without mention of obstruction
531.71	Chronic gastric ulcer without mention of hemorrhage or perforation, with obstruction
531.9	Gastric ulcer unspecified as acute or chronic without mention of hemorrhage or perforation
531.9	Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, without mention of obstruction
531.91	Gastric ulcer, unspecified as acute or chronic, without mention of hemorrhage or perforation, with obstruction

18. Colon Problem

555	Regional enteritis
555.1	Regional enteritis of large intestine
555.2	Regional enteritis of small intestine with large intestine
555.9	Regional enteritis of unspecified site
556	Ulcerative enterocolitis
556	Ulcerative (chronic) enterocolitis
556.4	Pseudopolyposis of colon
556.5	Left-sided ulcerative (chronic) colitis
556.6	Universal ulcerative (chronic) colitis
556.8	Other ulcerative colitis
556.9	Ulcerative colitis, unspecified
564	Functional digestive disorders not elsewhere classified
564.1	Irritable bowel syndrome

19. Liver Disease

571	Chronic liver disease and cirrhosis
571	Alcoholic fatty liver
571.1	Acute alcoholic hepatitis
571.2	Alcoholic cirrhosis of liver
571.3	Alcoholic liver damage, unspecified
571.4	Chronic hepatitis
571.4	Chronic hepatitis, unspecified
571.41	Chronic persistent hepatitis
571.42	Autoimmune hepatitis
571.49	Other chronic hepatitis
571.5	Cirrhosis of liver without mention of alcohol
571.6	Biliary cirrhosis
571.8	Other chronic nonalcoholic liver disease
571.9	Unspecified chronic liver disease without mention of alcohol

20. Urinary Problem

593	Other disorders of kidney and ureter
593.3	Stricture or kinking of ureter
593.4	Other ureteric obstruction
593.5	Hydroureter
593.7	Vesicoureteral reflux
593.7	Vesicoureteral reflux unspecified or without reflux nephropathy
593.71	Vesicoureteral reflux with reflux nephropathy, unilateral
593.72	Vesicoureteral reflux with reflux nephropathy, bilateral
593.73	Other vesicoureteral reflux with reflux nephropathy NOS
593.8	Other specified disorders of kidney and ureter
593.82	Ureteral fistula
593.89	Other specified disorders of kidney and ureter
593.9	Unspecified disorder of kidney and ureter
595	Cystitis
595.1	Chronic interstitial cystitis
595.2	Other chronic cystitis
595.9	Cystitis, unspecified

597	Urethritis not sexually transmitted and urethral syndrome
597.8	Urethritis, unspecified
597.81	Urethral syndrome NOS
597.82	Other urethritis
600	Hyperplasia of prostate
601	Inflammatory diseases of prostate
601.1	Chronic prostatitis
601.3	Prostatocystitis
601.8	Other specified inflammatory diseases of prostate
601.9	Prostatitis, unspecified
602	Other disorders of prostate
602	Calculus of prostate
602.1	Congestion or hemorrhage of prostate
602.2	Atrophy of prostate
602.3	Dysplasia of prostate
602.8	Other specified disorders of prostate
602.9	Unspecified disorder of prostate

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Appendix H. Multimorbidity Cluster Analysis Toolkit

Multimorbidity Cluster Analysis Toolkit

Background

In examining the burden of multimorbidity, which is the co-occurrence of multiple health issues within an individual, previous literature has focused on the descriptive counting of singular diseases and the link between non-random clusters of diseases (Garin et al., 2014; Prados-Torres et al., 2012). When examining clusters of diseases, the majority of research has been limited in reporting pairs or triplets of chronic disease occurrences. However, the analysis of cumulative interactions and the complete clustering that is occurring within a cohort will help lead to a more nuanced understanding of the complexity and uniqueness of individuals living with multimorbidity.

A computational cluster analysis can be used to explore and detect the distinct clinical profiles that exist within a sample of participants or patients in a research project. While the operationalization of multimorbidity can vary in research projects due to the lack of a gold standard measure, research has indicated that at least 12 chronic diseases should be included to capture the burden of multimorbidity (Fortin et al., 2012). As such, detecting all possible combinations (that is, unordered clusters) and permutations (that is, ordered clusters) in a dataset can become exponentially difficult. However, there is a need to identify these diverse patients and to understand how health outcomes might be impacted based on cluster type.

The Multimorbidity Cluster Analysis Tool (herein referred to as: Tool) and the accompanying Multimorbidity Cluster Analysis Toolkit (herein referred to as: Toolkit) have been created to allow researchers to identify distinct clusters or clinical profiles that exist within a sample of participants or patients living with multimorbidity. This computational program can be adapted

for research projects that utilize varying data sources, diagnostic or disease-reporting systems, multimorbidity measurements, sample sizes and research settings. Its intent is to facilitate a consistent approach to identifying subgroups of participants or patients who are living with multimorbidity, based on cluster type and cluster sequence. This information is driven by the data and the corresponding results should be assessed carefully. While this information can be a helpful resource for research, clinical care and health policy decisions, the results should be interpreted within the appropriate context. Interpretation of these should incorporate both clinical and patient-centered insight.

Development Of This Tool & Toolkit

The Tool and Toolkit was developed by a research team at Western University from the Department of Epidemiology & Biostatistics and the Department of Computer Science. The computational program was developed and prototyped using the electronic medical record (EMR) data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) database. This database is based at Queen's University and is funded by the Public Health Agency of Canada under a contribution agreement with the College of Family Physicians of Canada. The views expressed herein do not necessarily represent the views of the Public Health Agency of Canada or the College of Family Physicians of Canada.

The Tool and Toolkit is available for use by any academic researchers who are interested in exploring the nuanced characteristics of participants or patients living with multimorbidity. When used in research projects, the authors request that appropriate acknowledgement (below) is made in any publications or presentations.

Bauer M & Nicholson K. Multimorbidity Cluster Analysis Tool & Toolkit. 2016.

Who Should Use This Tool & Toolkit?

Once again, the Tool and Toolkit is available for use by any academic researchers who are interested in exploring the nuanced characteristics of participants or patients living with multimorbidity. As noted, the computational program can be adapted to the methodological elements of the research project. These variations include: 1) type of data (e.g., large secondary

datasets of electronic information; small primary datasets of self-reported information); 2) type of chronic disease information (e.g., ICD-10 Codes; ICD-9 Codes; ICPC-2 Codes; SNOMED CT Codes; Read Codes; self-reported diagnoses); 3) multimorbidity measurements (e.g., operationalization using 12, 20 or 100 chronic disease diagnoses or chronic disease categories); 4) sample sizes (e.g., from 2 to approximately 150,000 individual records from participants or patients); and 5) research settings (e.g., primary health care; administrative; community-dwelling).

The computational program will identify all existing, and mutually exclusive, combinations and permutations within the dataset. A description of each concept is included below.

An example of an unordered cluster or combination of multiple chronic diseases would be those individuals (participants or patients) who have been diagnosed or have self-reported the same three chronic diseases (e.g., obesity, hypertension, cancer), but these diseases did not occur in the same sequence between the individuals. For example, some individuals may have been diagnosed with hypertension, then cancer and then obesity. In comparison, other individuals may have been diagnosed with cancer, then obesity and then hypertension. These individuals would still be clustered within the same combination.

An example of an ordered cluster or permutation of multiple chronic diseases would be those individuals (participants or patients) who have been diagnosed or have self-reported the same three chronic diseases (e.g., obesity, hypertension, cancer), and these diseases did occur in the same sequence between the individuals. For example, all individuals who may have been diagnosed with hypertension, then cancer and then obesity would be clustered within the same permutation. In comparison, those individuals who were diagnosed with cancer, then obesity and then hypertension would be clustered within the same permutation.

This computational program will conduct an individual-level categorization to determine the frequency and type of mutually exclusive clusters of diseases (that is, combinations and permutations) among a sample of individuals with multimorbidity. This analysis could also be tailored to exploring the burden of multimorbidity among a specific subset of participants or

patients, such as among a cohort of individuals who are all living with diabetes or depression. In these analyses, the data input file will include only those individuals with the main chronic disease of interest, and as such, these results will create output that is more in accordance with the concept of co-morbidity. The concept of multimorbidity ensures that no one chronic disease diagnoses takes precedence or focus over any other co-occurring disease within an individual. As such, each chronic disease is of equal importance in the conceptualization and analysis of the data. Importantly, however, the results that are created by the computational program do not indicate any causal link between the diseases.

What Does This Tool & Toolkit Contain?

As a companion to the Multimorbidity Cluster Analysis Tool, this Toolkit contains the following items: 1) summary of the background, development and use of the Tool; 2) summary of the process of creating both the input and output files for the Tool; and 3) frequently asked questions. The Multimorbidity Cluster Analysis Tool (which consists of JAVA code and an executable file) has been developed and tested to support up to 150,000 individual records and up to 100 disease diagnoses or disease categories. The basic setup of the input data file was designed to allow for reasonable adaptability to methodological differences between research projects. The time that elapses between occurrences of another chronic disease can also be explored using this Tool, if the data are available within the research project.

How Should This Tool & Toolkit Be Used?

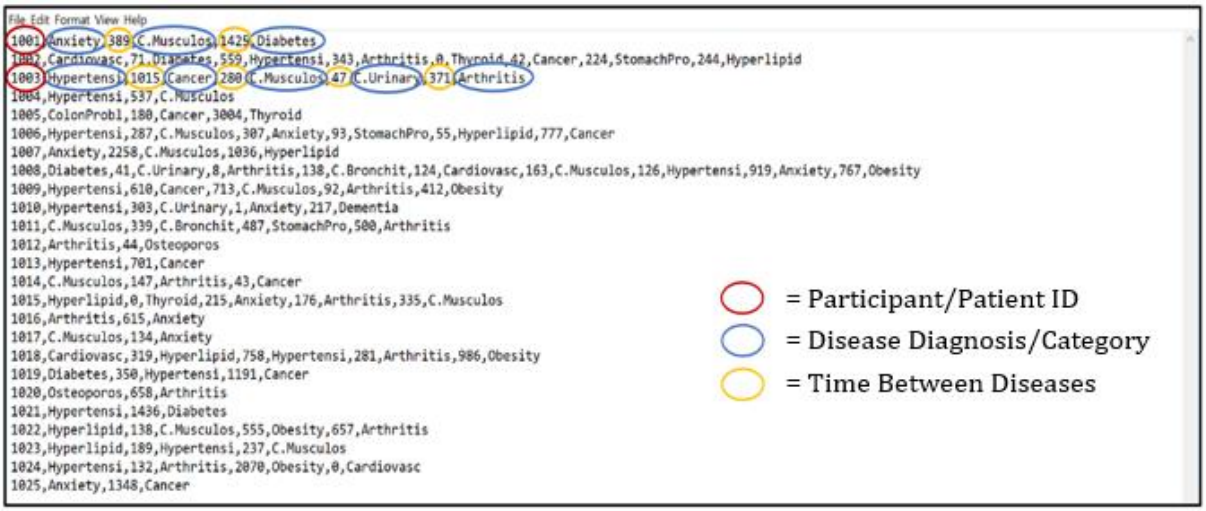
The process of using this Tool is outlined below in two multi-part steps. Step One describes how to create the required structure of the input data file and Step Two describes how to run the computational program that will create the output data files. Finally, although the purpose of the Multimorbidity Cluster Analysis Tool was developed (and will be explained) with a focus on multiple chronic diseases, the same approach could be applied using multiple disease symptoms or multiple acute diseases.

Step One

1. Unique Participant/Patient Identifier

- A unique identifier should be created for each participant or patient within the input data file (herein referred to as: ID). This ID can be maintained from the original study database (e.g., 12345, 12346) or can be created as a new unique identifier in the input file (e.g., 1, 2, 3).
- The unique ID for each participant or patient should begin each new line. This will be followed by the individual's corresponding chronic disease and the time elapsing between each occurrence (if applicable). Only one unique ID should be included on each line, and the diagnoses and time variables should be included on the same line and correspond directly to each ID.
- This structure forms the basis of the input data file. This file can be created in a data management program (e.g., SAS, Stata, Excel) and it must then be saved as or exported as a ".txt (comma separated values)" file.
- After the input data file has been saved, it is encouraged that the file is then opened and inspected to ensure for appropriate structure and layout (displayed in Figure 1).

Figure 1: Example Input Data File



2. Chronic Disease Diagnosis/ Disease Category

- The chronic disease diagnoses or chronic disease category (herein referred to as: Disease) that is included in the definition of multimorbidity should be created and finalized prior to creating the input data file. All relevant ICD-10 codes, Read codes or

self-reported diseases should be identified to identify those individuals living with multimorbidity. For example, the list of codes or self-reported diseases that constitute an occurrence of "diabetes" or "anxiety" should be applied to the dataset.

- The name of the diagnosis or category can be maintained from the original study, but only up to a maximum of ten characters (e.g., anxiety, cancer, Hypertensi). As such, the research team can decide to pre-emptively shorten the name of the diagnosis or category before running the computational program. It is important that the identification and naming of each chronic disease is maintained throughout the input data file to ensure appropriate interpretation of the output data files, where the same names will be used.

3. Time Between Chronic Diseases

- If available within the original database, the time elapsing between each date of chronic disease (herein referred to as: Time) should be calculated (e.g., in whole days, in whole years) and included in the input data file. The accuracy of these dates should be assessed, and biases should be acknowledged if necessary.
- Typically, the first date of chronic disease occurrence should be used in the calculation (to capture the incident chronic disease occurrence) and the resulting time value must be rounded to the nearest whole number.
- The time elapsing between individual chronic disease diagnoses can be calculated in the original database by the following equation: [Date of Diagnosis 2] – [Date of Diagnosis 1]. The same calculation should be used to determine the time elapsing between each chronic disease occurrence.
- It is important to structure the input data file as follows:

ID, Disease 1, Time 1, Disease 2, Time 2, Disease 3, Time 3, …

Where Time 1 = Time (whole number) elapsing between Disease 2 and Disease 1

Time 2 = Time (whole number) elapsing between Disease 3 and Disease 2

Time 3 = Time (whole number) elapsing between Disease 4 and Disease 3

Step One Summary

- The input data file should consist of the following information (separated by commas):

ID, Disease 1, Time 1, Disease 2, Time 2, Disease 3, Time 3, …

- The input data can be prepared in a data management program (e.g., SAS, Stata, Excel) and should be saved as or exported as a ".txt (comma separated values)" file for use in the computational program.
- This file should be named to be easily identifiable for use in the Multimorbidity Cluster Analysis Tool (e.g., mmpatients.txt).
- Finally, a new folder should be created to hold both the .txt input data file and the Multimorbidity Cluster Analysis Tool computational program (which will be accessed from the internet in Step Two).

Step Two

1. Running Computational Program

- Once the final input data file has been prepared and saved as a .txt file, the Multimorbidity Cluster Analysis Tool can now be utilized. Both the Tool and Toolkit are accessible from www.csd.uwo.ca/faculty/bauer/ under the link called "Multimorbidity Toolkit" (located to the left on the webpage).
- To download the program, click on "mm cluster tool". When asked to save the program, select "Yes". The program will download onto the computer system and is labelled as "mm cluster tool.jar". This .jar program should be saved and moved into the same folder as the final input data file that was previously created and saved.

➢ A JAVA runtime environment is required on the system. If the "mm cluster tool.jar" does not run, a JAVA runtime environment is needed. A JAVA runtime environment can be downloaded online. To download, select the version that is required for the system (e.g., Windows x86) and install this JAVA runtime environment.

- To run the Multimorbidity Cluster Analysis Tool, double click on the saved "mm cluster tool.jar" file. The program will first prompt for the input data file using an "Open" box. Select the appropriate input data file and select "Open".
- The program will produce a sequence of display messages, which will inform the user of completed steps (e.g., Reading from file; Number of records processed; Number of permutations/combinations found; Writing permutations to file; Completed writing permutations; Writing combinations to file; Completed writing combinations; Processing completed). Select "OK" for each step, as program waits for user response.

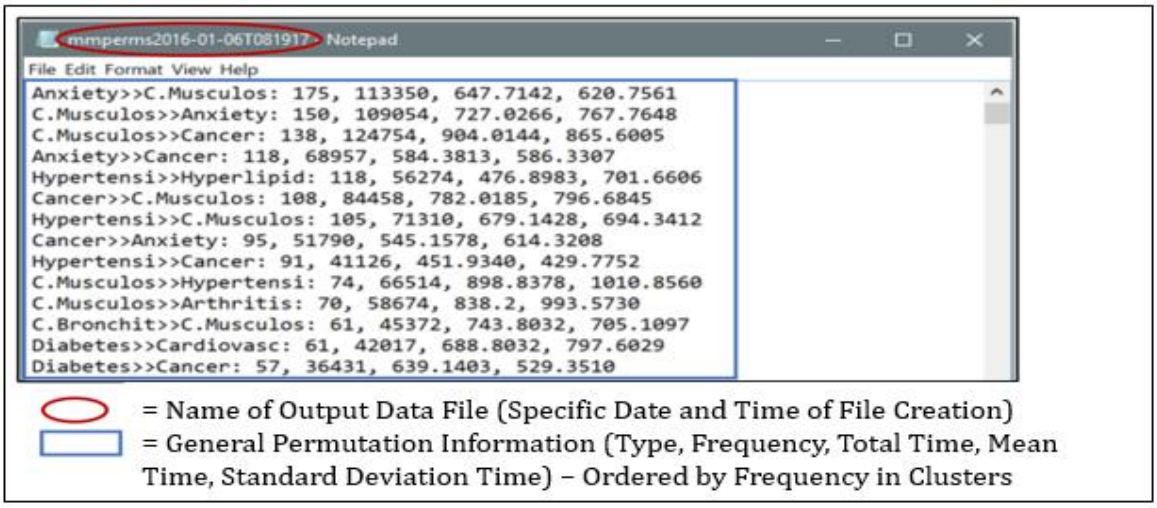
- Each output data file name indicates if it holds the permutations (mmperms.txt) or combinations (mmcombs.txt) and whether it holds detailed results (mmpermsDetails.txt or mmcombsDetails.txt). Each output file name also contains the date and time of file creation, which will be displayed below. This means that consecutive runs of the program will produce uniquely named files and previous files will not be overwritten.

2. Output Data Files

- After running through all completed steps, the program will automatically save the output data files (as .txt files) in the same folder as the .jar program and input data file.
- A total of four output files will be created and each are described further below. Example output data files are also included below.

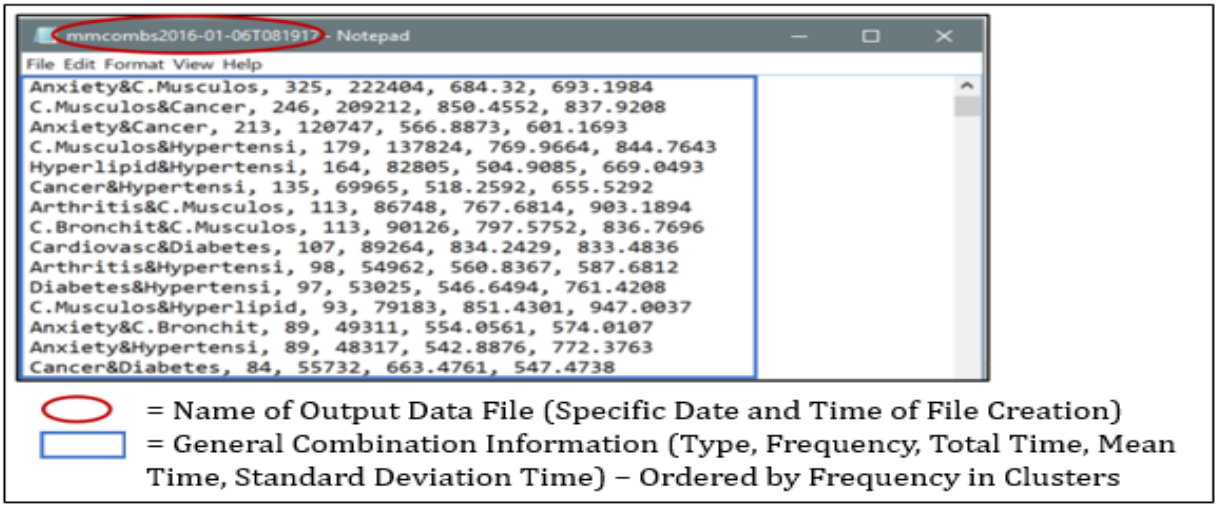
1) The "mmpermsDATETIME.txt" output data file contains all permutations (ordered clusters) of diagnoses or categories. The output is a sort list of permutations, which is presented in order from most frequent to least frequent for each group of participants or patients with the same number of diseases (e.g., 2 diseases, 3 diseases, 4 diseases). These permutations are represented using the ">>" character, which indicates an additional disease (in that specific sequence). The format of this output file is: Disease Permutation Type, Number of Occurrences (Number of Participants/Patients), Total Time (Cumulative from First to Last Disease in Days), Mean Time (Days), Standard Deviation Time (Days). This is displayed in Figure 2.

Figure 2: Output Data File of Permutations



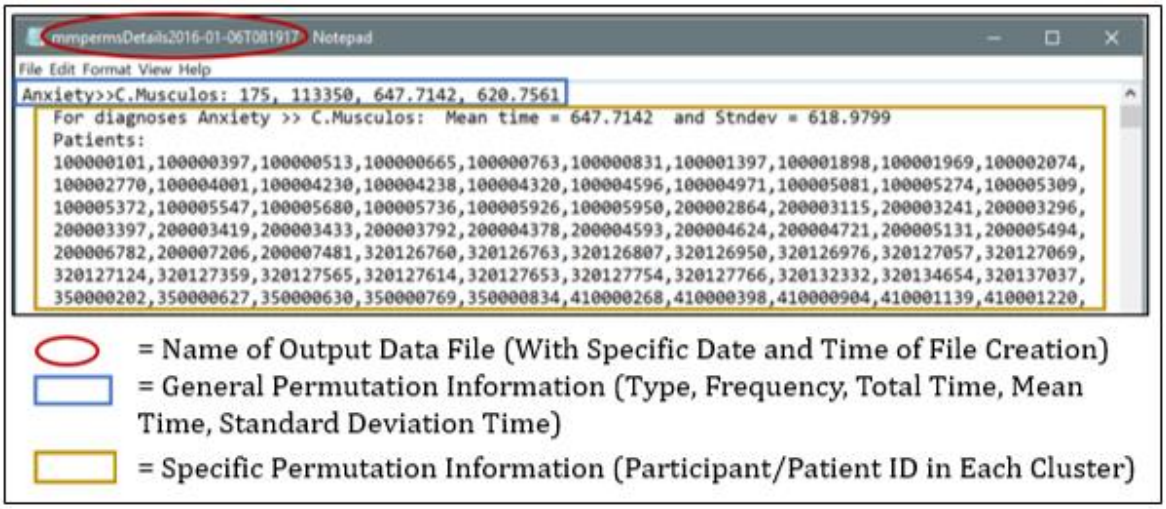
2) The “mmcombsDATETIME.txt” output data file contains all combinations (unordered clusters) of diagnoses or categories. The output is a sort list of combinations, which is presented in order from most frequent to least frequent for each group of participants or patients with the same number of diseases (e.g., 2 diseases, 3 diseases, 4 diseases). These combinations are represented using the “&” character, which indicates an additional disease (regardless of specific sequence). The format of this output file is: Disease Combination Type, Number of Occurrences (Number of Participants/Patients), Total Time (Cumulative from First to Last Disease in Days), Mean Time (Days), Standard Deviation Time (Days). This is displayed in Figure 3.

Figure 3: Output Data File of Combinations



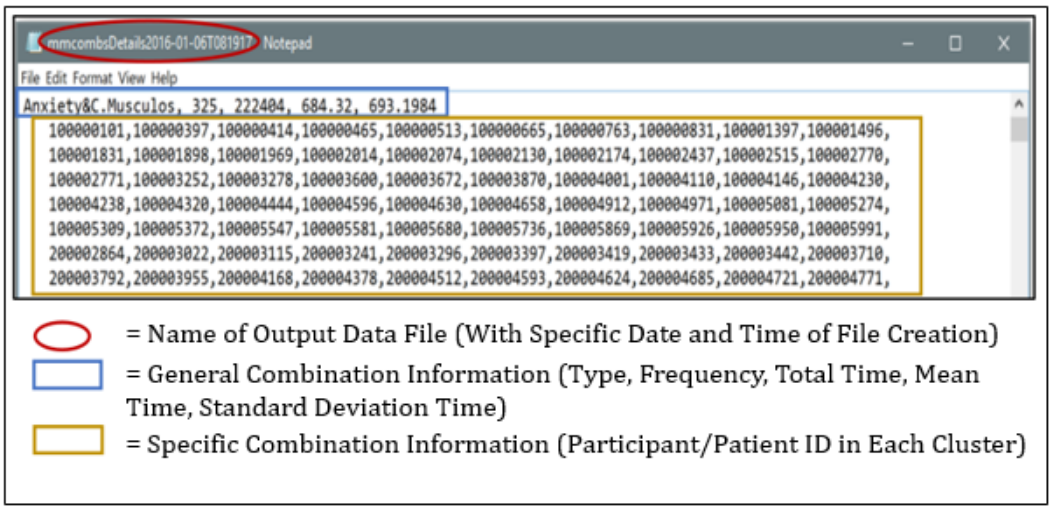
3) The “mmpermsDetailsDATETIME.txt” output data file contains the same permutations as the “mmpermsDATETIME.txt” output data file. This includes the Disease Permutation Type, Number of Occurrences (Number of Participants/Patients), Total Time (Cumulative from First to Last Disease in Days), Mean Time (Days), Standard Deviation Time (Days). To build from this information, the output data file contains further details for each permutation. More specifically, the Mean Time (Days) and Standard Deviation Time (Days) is presented for each sequence of diseases within a permutation. The IDs of individuals contained within these mutually exclusive clusters are also included in this output data file. This is displayed in Figure 4.

Figure 4: Output Data File of Permutation Details



4) The "mmcombsDetailsDATETIME.txt" output data file contains the same combinations as the "mmcombsDATETIME.txt" output data file. This includes the Disease Combination Type, Number of Occurrences (Number of Participants/Patients), Total Time (Cumulative from First to Last Disease in Days), Mean Time (Days), Standard Deviation Time (Days). To build from this information, the output data file contains further details for each combination. More specifically, the Mean Time (Days) and Standard Deviation Time (Days) is presented for each sequence of diseases within a combination. The IDs of individuals contained within these mutually exclusive clusters are also included in this output data file. This is displayed in Figure 5.

Figure 5: Output Data File of Permutation Details



Step Two Summary

- The Multimorbidity Cluster Analysis Tool and Toolkit can be accessed from www.csd.uwo.ca/faculty/bauer/ under the link called "Multimorbidity Toolkit". To run the computational program, the "mm cluster tool.jar" and a JAVA runtime environment must be downloaded onto the computer.
- After running through the complete computational program, a total of four output data files are created and automatically saved as .txt files within the same folder as the Tool and the input data file. If the program does not run properly, the process of addressing any issues in the input data file is outlined in Frequently Asked Questions.
- These files are named using unique titles based on the date and time of data analysis, which means that consecutive runs of the program will produce uniquely named files and previous files will not be overwritten.
- Finally, these four output data files capture both the general and specific information of the combinations (that is, unordered clusters) and the permutations (that is, ordered clusters) that exist among the participants or patients within the input data file. These output files can be then be imported into data management programs (e.g., Excel) for further processing.

Frequently Asked Questions

Question: Do I have to abbreviate the chronic disease diagnosis/chronic disease category names myself?

Answer: You may choose to shorten the condition/disease category names yourself or the program will automatically shorten the category names to ten characters.

Question: I cannot find the "mm cluster tool.jar" file on my computer after accessing and downloading the Tool online. Where is it located on my computer?

Answer: After accessing the Tool online and downloading the file to your computer, the file may automatically be placed in the "Downloads" folder or the "Desktop". You can also "Search" for the file on your computer. Once the file has been

located, the file should then be relocated into the same folder that holds the input data file.

Question: The data that I will be using to create my input data file does not contain information on the date of diagnoses, so I cannot calculate the time between diagnoses. Can I still use this Tool to determine the most frequently occurring clusters?

Answer: Yes, researchers who do not have data on the time between diagnoses can still use this Tool. In order for the computational program to run properly, however, it is important to maintain a column for the time variable between each diagnoses (space holder = 0). For example, it is important to structure the input data file as follows:

ID, Disease 1, Time 1, Disease 2, Time 2, Disease 3, Time 3, …

Where Time 1, Time 2 and Time 3 = 0

Question: I have prepared the input data file as outlined in this Toolkit and have saved it as a common separated text file (.txt file). After ensuring that the input data file is saved in the same folder as the "mm cluster tool.jar" file on my computer and selecting this data file for the computational program, I am still receiving an error message that the program cannot run. Why isn't the program working?

Answer: There may be a few reasons why the Multimorbidity Cluster Analysis Tool is not working properly. Typically, this is resolved by carefully reviewing your data file after exporting the data from the data management program. Firstly, it is important to ensure that you have the correct data structure in your file: Participant/Patient ID, Disease Diagnosis/Disease Category, Time Between Diseases. Secondly, it is important to ensure that the Time Between Diseases is rounded to the nearest whole number (no decimal points or values below zero). Finally, it is important to ensure that there are no extra commas (,) or blank data lines in the input data file. Each of these steps should alleviate errors previously encountered, after careful review of the input data file.

Question: If I have a follow-up question or comment about the Multimorbidity Cluster Analysis Tool and/or Toolkit, where can these be submitted?

Answer: Further questions or comments about the Multimorbidity Cluster Analysis Tool and/or Toolkit can be directed to: [redacted].

Appendix I. Identifying "First Occurrence" Chronic Disease Diagnoses

For each eligible adult patient, the first occurrence of a chronic disease diagnoses (from the list of twenty chronic disease categories in **Table 4.2**) was identified. This approach captured the patient's first recorded diagnosis for a chronic disease, as well as the corresponding diagnosis date. This represented the first time a patient received documentation of a diagnoses within their EMR. Importantly, the term "incident" was not selected for these chronic disease diagnoses, as one cannot definitively state that the diagnostic codes that appear in the patient's EMR are true incident cases of the disease. For example, a patient may be experiencing symptoms of Anxiety or Depression, without receiving a diagnostic code within their EMR. In these cases, while the diagnostic code was not recorded in the patient's EMR, the patient is very much living with this chronic disease. Alternatively, a patient may have already received a diagnosis for Anxiety or Depression from a PHC provider who is not participating in the CPCSSN database. In these cases, the diagnosis for Anxiety or Depression may eventually appear within the patient's EMR, but does not represent the true incidence of this disease (which was detected first by the non-participating PHC provider). Instead, the diagnosis recorded by the participating provider would constitute the "first occurrence" of this chronic disease in the CPCSSN database. To detect each patient's first occurrence of a chronic disease diagnosis, patient data were sorted by Patient ID and Encounter Date or Service Date variables (for Encounter Diagnosis codes and Billing Diagnosis codes, respectively) and the first chronologically diagnosed chronic disease (again, from the list of twenty) was identified.

The corresponding date on which these chronic disease diagnoses were made was another important consideration for Objective Two and its time-to-event analysis. Within the Billing Diagnosis and Encounter Diagnosis tables, date information could be found within two variables:

Encounter Date (which represented the actual date of the encounter) and Date Created (which represented the date the code was input into the EMR). A systematic approach was used to assign the most appropriate date to each chronic disease diagnosis. To begin, the Encounter Date was selected if available; if this date was missing, the Date Created was used as the alternate date source. Consistency between dates was checked for diagnoses that had both an Encounter Date and Date Created. Consistency between dates was reasonable and did not represent a large discrepancy (e.g., the majority of Date Created entries were within one week of the Encounter Date), indicating that this was a feasible approach to obtaining the approximate date of each chronic disease diagnosis.

Appendix J: Comparative prevalence estimates for selected self-reported chronic disease diagnoses from the 2013 Canadian Community Health Survey (CCHS) and the chronic disease categories from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) data

	Prevalence (95% CI)					
Data Source	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**
Disease Category	**High Blood Pressure**	**Hypertension Category**	**Overweight or Obese**	**Obesity Category**	**Diabetes**	**Diabetes Category**
Females (Age Category, Years)						
18 – 34	1.9 (1.6 – 2.1)	1.0 (1.0 – 1.2)	33.0 (32.2 – 33.8)	19.7 (19.3 – 20.0)	1.1 (0.9 – 1.3)	0.8 (0.7 – 0.8)
35 – 44	5.9 (5.4 – 6.5)	2.9 (2.8 – 3.1)	44.9 (43.9 – 46.0)	25.3 (24.9 – 25.8)	3.3 (2.9 – 3.7)	1.2 (1.1 – 1.3)
45 – 64	24.9 (24.3 – 25.4)	9.4 (9.2 – 9.6)	53.4 (52.8 – 54.1)	26.3 (26.0 – 26.6)	8.8 (8.4 – 9.1)	2.7 (2.6 – 2.8)
65 – 79	48.3 (47.6 – 49.1)	21.0 (20.6 – 21.4)	55.8 (55.0 – 56.7)	23.4 (23.0 – 23.8)	15.8 (15.2 – 16.4)	6.1 (5.9 – 6.4)
≥ 80 **	56.4 (55.1 – 57.6)	28.9 (28.3 – 29.6)	41.0 (39.7 – 42.2)	13.1 (12.7 – 13.6)	15.2 (14.3 – 16.1)	6.9 (6.6 – 7.3)
Males (Age Category, Years)						
18 – 34	2.8 (2.5 – 3.1)	1.6 (1.5 – 1.7)	46.4 (45.4 – 47.3)	18.8 (18.4 – 19.3)	0.9 (0.7 – 1.1)	0.8 (0.7 – 1.0)
35 – 44	9.2 (8.6 – 9.9)	4.5 (4.2 – 4.7)	66.7 (65.6 – 67.8)	27.6 (27.0 – 28.1)	3.1 (2.6 – 3.5)	1.8 (1.7 – 2.0)
45 – 64	28.9 (28.3 – 29.6)	11.6 (11.3 – 11.8)	69.1 (68.4 – 69.7)	31.8 (31.4 – 32.1)	11.2 (10.7 – 11.6)	4.5 (4.4 – 4.7)
65 – 79	46.3 (45.5 – 47.2)	19.4 (19.0 – 19.9)	65.4 (64.6 – 66.2)	28.2 (27.7 – 28.8)	21.6 (20.9 – 22.4)	9.3 (9.0 – 9.7)
≥ 80 **	46.9 (45.2 – 48.6)	23.0 (22.3 – 23.7)	44.8 (43.2 – 46.5)	18.5 (17.8 – 19.1)	18.4 (17.2 – 19.7)	9.5 (9.0 – 10.0)

Note: All prevalence estimates and 95% CIs calculated by author

* CI = Confidence interval

** The oldest age category in the 2013 CCHS was 80 years and older

Appendix J: Comparative prevalence estimates for selected self-reported chronic disease diagnoses from the 2013 Canadian Community Health Survey (CCHS) and the chronic disease categories from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) data, *Continued*

	Prevalence (95% CI)				
Data Source	**CCHS**	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**
Disease Category	**Chronic Obstructive Pulmonary Disease**	**Asthma**	**Chronic Obstructive Pulmonary Disease or Asthma Category**	**Cancer**	**Cancer Category**
Females (Age Category, Years)					
18 – 34	Not Reported	10.4 (9.9 – 11.0)	3.9 (3.8 – 4.1)	0.3 (0.2 – 0.4)	4.9 (4.7 – 5.1)
35 – 44	1.6 (1.3 – 1.9)	10.0 (9.4 – 10.7)	3.9 (3.7 – 4.1)	0.8 (0.6 – 1.0)	5.7 (5.5 – 6.0)
45 – 64	5.0 (4.8 – 5.3)	9.6 (9.2 – 10.0)	3.2 (3.1 – 3.3)	2.5 (2.4 – 2.8)	5.9 (5.8 – 6.1)
65 – 79	8.5 (8.1 – 9.0)	9.2 (8.8 – 9.7)	2.5 (2.3 – 2.6)	4.8 (4.5 – 5.2)	5.2 (5.0 – 5.4)
≥ 80 **	8.0 (7.4 – 8.7)	6.8 (6.2 – 7.4)	2.0 (1.8 – 2.2)	5.4 (4.9 – 6.0)	4.8 (4.5 – 5.1)
Males (Age Category, Years)					
18 – 34	Not Reported	8.5 (8.0 – 9.0)	4.5 (4.3 – 4.8)	0.2 (0.1 – 0.3)	3.2 (3.0 – 3.4)
35 – 44	1.3 (1.0 – 1.6)	7.0 (6.5 – 7.7)	3.7 (3.5 – 4.0)	0.3 (0.2 – 0.4)	3.2 (3.0 – 3.4)
45 – 64	4.6 (4.3 – 4.9)	6.3 (5.9 – 6.6)	2.5 (2.4 – 2.6)	2.4 (2.2 – 2.6)	3.4 (3.2 – 3.5)
65 – 79	7.3 (6.8 – 7.7)	6.0 (5.6 – 6.4)	1.9 (1.8 – 2.1)	6.1 (5.7 – 6.5)	4.9 (4.7 – 5.2)
≥ 80 **	9.1 (8.1 – 10.1)	6.5 (5.7 – 7.4)	2.1 (1.8 – 2.3)	9.6 (8.6 – 10.6)	7.0 (6.6 – 7.4)

Note: All prevalence estimates and 95% CIs calculated by author

* CI = Confidence interval

** The oldest age category in the 2013 CCHS was 80 years and older

Appendix J: Comparative prevalence estimates for selected self-reported chronic disease diagnoses from the 2013 Canadian Community Health Survey (CCHS) and the chronic disease categories from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) data, *Continued*

	Prevalence (95% CI)				
Data Source	**CCHS**	**CPCSSN**	**CCHS**	**CCHS**	**CPCSSN**
Disease Category	**Heart Disease**	**Cardiovascular Disease Category**	**Anxiety**	**Depression**	**Anxiety or Depression Category**
Females (Age Category, Years)					
18 – 34	0.8 (0.7 – 1.0)	0.6 (0.5 – 0.7)	11.5 (11.0 – 12.1)	33.0 (32.2 – 33.8)	12.1 (11.8 – 12.4)
35 – 44	1.0 (0.8 – 1.3)	0.7 (0.6 – 0.8)	9.7 (9.1 – 10.4)	32.2 (31.2 – 33.2)	12.1 (11.8 – 12.4)
45 – 64	4.1 (3.8 – 4.3)	1.0 (0.9 – 1.1)	9.7 (9.3 – 10.1)	33.9 (33.3 – 34.5)	9.6 (9.4 – 9.8)
65 – 79	11.8 (11.3 – 12.3)	2.1 (1.9 – 2.2)	6.6 (6.2 – 7.0)	33.3 (32.6 – 34.0)	5.2 (5.0 – 5.5)
≥ 80 **	23.1 (22.0 – 24.1)	5.5 (5.2 – 5.9)	4.1 (3.7 – 4.7)	31.7 (30.5 – 32.9)	3.6 (3.4 – 3.9)
Males (Age Category, Years)					
18 – 34	0.8 (0.6 – 0.9)	0.6 (0.5 – 0.7)	6.6 (6.1 – 7.1)	31.9 (31.0 – 32.7)	10.7 (10.3 – 11.0)
35 – 44	1.6 (1.3 – 1.9)	0.6 (0.5 – 0.7)	6.2 (5.7 – 6.8)	32.4 (31.3 – 33.5)	8.9 (8.5 – 9.2)
45 – 64	7.7 (7.3 – 8.1)	1.7 (1.6 – 1.8)	5.9 (5.6 – 6.2)	33.3 (32.6 – 33.9)	5.8 (5.6 – 6.0)
65 – 79	19.1 (18.4 – 19.8)	4.8 (4.5 – 5.0)	3.7 (3.4 – 4.0)	34.0 (33.2 – 34.9)	3.0 (2.8 – 3.2)
≥ 80 **	26.0 (24.5 – 27.5)	8.3 (7.9 – 8.8)	2.6 (2.1 – 3.2)	29.9 (28.4 – 31.4)	2.1 (1.9 – 2.4)

Note: All prevalence estimates and 95% CIs calculated by author

* CI = Confidence interval

** The oldest age category in the 2013 CCHS was 80 years and older

Appendix J: Comparative prevalence estimates for selected self-reported chronic disease diagnoses from the 2013 Canadian Community Health Survey (CCHS) and the chronic disease categories from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) data, *Continued*

	Prevalence (95% CI)					
Data Source	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**
Disease Category	**Arthritis**	**Osteoarthritis or Rheumatoid Arthritis Category**	**Stroke**	**Stroke or Transient Ischemic Attack Category**	**Back Problems**	**Musculoskeletal Problem Category**
Females (Age Category, Years)						
18 – 34	3.1 (2.8 – 3.4)	0.4 (0.4 – 0.5)	2.0 (1.8 – 2.3)	0.01 (0.0 – 0.02)	14.1 (13.5 – 14.7)	7.1 (6.8 – 7.3)
35 – 44	8.7 (8.1 – 9.3)	0.8 (0.7 – 0.9)	2.2 (1.9 – 2.5)	0.02 (0.01 – 0.05)	18.2 (17.4 – 19.1)	9.5 (9.2 – 9.8)
45 – 64	30.4 (29.8 – 31.0)	2.7 (2.6 – 2.8)	3.5 (3.3 – 3.8)	0.05 (0.04 – 0.07)	25.4 (24.8 – 26.0)	10.7 (10.5 – 11.0)
65 – 79	50.0 (48.9 – 50.5)	4.9 (4.7 – 5.1)	3.6 (3.4 – 3.9)	0.2 (0.1 – 0.2)	26.6 (25.9 – 27.3)	6.5 (6.2 – 6.7)
≥ 80 **	57.2 (55.9 – 58.4)	5.7 (5.4 – 6.0)	3.6 (3.2 – 4.1)	0.5 (0.4 – 0.6)	28.3 (27.2 – 29.5)	5.2 (4.9 – 5.5)
Males (Age Category, Years)						
18 – 34	2.4 (2.1 – 2.7)	0.5 (0.4 – 0.6)	1.7 (1.5 – 2.0)	0.01 (0.01 – 0.04)	10.5 (9.9 – 11.1)	9.9 (9.6 – 10.3)
35 – 44	7.1 (6.5 – 7.7)	0.9 (0.8 – 1.0)	2.2 (1.9 – 2.5)	0.01 (0.00 – 0.03)	19.0 (18.1 – 20.0)	12.5 (12.1 – 12.9)
45 – 64	21.1 (20.5 – 21.7(	2.2 (2.1 – 2.3)	2.9 (2.6 – 3.2)	0.1 (0.1 – 0.2)	25.8 (25.2 – 26.4)	10.8 (10.6 – 11.1)
65 – 79	34.1 (33.2 – 34.9)	3.5 (3.2 – 3.7)	2.9 (2.6 – 3.2)	0.1 (0.1 – 0.2)	25.6 (24.8 – 26.4)	5.6 (5.3 – 5.8)
≥ 80 **	42.1 (40.4 – 43.7)	4.1 (3.8 – 4.4)	3.2 (2.6 – 3.8)	0.5 (0.4 – 0.7)	24.3 (22.9 – 25.8)	4.5 (4.1 – 4.9)

Note: All prevalence estimates and 95% CIs calculated by author

* CI = Confidence interval

** The oldest age category in the 2013 CCHS was 80 years and older

Appendix J: Comparative prevalence estimates for selected self-reported chronic disease diagnoses from the 2013 Canadian Community Health Survey (CCHS) and the chronic disease categories from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) electronic medical record (EMR) data, *Continued*

	Prevalence (95% CI)			
Data Source	**CCHS**	**CPCSSN**	**CCHS**	**CPCSSN**
Disease Category	**Stomach Problems**	**Stomach Problem Category**	**Bowel Problems**	**Colon Problem Category**
Females (Age Category, Years)				
18 – 34	1.1 (0.9 – 1.3)	0.7 (0.6 – 0.8)	0.2 (0.1 – 0.3)	1.8 (1.7 – 1.9)
35 – 44	3.0 (2.7 – 3.4)	0.7 (0.7 – 0.8)	0.4 (0.2 – 0.5)	1.3 (1.2 – 1.5)
45 – 64	9.0 (8.7 – 9.4)	0.8 (0.8 – 0.9)	1.3 (1.1 – 1.4)	1.1 (1.0 – 1.2)
65 – 79	16.4 (15.8 – 17.0)	0.9 (0.8 – 1.0)	2.5 (2.3 – 2.8)	0.8 (0.7 – 0.9)
≥ 80 **	20.6 (19.6 – 21.7)	0.7 (0.6 – 0.8)	5.2 (4.7 – 5.8)	0.6 (0.5 – 0.7)
Males (Age Category, Years)				
18 – 34	0.5 (0.4 – 0.7)	1.1 (1.0 – 1.2)	0.1 (0.1 – 0.2)	1.1 (1.0 – 1.3)
35 – 44	1.2 (1.0 – 1.5)	1.2 (1.1 – 1.4)	0.4 (0.3 – 0.6)	1.0 (0.9 – 1.1)
45 – 64	4.9 (4.6 – 5.2)	1.0 (0.9 – 1.1)	1.5 (1.3 – 1.7)	0.7 (0.6 – 0.8)
65 – 79	15.3 (14.7 – 16.0)	0.8 (0.7 – 0.9)	4.0 (3.6 – 4.3)	0.6 (0.5 – 0.7)
≥ 80 **	22.0 (20.6 – 23.5)	0.6 (0.5 – 0.8)	6.1 (5.4 – 7.0)	0.7 (0.6 – 0.9)

Note: All prevalence estimates and 95% CIs calculated by author

* CI = Confidence interval

** The oldest age category in the 2013 CCHS was 80 years and older

Appendix K: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients of all ages with multimorbidity (n = 113,209)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, All Ages
2	Anxiety or Depression & Obesity	3,991	3.5
(n = 41,890)	Musculoskeletal Problem & Obesity	3,837	3.4
	Hypertension & Obesity	3,491	3.1
	Cancer & Obesity	2,791	2.5
	Anxiety or Depression & Musculoskeletal Problem	2,291	2.0
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	1,621	1.4
(n = 29,597)	Hypertension & Musculoskeletal Problem & Obesity	1,019	0.9
	Diabetes & Hypertension & Obesity	869	0.8
	Anxiety or Depression & Cancer & Obesity	854	0.8
	Anxiety or Depression & Hypertension & Obesity	816	0.7
4	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	454	0.4
(n = 19,043)	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	428	0.4
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	346	0.3
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	329	0.3
	Diabetes & Hyperlipidemia & Hypertension & Obesity	308	0.3
≥ 5	Anxiety or Depression & Cancer & Hypertension & Musculoskeletal Problem & Obesity	155	0.1
(n = 22,679)	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	149	0.1
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	138	0.1
	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	138	0.1
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	115	0.1

* Combinations listed in alphabetical order

Appendix L: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 18 – 34 years with multimorbidity (n = 11,507)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 18 – 34 Years
2	Anxiety or Depression & Obesity	1,197	10.4
(n = 7,143)	Musculoskeletal Problem & Obesity	817	7.1
	Anxiety or Depression & Musculoskeletal Problem	608	5.3
	Cancer & Obesity	581	5.0
	Anxiety or Depression & Cancer	332	2.9
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	373	3.2
(n = 2,914)	Anxiety or Depression & Cancer & Obesity	205	1.8
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Obesity	131	1.1
	Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	104	0.9
	Cancer & Musculoskeletal Problem & Obesity	100	0.9
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	68	0.6
(n = 1,026)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	58	0.5
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Urinary Problem	37	0.3
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Thyroid Problem	28	0.2
	Anxiety or Depression & Colon Problem & Musculoskeletal Problem & Obesity	28	0.2
≥ 5	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Thyroid Problem	10	0.1
(n = 424)	Anxiety or Depression & Cancer & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	10	0.1
	Anxiety or Depression & Cancer & Colon Problem & Musculoskeletal Problem & Obesity	9	0.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Urinary Problem	9	0.1
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Colon Problem & Musculoskeletal Problem & Obesity	8	0.1

* Combinations listed in alphabetical order

Appendix M: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 35 – 44 years with multimorbidity (n = 14,756)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 35 – 44 Years
2	Anxiety or Depression & Obesity	1,140	7.7
(n = 7,696)	Musculoskeletal Problem & Obesity	1,034	7.0
	Cancer & Obesity	654	4.4
	Anxiety or Depression & Musculoskeletal Problem	634	4.3
	Hypertension & Obesity	338	2.3
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	483	3.3
(n = 4,145)	Anxiety or Depression & Cancer & Obesity	234	1.6
	Cancer & Musculoskeletal Problem & Obesity	170	1.2
	Anxiety or Depression & Cancer & Musculoskeletal Problem	156	1.1
	Anxiety or Depression & Obesity & Thyroid Problem	130	0.9
4	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	110	0.7
(n = 1,834)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	86	0.6
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	76	0.5
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Thyroid Problem	56	0.4
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Urinary Problem	54	0.4
≥ 5	Anxiety or Depression & Cancer & Hypertension & Musculoskeletal Problem & Obesity	24	0.2
(n = 1,081)	Anxiety or Depression & Cancer & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	24	0.2
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Hypertension & Musculoskeletal Problem & Obesity	22	0.1
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity & Thyroid Problem	22	0.1
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity & Thyroid Problem	13	0.1

* Combinations listed in alphabetical order

Appendix N: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 45 – 64 years with multimorbidity (n = 44,712)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 45 – 64 Years
2	Musculoskeletal Problem & Obesity	1,693	3.8
(n = 17,048)	Hypertension & Obesity	1,595	3.6
	Anxiety or Depression & Obesity	1,439	3.2
	Cancer & Obesity	1,181	2.6
	Anxiety or Depression & Musculoskeletal Problem	935	2.1
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	680	1.5
(n = 12,480)	Hypertension & Musculoskeletal Problem & Obesity	551	1.2
	Cancer & Musculoskeletal Problem & Obesity	426	1.0
	Anxiety or Depression & Hypertension & Obesity	425	1.0
	Hyperlipidemia & Hypertension & Obesity	360	0.8
4	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	238	0.5
(n = 7,693)	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	222	0.5
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	187	0.4
	Anxiety or Depression & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	139	0.3
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	130	0.3
≥ 5	Anxiety or Depression & Cancer & Hypertension & Musculoskeletal Problem & Obesity	86	0.2
(n = 7,491)	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	81	0.2
	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	76	0.2
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	64	0.1
	Anxiety or Depression & Diabetes & Hypertension & Musculoskeletal Problem & Obesity	58	0.1

* Combinations listed in alphabetical order

Appendix O: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 65 – 84 years with multimorbidity (n = 33,264)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, 65 – 84 Years
2	Hypertension & Obesity	1,181	3.6
(n = 7,820)	Diabetes & Obesity	446	1.3
	Cancer & Obesity	343	1.0
	Hyperlipidemia & Hypertension	323	1.0
	Musculoskeletal Problem & Obesity	275	0.8
3	Diabetes & Hypertension & Obesity	427	1.3
(n = 8,016)	Hyperlipidemia & Hypertension & Obesity	386	1.2
	Hypertension & Musculoskeletal Problem & Obesity	292	0.9
	Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	269	0.8
	Cancer & Hypertension & Obesity	252	0.8
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	158	0.5
(n = 6,811)	Diabetes & Hyperlipidemia & Hypertension & Obesity	153	0.5
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	141	0.4
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	131	0.4
	Diabetes & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	110	0.3
≥ 5	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	69	0.2
(n = 10,617)	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	66	0.2
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	63	0.2
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Thyroid Problem	56	0.2
	Cancer & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	50	0.2

* Combinations listed in alphabetical order

Appendix P: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 85 years and older with multimorbidity (n = 8,970)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Female Patients, ≥ 85 Years
2	Hypertension & Obesity	212	2.4
(n = 2,183)	Dementia & Hypertension	151	1.7
	Cardiovascular Disease & Hypertension	126	1.4
	Diabetes & Hypertension	99	1.1
	Cancer & Hypertension	98	1.1
3	Diabetes & Hypertension & Obesity	59	0.7
(n = 2,042)	Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	54	0.6
	Cancer & Hypertension & Obesity	53	0.6
	Hypertension & Musculoskeletal Problem & Obesity	46	0.5
	Cardiovascular Disease & Hypertension & Obesity	46	0.5
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	33	0.4
(n = 1,679)	Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Osteoarthritis or Rheumatoid Arthritis	21	0.2
	Anxiety or Depression & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	20	0.2
	Cardiovascular Disease & Diabetes & Hypertension & Obesity	17	0.2
	Diabetes & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	16	0.2
≥ 5	Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	14	0.2
(n = 3,066)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	14	0.2
	Cancer & Cardiovascular Disease & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	12	0.1
	Dementia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	11	0.1
	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis & Thyroid Problem	10	0.1

* Combinations listed in alphabetical order

Appendix Q: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients of all ages with multimorbidity (n = 82,622)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, All Ages
2	Hypertension & Obesity	3,866	4.7
(n = 32,080)	Musculoskeletal Problem & Obesity	3,580	4.3
	Anxiety or Depression & Obesity	2,431	2.9
	Hyperlipidemia & Obesity	2,109	2.6
	Diabetes & Obesity	1,966	2.4
3	Hyperlipidemia & Hypertension & Obesity	1,389	1.7
(n = 22,010)	Diabetes & Hypertension & Obesity	1,226	1.5
	Hypertension & Musculoskeletal Problem & Obesity	1,061	1.3
	Anxiety or Depression & Musculoskeletal Problem & Obesity	823	1.0
	Hyperlipidemia & Musculoskeletal Problem & Obesity	755	0.9
4	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	551	0.7
(n = 13,823)	Diabetes & Hyperlipidemia & Hypertension & Obesity	539	0.7
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	376	0.5
	Cancer & Hyperlipidemia & Hypertension & Obesity	283	0.3
	Cancer & Hypertension & Musculoskeletal Problem & Obesity	244	0.3
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	254	0.3
(n = 14,709)	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	138	0.2
	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	127	0.2
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	97	0.1
	Cancer & Diabetes & Hyperlipidemia & Hypertension & Obesity	93	0.1

* Combinations listed in alphabetical order

Appendix R: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 18 – 34 years with multimorbidity (n = 5,959)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 18 – 34 Years
2	Anxiety or Depression & Obesity	713	12.0
(n = 4,204)	Musculoskeletal Problem & Obesity	648	10.9
	Anxiety or Depression & Musculoskeletal Problem	422	7.1
	Chronic Obstructive Pulmonary Disease or Asthma & Obesity	260	4.4
	Cancer & Obesity	227	3.8
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	171	2.9
(n = 1,331)	Cancer & Musculoskeletal Problem & Obesity	67	1.1
	Anxiety or Depression & Cancer & Obesity	60	1.0
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem	53	0.9
	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Obesity	52	0.9
4	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	18	0.3
(n = 327)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Musculoskeletal Problem & Obesity	18	0.3
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	13	0.2
	Diabetes & Hyperlipidemia & Hypertension & Obesity	10	0.2
	Anxiety or Depression & Colon Problem & Musculoskeletal Problem & Obesity	10	0.2
≥ 5 (n = 97)	*Results Supressed (<5 Patients)*		

* Combinations listed in alphabetical order

Appendix S: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 35 – 44 years with multimorbidity (n = 9,098)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 35 – 44 Years
2	Musculoskeletal Problem & Obesity	932	10.2
(n = 5,439)	Anxiety or Depression & Obesity	653	7.2
	Hypertension & Obesity	479	5.3
	Anxiety or Depression & Musculoskeletal Problem	369	4.1
	Hyperlipidemia & Obesity	340	3.7
3	Anxiety or Depression & Musculoskeletal Problem & Obesity	241	2.6
(n = 2,357)	Hypertension & Musculoskeletal Problem & Obesity	127	1.4
	Cancer & Musculoskeletal Problem & Obesity	122	1.3
	Hyperlipidemia & Hypertension & Obesity	104	1.1
	Hyperlipidemia & Musculoskeletal Problem & Obesity	99	1.1
4	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	31	0.3
(n = 873)	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	30	0.3
	Anxiety or Depression & Cancer & Musculoskeletal Problem & Obesity	28	0.3
	Diabetes & Hyperlipidemia & Hypertension & Obesity	24	0.3
	Chronic Obstructive Pulmonary Disease or Asthma & Hypertension & Musculoskeletal Problem & Obesity	22	0.2
≥ 5	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	13	0.1
(n = 429)	Anxiety or Depression & Chronic Obstructive Pulmonary Disease or Asthma & Hypertension & Musculoskeletal Problem & Obesity	10	0.1
	Chronic Obstructive Pulmonary Disease or Asthma & Diabetes & Hypertension & Musculoskeletal Problem & Obesity	7	0.1
	Anxiety or Depression & Diabetes & Hypertension & Musculoskeletal Problem & Obesity	7	0.1
	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	6	0.1

* Combinations listed in alphabetical order

Appendix T: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 45 – 64 years with multimorbidity (n = 34,856)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 45 – 64 Years
2	Hypertension & Obesity	1,999	5.7
(n = 14,268)	Musculoskeletal Problem & Obesity	1,725	4.9
	Hyperlipidemia & Obesity	1,310	3.8
	Diabetes & Obesity	937	2.7
	Anxiety or Depression & Obesity	919	2.6
3	Hyperlipidemia & Hypertension & Obesity	785	2.3
(n = 10,148)	Hypertension & Musculoskeletal Problem & Obesity	605	1.7
	Diabetes & Hypertension & Obesity	559	1.6
	Hyperlipidemia & Musculoskeletal Problem & Obesity	532	1.5
	Anxiety or Depression & Musculoskeletal Problem & Obesity	378	1.1
4	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	347	1.0
(n = 5,834)	Diabetes & Hyperlipidemia & Hypertension & Obesity	277	0.8
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	188	0.5
	Anxiety or Depression & Hypertension & Musculoskeletal Problem & Obesity	145	0.4
	Anxiety or Depression & Hyperlipidemia & Hypertension & Obesity	137	0.4
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	148	0.4
(n = 4,606)	Anxiety or Depression & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	75	0.2
	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	62	0.2
	Cardiovascular Disease & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	45	0.1
	Anxiety or Depression & Diabetes & Hyperlipidemia & Hypertension & Obesity	44	0.1

* Combinations listed in alphabetical order

Appendix U: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 65 – 84 years with multimorbidity (n = 27,430)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, 65 – 84 Years
2	Hypertension & Obesity	1,092	4.0
(n = 6,914)	Diabetes & Obesity	678	2.5
	Cancer & Obesity	377	1.4
	Hyperlipidemia & Obesity	361	1.3
	Cardiovascular Disease & Obesity	267	1.0
3	Diabetes & Hypertension & Obesity	536	2.0
(n = 6,981)	Hyperlipidemia & Hypertension & Obesity	468	1.7
	Cancer & Hypertension & Obesity	262	1.0
	Hypertension & Musculoskeletal Problem & Obesity	258	0.9
	Cardiovascular Disease & Hypertension & Obesity	237	0.9
4	Diabetes & Hyperlipidemia & Hypertension & Obesity	221	0.8
(n = 5,768)	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	159	0.6
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity	158	0.6
	Cancer & Hyperlipidemia & Hypertension & Obesity	146	0.5
	Cardiovascular Disease & Diabetes & Hypertension & Obesity	143	0.5
≥ 5	Diabetes & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	95	0.3
(n = 7,767)	Cancer & Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity	68	0.2
	Hyperlipidemia & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	61	0.2
	Cancer & Diabetes & Hyperlipidemia & Hypertension & Obesity	54	0.2
	Diabetes & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	53	0.2

* Combinations listed in alphabetical order

Appendix V: Most frequently occurring combinations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 85 years and older with multimorbidity (n = 5,279)

Total Number of Chronic Diseases	Combinations*	Total Number of Patients	% of Male Patients, ≥ 85 Years
2	Hypertension & Obesity	124	2.3
(n = 1,255)	Cancer & Hypertension	71	1.3
	Cardiovascular Disease & Hypertension	63	1.2
	Diabetes & Obesity	62	1.2
	Diabetes & Hypertension	58	1.1
3	Diabetes & Hypertension & Obesity	53	1.0
(n = 1,193)	Cardiovascular Disease & Hypertension & Obesity	38	0.7
	Cancer & Hypertension & Obesity	29	0.5
	Hypertension & Musculoskeletal Problem & Obesity	28	0.5
	Cancer & Cardiovascular Disease & Hypertension	25	0.5
4	Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	23	0.4
(n = 1,021)	Cancer & Cardiovascular Disease & Hypertension & Obesity	23	0.4
	Cardiovascular Disease & Diabetes & Hypertension & Obesity	18	0.3
	Cancer & Diabetes & Hypertension & Obesity	17	0.3
	Cancer & Hypertension & Musculoskeletal Problem & Obesity	12	0.2
≥ 5	Cancer & Cardiovascular Disease & Hypertension & Musculoskeletal Problem & Obesity	8	0.2
(n = 1,810)	Cancer & Hypertension & Musculoskeletal Problem & Obesity & Osteoarthritis or Rheumatoid Arthritis	7	0.1
	Cancer & Hypertension & Musculoskeletal Problem & Osteoarthritis or Rheumatoid Arthritis & Urinary Problem	7	0.1
	Cancer & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis & Urinary Problem	7	0.1
	Cardiovascular Disease & Dementia & Hypertension & Obesity & Osteoarthritis or Rheumatoid Arthritis	6	0.1

* Combinations listed in alphabetical order

Appendix W: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients of all ages with multimorbidity (n = 113,209)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, All Ages
2	Obesity >> Musculoskeletal Problem	2,455	2.2
(n = 41,890)	Obesity >> Anxiety or Depression	2,286	2.0
	Obesity >> Cancer	1,942	1.7
	Obesity >> Hypertension	1,869	1.7
	Anxiety or Depression >> Obesity	1,705	1.5
3	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	389	0.3
(n = 29,597)	Obesity >> Musculoskeletal Problem >> Anxiety or Depression	311	0.3
	Hypertension >> Obesity >> Musculoskeletal Problem	275	0.2
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	274	0.2
	Obesity >> Hypertension >> Musculoskeletal Problem	252	0.2
4	Obesity >> Hypertension >> Anxiety or Depression >> Musculoskeletal Problem	39	0.0
(n = 19,043)	Obesity >> Anxiety or Depression >> Cancer >> Musculoskeletal Problem	37	0.0
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	36	0.0
	Obesity >> Hypertension >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	36	0.0
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	35	0.0
≥ 5	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem >> Anxiety or	7	0.0
(n = 22,679)	Depression		
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	6	0.0
	Hypertension >> Diabetes >> Obesity >> Hyperlipidemia >> Cancer	6	0.0
	Obesity >> Hypertension >> Hyperlipidemia >> Cancer >> Musculoskeletal Problem	6	0.0
	Hypertension >> Obesity >> Diabetes >> Musculoskeletal Problem >> Cancer	5	0.0

* Permutations listed in sequential order

Appendix X: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 18 – 34 years with multimorbidity (n = 11,507)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 18 – 34 Years
2	Obesity >> Anxiety or Depression	667	5.8
(n = 7,143)	Anxiety or Depression >> Obesity	530	4.6
	Obesity >> Musculoskeletal Problem	507	4.4
	Obesity >> Cancer	400	3.5
	Anxiety or Depression >> Musculoskeletal Problem	351	3.1
3	Obesity >> Musculoskeletal Problem >> Anxiety or Depression	92	0.8
(n = 2,914)	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	76	0.7
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	57	0.5
	Obesity >> Cancer >> Anxiety or Depression	54	0.5
	Obesity >> Anxiety or Depression >> Cancer	53	0.5
4	Obesity >> Anxiety or Depression >> Cancer >> Musculoskeletal Problem	8	0.1
(n = 1,026)	Obesity >> Cancer >> Anxiety or Depression >> Musculoskeletal Problem	7	0.1
	Chronic Obstructive Pulmonary Disease or Asthma >> Obesity >> Anxiety or Depression >> Musculoskeletal Problem	7	0.1
	Thyroid Problem >> Anxiety or Depression >> Obesity >> Musculoskeletal Problem	6	0.1
	Obesity >> Chronic Obstructive Pulmonary Disease or Asthma >> Musculoskeletal Problem >> Anxiety or Depression	6	0.1
≥ 5			
(n = 424)			
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Appendix Y: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 35 – 44 years with multimorbidity (n = 14,756)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 35 – 44 Years
2 (n = 7,696)	Obesity >> Anxiety or Depression	665	4.5
	Obesity >> Musculoskeletal Problem	653	4.4
	Anxiety or Depression >> Obesity	475	3.2
	Obesity >> Cancer	429	2.9
	Musculoskeletal Problem >> Obesity	381	2.6
3 (n = 4,145)	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	132	0.9
	Obesity >> Musculoskeletal Problem >> Anxiety or Depression	88	0.6
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	75	0.5
	Obesity >> Anxiety or Depression >> Cancer	72	0.5
	Anxiety or Depression >> Musculoskeletal Problem >> Obesity	69	0.5
4 (n = 1,834)	Anxiety or Depression >> Musculoskeletal Problem >> Obesity >> Cancer	11	0.1
	Obesity >> Anxiety or Depression >> Cancer >> Musculoskeletal Problem	10	0.1
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem >> Cancer	10	0.1
	Obesity >> Chronic Obstructive Pulmonary Disease or Asthma >> Anxiety or Depression >> Musculoskeletal Problem	9	0.1
	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	8	0.1
≥ 5 (n = 1,081)			
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Appendix Z: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 45 – 64 years with multimorbidity (n = 44,712)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 45 – 64 Years
2 (n = 17,048)	Obesity >> Musculoskeletal Problem	1,096	2.5
	Obesity >> Hypertension	905	2.0
	Obesity >> Cancer	844	1.9
	Obesity >> Anxiety or Depression	819	1.8
	Hypertension >> Obesity	690	1.5
3 (n = 12,480)	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	156	0.3
	Hypertension >> Obesity >> Musculoskeletal Problem	151	0.3
	Obesity >> Hypertension >> Musculoskeletal Problem	137	0.3
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	125	0.3
	Hypertension >> Obesity >> Hyperlipidemia	114	0.3
4 (n = 7,693)	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	20	0.0
	Hypertension >> Obesity >> Musculoskeletal Problem >> Anxiety or Depression	20	0.0
	Obesity >> Hypertension >> Anxiety or Depression >> Musculoskeletal Problem	20	0.0
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	18	0.0
	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem	17	0.0
≥ 5 (n = 7,491)	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem >> Anxiety or Depression	5	0.0
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Appendix AA: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 65 – 84 years with multimorbidity (n = 33,264)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, 65 – 84 Years
2 (n = 7,820)	Hypertension >> Obesity	604	1.8
	Obesity >> Hypertension	577	1.7
	Obesity >> Diabetes	257	0.8
	Obesity >> Cancer	249	0.7
	Hypertension >> Hyperlipidemia	224	0.7
3 (n = 8,016)	Hypertension >> Obesity >> Hyperlipidemia	110	0.3
	Obesity >> Hypertension >> Hyperlipidemia	94	0.3
	Obesity >> Diabetes >> Hypertension	91	0.3
	Diabetes >> Obesity >> Hypertension	90	0.3
	Hypertension >> Obesity >> Musculoskeletal Problem	86	0.3
4 (n = 6,811)	Obesity >> Hypertension >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	18	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	17	0.1
	Obesity >> Hypertension >> Cancer >> Musculoskeletal Problem	16	0.0
	Hypertension >> Obesity >> Musculoskeletal Problem >> Hyperlipidemia	15	0.0
	Hypertension >> Diabetes >> Obesity >> Osteoarthritis or Rheumatoid Arthritis	15	0.0
≥ 5 (n = 10,617)	Obesity >> Hypertension >> Thyroid Problem >> Musculoskeletal Problem >> Hyperlipidemia	5	0.0
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Appendix AB: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among female patients aged 85 years and older with multimorbidity (n = 8,970)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Female Patients, ≥ 85 Years
2	Hypertension >> Obesity	119	1.3
(n = 2,183)	Hypertension >> Dementia	108	1.2
	Obesity >> Hypertension	93	1.0
	Hypertension >> Cardiovascular Disease	74	0.8
	Hypertension >> Cancer	72	0.8
3	Hypertension >> Obesity >> Cancer	22	0.2
(n = 2,042)	Hypertension >> Obesity >> Osteoarthritis or Rheumatoid Arthritis	20	0.2
	Obesity >> Hypertension >> Cancer	16	0.2
	Hypertension >> Obesity >> Dementia	15	0.2
	Hypertension >> Obesity >> Musculoskeletal Problem	15	0.2
4	Hypertension >> Obesity >> Musculoskeletal Problem >> Osteoarthritis or Rheumatoid Arthritis	6	0.1
(n = 1,679)	Hypertension >> Obesity >> Musculoskeletal Problem >> Osteoporosis	5	0.1
≥ 5 (n = 3,066)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Appendix AC: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients of all ages with multimorbidity (n = 82,622)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, All Ages
2 (n = 32,080)	Obesity >> Hypertension	2,201	2.7
	Obesity >> Musculoskeletal Problem	2,138	2.6
	Hypertension >> Obesity	1,665	2.0
	Obesity >> Hyperlipidemia	1,530	1.9
	Obesity >> Anxiety or Depression	1,467	1.8
3 (n = 22,010)	Obesity >> Hypertension >> Hyperlipidemia	382	0.5
	Hypertension >> Obesity >> Hyperlipidemia	336	0.4
	Obesity >> Hypertension >> Musculoskeletal Problem	286	0.3
	Obesity >> Hyperlipidemia >> Hypertension	271	0.3
	Obesity >> Hyperlipidemia >> Musculoskeletal Problem	237	0.3
4 (n = 13,823)	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem	64	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	51	0.1
	Obesity >> Hyperlipidemia >> Hypertension >> Musculoskeletal Problem	42	0.1
	Obesity >> Hypertension >> Diabetes >> Hyperlipidemia	36	0.0
	Obesity >> Diabetes >> Hypertension >> Musculoskeletal Problem	35	0.0
≥ 5 (n = 14,709)	Obesity >> Diabetes >> Hyperlipidemia >> Hypertension >> Musculoskeletal Problem	8	0.0
	Diabetes >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem >> Obesity	8	0.0
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem >> Diabetes	6	0.0
	Hypertension >> Hyperlipidemia >> Cancer >> Obesity >> Musculoskeletal Problem	6	0.0
	Musculoskeletal Problem >> Hypertension >> Hyperlipidemia >> Obesity >> Urinary Problem	6	0.0

* Permutations listed in sequential order

Appendix AD: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 18 – 34 years with multimorbidity (n = 5,959)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 18 – 34 Years
2	Obesity >> Anxiety or Depression	437	7.3
(n = 4,204)	Obesity >> Musculoskeletal Problem	356	6.0
	Musculoskeletal Problem >> Obesity	292	4.9
	Anxiety or Depression >> Obesity	276	4.6
	Musculoskeletal Problem >> Anxiety or Depression	213	3.6
3	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	54	0.9
(n = 1,331)	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	34	0.6
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	24	0.4
	Obesity >> Anxiety or Depression >> Cancer	23	0.4
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	20	0.3
4 (n = 327)			
≥ 5 (n = 97)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Appendix AE: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 35 – 44 years with multimorbidity (n = 9,098)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 35 – 44 Years
2	Obesity >> Musculoskeletal Problem	532	5.8
(n = 5,439)	Musculoskeletal Problem >> Obesity	400	4.4
	Obesity >> Anxiety or Depression	379	4.2
	Obesity >> Hypertension	288	3.2
	Anxiety or Depression >> Obesity	274	3.0
3	Obesity >> Anxiety or Depression >> Musculoskeletal Problem	55	0.6
(n = 2,357)	Obesity >> Musculoskeletal Problem >> Anxiety or Depression	47	0.5
	Anxiety or Depression >> Obesity >> Musculoskeletal Problem	41	0.5
	Musculoskeletal Problem >> Obesity >> Anxiety or Depression	37	0.4
	Musculoskeletal Problem >> Anxiety or Depression >> Obesity	36	0.4
4	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem	5	0.1
(n = 873)			
≥ 5	*Results Supressed (<5 Patients)*		
(n = 429)			

* Permutations listed in sequential order

Appendix AF: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 45 – 64 years with multimorbidity (n = 34,856)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 45 – 64 Years
2 (n = 14,268)	Obesity >> Hypertension	1,167	3.3
	Obesity >> Musculoskeletal Problem	1,066	3.1
	Obesity >> Hyperlipidemia	963	2.8
	Hypertension >> Obesity	832	2.4
	Musculoskeletal Problem >> Obesity	659	1.9
3 (n = 10,148)	Obesity >> Hypertension >> Hyperlipidemia	214	0.6
	Hypertension >> Obesity >> Hyperlipidemia	185	0.5
	Obesity >> Hypertension >> Musculoskeletal Problem	174	0.5
	Obesity >> Hyperlipidemia >> Musculoskeletal Problem	172	0.5
	Obesity >> Hyperlipidemia >> Hypertension	156	0.4
4 (n = 5,834)	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem	33	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	27	0.1
	Obesity >> Hypertension >> Musculoskeletal Problem >> Hyperlipidemia	25	0.1
	Obesity >> Hyperlipidemia >> Hypertension >> Musculoskeletal Problem	23	0.1
	Obesity >> Diabetes >> Hyperlipidemia >> Hypertension	22	0.1
≥ 5 (n = 4,606)	Obesity >> Diabetes >> Hyperlipidemia >> Hypertension >> Musculoskeletal Problem	5	0.0
	Obesity >> Hyperlipidemia >> Diabetes >> Hypertension >> Musculoskeletal Problem	5	0.0

Results Supressed (<5 Patients)

* Permutations listed in sequential order

Appendix AG: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 65 – 84 years with multimorbidity (n = 27,430)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, 65 – 84 Years
2 (n = 6,914)	Obesity >> Hypertension	584	2.1
	Hypertension >> Obesity	508	1.9
	Obesity >> Diabetes	364	1.3
	Diabetes >> Obesity	314	1.1
	Obesity >> Cancer	288	1.0
3 (n = 6,981)	Obesity >> Hypertension >> Hyperlipidemia	134	0.5
	Hypertension >> Obesity >> Hyperlipidemia	118	0.4
	Obesity >> Diabetes >> Hypertension	113	0.4
	Diabetes >> Hypertension >> Obesity	96	0.3
	Diabetes >> Obesity >> Hypertension	95	0.3
4 (n = 5,768)	Obesity >> Hypertension >> Hyperlipidemia >> Musculoskeletal Problem	24	0.1
	Hypertension >> Obesity >> Hyperlipidemia >> Musculoskeletal Problem	19	0.1
	Obesity >> Hypertension >> Cancer >> Musculoskeletal Problem	19	0.1
	Obesity >> Diabetes >> Hypertension >> Musculoskeletal Problem	19	0.1
	Obesity >> Hypertension >> Hyperlipidemia >> Cancer	18	0.1
≥ 5 (n = 7,767)			
	Results Supressed (<5 Patients)		

* Permutations listed in sequential order

Appendix AH: Most frequently occurring permutations of multimorbidity, stratified by total number of chronic diseases, among male patients aged 85 years and older with multimorbidity (n = 5,279)

Total Number of Chronic Diseases	Permutations*	Total Number of Patients	% of Male Patients, ≥ 85 Years
2	Hypertension >> Obesity	68	1.3
(n = 1,255)	Obesity >> Hypertension	56	1.1
	Hypertension >> Cancer	52	1.0
	Hypertension >> Cardiovascular Disease	41	0.8
	Obesity >> Diabetes	38	0.7
3	Diabetes >> Obesity >> Hypertension	14	0.3
(n = 1,193)	Hypertension >> Obesity >> Musculoskeletal Problem	13	0.2
	Hypertension >> Obesity >> Dementia	11	0.2
	Hypertension >> Obesity >> Cancer	11	0.2
	Hypertension >> Diabetes >> Obesity	11	0.2
4 (n = 1,021)			
≥ 5 (n = 1,810)	*Results Supressed (<5 Patients)*		

* Permutations listed in sequential order

Appendix AI: Time (in days) until subsequent chronic disease diagnosis (including zero days elapsing between diagnoses), stratified by patient age category (years), patient sex and total number of chronic diseases

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
T1 → T2	178.0	158.0	63.0	10.6	5.2	87.0	63.0	21.7	5.5	7.5
(n = 286,998)	442.6	453.5	383.5	266.5	224.4	424.1	403.9	345.3	256.1	232.8
	(612.2)	(654.8)	(646.6)	(577.5)	(527.7)	(654.9)	(647.8)	(630.9)	(581.0)	(540.2)
T2 → T3	372.5	374.0	297.6	192.7	168.0	340.7	327.1	268.0	194.2	173.0
(n = 195,838)	587.5	616.9	554.9	464.1	406.2	577.1	583.2	542.2	468.6	396.1
	(756.1)	(802.6)	(804.8)	(838.6)	(763.5)	(792.2)	(821.6)	(819.7)	(842.4)	(723.6)
T3 → T4	337.6	348.0	283.7	219.8	203.9	334.0	304.2	285.0	224.0	208.0
(n = 121,864)	488.1	517.4	466.9	398.4	378.6	517.1	498.5	476.6	416.4	373.0
	(507.3)	(579.2)	(560.8)	(532.6)	(485.2)	(567.8)	(599.3)	(587.4)	(586.1)	(490.3)
T4 → T5	282.4	346.0	285.2	243.9	224.0	290.1	295.6	300.1	264.0	239.0
(n = 70,256)	427.3	501.5	449.9	395.9	386.5	426.4	483.1	461.7	420.0	385.0
	(465.2)	(532.6)	(503.6)	(455.3)	(475.0)	(454.5)	(535.6)	(512.4)	(484.5)	(445.2)
T5 → T6	332.0	280.0	259.7	252.0	276.8	276.8	291.9	301.0	269.0	242.2
(n = 37,390)	482.4	424.9	402.2	402.3	431.0	431.0	446.0	455.6	416.4	389.6
	(496.7)	(462.3)	(445.1)	(446.2)	(505.0)	(505.0)	(469.4)	(494.3)	(453.8)	(444.8)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red

Appendix AI: Time (in days) until subsequent chronic disease diagnosis (including zero days elapsing between diagnoses), stratified by patient age category (years), patient sex and total number of chronic diseases, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Hypertension → T2	67.8	40.5	3.0	1.2	1.0	8.2	1.1	1.0	1.0	3.2
	343.3	313.6	242.1	191.0	171.9	328.3	273.0	234.0	181.8	192.5
	(549.9)	(527.3)	(527.0)	(482.0)	(462.7)	(624.9)	(567.0)	(523.0)	(479.3)	(484.5)
Obesity → T2	27.2	5.7	1.0	1.0	4.0	1.0	1.0	1.0	1.0	1.0
	203.0	235.9	209.6	161.9	92.2	311.8	259.2	249.9	113.9	109.3
	(346.4)	(429.7)	(436.0)	(382.8)	(165.9)	(648.1)	(545.5)	(524.0)	(253.8)	(188.5)
Diabetes → T2	6.6	25.7	2.0	1.0	1.0	1.0	2.0	1.0	1.0	2.0
	301.8	342.9	204.7	187.6	166.2	181.4	235.1	201.1	153.0	184.7
	(595.5)	(640.4)	(482.8)	(520.0)	(472.8)	(455.3)	(515.3)	(493.4)	(429.4)	(487.7)
Chronic Obstructive Pulmonary	70.0	109.4	45.6	19.9	21.0	8.4	22.0	14.5	20.0	6.6
Disease or Asthma → T2	322.3	391.2	358.4	277.0	279.9	275.9	344.0	348.4	324.8	191.2
	(523.3)	(600.6)	(663.2)	(580.0)	(594.7)	(502.0)	(579.4)	(669.0)	(705.7)	(428.0)
Hyperlipidemia → T2	194.3	109.6	69.5	21.0	1.0	47.0	38.4	31.2	13.5	4.5
	486.9	414.9	363.3	228.9	145.0	297.6	312.4	307.9	229.0	162.4
	(727.9)	(587.1)	(626.8)	(464.1)	(398.1)	(517.6)	(529.8)	(572.3)	(495.9)	(341.5)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

Appendix AI: Time (in days) until subsequent chronic disease diagnosis (including zero days elapsing between diagnoses), stratified by patient age category (years), patient sex and total number of chronic diseases, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Cancer → T2	237.5	231.8	139.1	35.0	7.3	99.8	80.3	58.4	15.4	19.2
	460.9	504.8	456.0	341.7	243.0	439.3	431.7	400.0	319.6	283.7
	(603.0)	(669.2)	(684.2)	(669.8)	(525.4)	(664.9)	(656.9)	(650.3)	(652.4)	(637.5)
Cardiovascular Disease → T2	307.9	225.0	114.0	17.4	12.2	65.0	62.0	29.6	10.5	4.2
	528.3	513.8	470.2	323.7	265.4	461.2	391.3	420.9	323.7	233.9
	(655.8)	(692.7)	(709.4)	(618.2)	(593.8)	(714.2)	(564.9)	(711.4)	(693.9)	(548.3)
Heart Failure → T2	14.0	28.0	176.6	9.1	29.0	141.9	60.3	17.0	16.6	21.7
	165.6	381.6	440.1	248.4	240.9	561.3	117.1	372.0	273.1	209.2
	(301.1)	(467.2)	(872.5)	(562.9)	(481.1)	(1,010.2)	(189.0)	(725.2)	(534.9)	(456.5)
Anxiety or Depression → T2	149.8	132.3	68.0	26.5	19.4	80.2	56.6	24.5	10.6	49.7
	435.7	430.7	392.2	319.1	288.8	413.4	407.9	341.3	344.7	329.9
	(614.8)	(638.1)	(634.5)	(644.7)	(648.0)	(634.6)	(663.8)	(614.7)	(679.3)	(596.7)
Osteoarthritis or Rheumatoid	140.0	216.3	136.5	39.9	31.5	137.8	94.0	70.5	29.7	17.4
Arthritis → T2	428.8	495.2	494.7	388.4	358.9	523.9	489.1	477.7	418.6	368.9
	(587.2)	(658.5)	(738.7)	(710.2)	(667.9)	(755.7)	(725.5)	(744.4)	(784.2)	(734.5)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

Appendix AI: Time (in days) until subsequent chronic disease diagnosis (including zero days elapsing between diagnoses), stratified by patient age category (years), patient sex and total number of chronic diseases, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Stroke or Transient Ischemic Attack → T2	*Results Supressed*	1.00	74.0	46.9	7.6	996.5	*Results Supressed*	7.0	8.4	3.0
		103.6	595.8	507.6	392.5	1,177.0		289.5	235.8	199.7
		(190.0)	(868.9)	(829.9)	(711.2)	(1,390.7)		(498.9)	(456.2)	(575.0)
Thyroid Problem → T2	91.9	63.0	31.6	7.6	10.1	39.0	29.6	10.5	4.0	8.6
	364.9	349.4	319.0	232.8	215.9	286.1	263.7	303.4	241.6	274.4
	(554.8)	(569.2)	(577.2)	(525.5)	(536.9)	(575.1)	(552.6)	(608.3)	(476.8)	(610.0)
Kidney Disease or Failure → T2	48.8	124.5	26.7	183.3	95.7	7.6	52.8	124.8	50.0	1.0
	162.5	361.1	139.8	712.9	566.5	58.7	89.6	547.8	466.4	92.9
	(263.9)	(520.1)	(217.5)	(1,052.0)	(910.8)	(98.2)	(103.6)	(830.8)	(867.5)	(248.2)
Osteoporosis → T2	199.0	110.5	71.3	14.5	1.0	28.0	3.0	92.3	25.3	64.0
	650.8	383.7	369.1	247.9	168.6	95.6	182.8	326.5	197.0	269.6
	(859.7)	(599.2)	(604.4)	(455.0)	(378.4)	(152.8)	(314.1)	(474.9)	(346.3)	(354.5)
Dementia → T2	451.0	130.2	166.3	6.6	5.3	555.7	554.7	188.0	25.2	6.0
	505.1	355.7	500.7	297.0	216.2	666.6	705.6	507.4	326.3	202.4
	(526.0)	(733.7)	(773.9)	(661.2)	(476.4)	(707.7)	(658.8)	(700.4)	(590.0)	(475.3)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

** Results were supressed when < 5 patients were included in the category

Appendix AI: Time (in days) until subsequent chronic disease diagnosis (including zero days elapsing between diagnoses), stratified by patient age category (years), patient sex and total number of chronic diseases, *Continued*

	Female					Male				
	18 – 34	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**	**18 – 34**	**35 – 44**	**45 – 64**	**65 – 84**	**≥ 85**
Musculoskeletal Problem → T2	245.4	257.6	159.6	61.1	52.0	191.0	196.0	113.3	38.6	62.5
	524.7	553.1	483.4	360.8	311.4	528.2	508.6	471.0	368.0	330.3
	(664.9)	(718.5)	(711.0)	(651.2)	(591.4)	(726.9)	(710.8)	(720.2)	(670.3)	(638.0)
Stomach Problem → T2	197.4	137.4	118.8	75.8	54.3	141.1	132.0	99.0	56.5	39.2
	385.2	444.4	397.9	296.2	178.0	451.1	438.8	416.1	343.3	243.0
	(485.4)	(653.0)	(614.1)	(548.0)	(294.8)	(639.2)	(656.6)	(673.3)	(651.7)	(454.7)
Colon Problem → T2	252.0	137.9	98.0	60.0	67.0	161.0	36.9	53.0	81.7	85.6
	477.5	421.9	390.6	359.8	224.5	432.3	332.1	368.3	346.7	324.4
	(609.3)	(658.8)	(610.8)	(668.1)	(402.9)	(610.8)	(499.0)	(610.5)	(585.7)	(557.7)
Liver Disease → T2	320.6	0.0	34.0	0.0	367.7	643.5	564.6	101.8	34.0	0.00
	437.6	70.2	248.0	262.2	367.7	734.4	731.4	384.1	321.1	9.8
	(414.0)	(102.9)	(473.5)	(524.5)	(519.4)	(619.2)	(935.9)	(581.4)	(663.4)	(17.1)
Urinary Problem → T2	342.4	385.4	276.2	154.0	46.2	268.6	185.5	130.0	26.5	35.5
	569.5	647.3	589.2	471.4	287.8	565.7	513.2	480.7	338.4	264.9
	(650.8)	(763.4)	(784.9)	(774.4)	(591.4)	(734.1)	(724.6)	(725.0)	(665.3)	(565.9)

* Each cell contains median time, mean time and standard deviation, all measured in days; longest time between diagnoses highlighted in green and shortest time between diagnoses highlighted in red for each patient category

Appendix AJ: Results of multilevel, single event survival analyses among adult patients with one or more chronic diseases

Independent Variable	Hazard Ratio (95% CI)				
	≥ 1 Chronic Diseases (n = 238,237)	**≥ 2 Chronic Diseases (n = 159,365)**	**≥ 3 Chronic Diseases (n = 96,945)**	**≥ 4 Chronic Diseases (n = 54,753)**	**≥ 5 Chronic Diseases (n = 28,675)**
Patient-Level					
Age	1.00 (1.00 – 1.00) ***	1.00 (1.00 – 1.00) ***	1.00 (1.00 – 1.00) **	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)
Sex (Female)	0.81 (0.78 – 0.85) ***	0.83 (0.78 – 0.87) ***	0.78 (0.72 – 0.85) ***	0.74 (0.66 – 0.83) ***	0.80 (0.66 – 0.95) **
Residential Location (Urban)	0.99 (0.97 – 1.01)	0.98 (0.96 – 1.01)	0.98 (0.95 – 1.01)	0.96 (0.92 – 1.00)	0.95 (0.89 – 1.02)
Median Household Income	1.00 (1.00 – 1.00) **	1.00 (1.00 – 1.00) **	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)
Total Number of Chronic Diseases	1.33 (1.33 – 1.34) ***	1.29 (1.29 – 1.30) ***	1.23 (1.22 – 1.24) ***	1.19 (1.17 – 1.20) ***	1.16 (1.14 – 1.18) ***
Provider-Level					
Age	0.98 (0.98 – 0.99) ***	0.99 (0.98 – 0.99) ***	0.99 (0.98 – 0.99) ***	0.98 (0.98 – 0.99) ***	0.98 (0.98 – 0.99) ***
Female	0.92 (0.85 – 0.99) **	0.97 (0.88 – 1.05)	0.97 (0.88 – 1.08)	0.95 (0.84 – 1.06)	0.94 (0.83 – 1.06)
Practice-Level					
EMR Type					
Accuro	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Bell	1.43 (1.21 – 1.69) ***	1.27 (1.04 – 1.55) **	1.15 (0.90 – 1.48)	1.04 (0.76 – 1.43)	0.99 (0.68 – 1.44)
DaVinci	0.85 (0.72 – 1.03)	0.77 (0.71 – 1.04)	0.72 (0.61 – 1.05)	0.67 (0.54 – 1.01)	0.72 (0.58 – 1.04)
Jonoke	0.91 (0.80 – 1.10)	0.82 (0.73 – 1.01)	0.82 (0.77 – 1.02)	0.74 (0.63 – 1.05)	0.79 (0.67 – 1.02)
Med Access	0.87 (0.74 – 1.01)	0.80 (0.67 – 0.96) **	0.76 (0.62 – 0.93) **	0.70 (0.56 – 0.88) **	0.74 (0.58 – 0.94) **
Nightingale	0.95 (0.85 – 1.05)	0.86 (0.77 – 0.97) **	0.84 (0.73 – 0.96) **	0.79 (0.68 – 0.91) **	0.81 (0.69 – 0.95) **
Oscar	1.56 (1.35 – 1.80) ***	1.47 (1.24 – 1.74) ***	1.34 (1.10 – 1.63) **	1.29 (1.01 – 1.63) **	1.35 (1.00 – 1.82) **
Practice Solutions	0.43 (0.37 – 0.50) ***	0.41 (0.35 – 0.49) ***	0.43 (0.36 – 0.53) ***	0.44 (0.36 – 0.55) ***	0.51 (0.40 – 0.63) ***
Wolf	0.73 (0.64 – 0.84) ***	0.68 (0.58 – 0.80) ***	0.63 (0.53 – 0.75) ***	0.59 (0.48 – 0.72) ***	0.62 (0.50 – 0.76) ***
Xwave	1.91 (0.82 – 4.46)	1.79 (0.62 – 5.16)	1.56 (0.40 – 6.12)	0.66 (0.08 – 5.60)	0.67 (0.08 – 5.65)
Practice Location (Urban)	0.74 (0.67 – 0.83) ***	0.75 (0.66 – 0.85) ***	0.71 (0.61 – 0.82) ***	0.69 (0.58 – 0.82) ***	0.72 (0.60 – 0.88) **
Interaction Term					
Patient Age & Patient Sex	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.00)	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.00)
% Variance (95% CI) Contributed by Each Level					
Within Provider	9.10 (6.82 – 12.14)	11.66 (8.45 – 16.08)	14.48 (12.00 – 17.47)	16.98 (13.84 – 20.84)	16.41 (13.01 – 20.69)
Within Site	0.18 (0.00 – 2.13)	0.20 (0.00 – 3.63)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)	0.00 (0.00 – 0.00)

* CI = Confidence interval; ** p-value < 0.05; *** p-value < 0.001

Curriculum Vitae

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	Transdisciplinary Understanding and Training on Research in Primary Health Care Fellowship 2013 – 2014
Related Work Experience:	Teaching Assistant, Western University 2012 – 2016
	Research Assistant, Gateway Centre of Excellence in Rural Health 2012 – 2016

Peer-Reviewed Publications:

Nicholson K, Terry AL, Fortin M, Williamson T, Bauer M, Thind A. Examining the prevalence and patterns of multimorbidity in Canadian primary healthcare: a methodologic protocol using a national electronic medical record database. Journal of Comorbidity. 2015;5(1):150-161.

Nicholson K, Terry AL, Fortin M, Williamson T, Thind A. Understanding multimorbidity in primary health care: the challenge and necessity of a pan-Canadian electronic medical record database. Canadian Family Physician. 2015;61(10):918.

Li Y, Carpenter C, Nicholson K, Milne K. Diagnostic accuracy of the iCare Rebound Tonometer compared to the Perkins Applanation Tonometer in assessing intraocular pressure in rural patients. Diagnosis. 2015;2(4):227-234.

Nicholson K, Randhawa J, Steele M. Establishing the South Western Academic Health Network (SWAHN): a survey exploring the needs of academic and community networks in South Western Ontario. Journal of Community Health. 2015;40(5):927-939.

Nicholson K, Stewart M, Thind A. Examining the symptom of fatigue in primary care: a comparative study using electronic medical records. Journal of Innovation in Health Informatics. 2015;22(1):235-243.

Nicholson K, Sasseville M, Contant E. Multimorbidity: a complex reality in primary health care. Health Science Inquiry. 2014;5(1):71-73.

Contant E, Nicholson K. Transdisciplinary collaboration: the future of primary health care. Health Science Inquiry. 2014;5(1):101-102.

Pinto F, Bhimani M, Milne WK, Nicholson K. Procedural sedation and analgesia in rural and regional emergency departments. Canadian Journal of Rural Medicine. 2013;18(4):130-136.