Using primary care electronic medical record data to establish a case definition and describe the burden of young-adult onset metabolic syndrome in Northern Alberta

by

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Thesis Abstract

Background: There is little evidence on the prevalence of metabolic syndrome (MetS) in the younger adult Canadian population. Moreover, MetS is even less studied within the primary care setting due to multiple barriers including difficulty for providers to identify patients given the multitude of definitions used in practice, varying electronic medical record systems (EMRs) used, and the presumption that younger people are generally healthier. With the growing prevalence of preventable chronic diseases worldwide, the need to expand our understanding of MetS in younger adults is critical to preventing its long-term sequelae.

Objectives:

1. Develop a case definition and case-finding algorithm for MetS using primary care electronic medical record data.
2. Describe the patterns and prevalence of MetS in younger adults, aged 18-40 years old.
3. Describe the patterns and prevalence of MetS between sexes, aged 18-40 years old.

Methods: Using a cross-sectional study design, we developed a case definition and case-finding algorithm for the identification of MetS. Electronic medical record (EMR) data from the Northern Alberta Primary Care Research Network (NAPCReN), a part of the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), was used with a focus on younger adults who were 18-40 years of age. Both studies for this thesis used data including anthropometric measurements, laboratory investigations, and CPCSSN-validated disease diagnoses to establish prevalence and patterns of MetS. The first study outlines the case definition and case-finding algorithm and describes the patterns of MetS in the NAPCReN younger adult population who attend primary care clinics in Northern Alberta. The second study aims to describe the patterns of young-adult onset MetS stratified by sex. The analysis was performed in RStudio (version 1.1.453) and includes descriptive statistics, multiple comparisons ($p < .05$), and a linear search (case-finding) algorithm development.

Results: According to the MetS case-finding algorithm, the prevalence of MetS in younger adults was 4.4%. Nearly all individuals with MetS were overweight and obese (91.2%). The most frequent 3-factor combination of MetS consisted of being overweight or obese, having elevated blood pressure (BP), and hypertriglyceridemia (41.4% of cases). Half of the individuals with MetS were missing measures for FBG, and one-fifth were missing a HbA1c measure. The proportions of missing laboratory data were even greater for all individuals who were overweight and obese. Of the CPCSSN validated diseases among individuals with MetS, depression (16.5%) had the highest prevalence followed by diabetes (15.2%), hypertension (14.2%), and osteoarthritis (2.6%). When assessing the differences in sex, there were more females than males in this sample with females having more favourable metabolic profiles compared to males. In those with MetS, the reverse was found where males had better measures for BMI and HDL-C compared to females. The most prevalent 3-factor MetS combination among males consisted of being overweight, having elevated BP, and hypertriglyceridemia. The most prevalent 3-factor MetS combination among females consisted of being overweight, having elevated BP, and low HDL-C. Being overweight as defined by a BMI ≥25 kg/m^2, was the most common factor among both sexes with MetS. The prevalence of chronic diseases such as depression and diabetes were higher in females compared to males however, hypertension was higher among males.

Conclusion: We found that one in twenty-five younger adults attending a primary care clinic had MetS, which is likely an underestimate given the high levels of missing data for those noted to be overweight and obese. In those with MetS, women appear to have more metabolic dysfunction than men. The large proportion of missing data, especially amongst those who are overweight and obese, calls for exploration of whether levels of missed testing are appropriate and sets the stage for future quality improvement to do earlier risk stratification and prevention of metabolic syndrome sequelae.

Preface

This thesis is an original work by Jamie Boisvenue. The identification and design of the research study was done in collaboration with Dr. Donna Manca and the NAPCReN team, Jeffrey A. Johnson, PhD, and Dr. Roseanne O. Yeung. This thesis is considered a part of the overall research study under the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) project, which has received ethics approval from the University of Alberta Research Ethics Board, “The Primary Care Sentinel Surveillance Network (CPCSSN) project 2.0”, Pro. 00073600_REN1, September 21, 2018. The research contributed through this thesis will be used to inform the work in establishing a clinical case definition for metabolic syndrome by Dr. Donna P. Manca and the CPCSSN case definition working group.

All code development, programming, and review were performed in collaboration with the expert guidance of Mr. Carlo Oliva, Department of Computer Science, University of Alberta. Data extraction and cleaning was done courtesy of Mr. Brian Forst, NAPCReN Data Manager.

No part of this thesis has been previously published.

Dedication

“The noblest pleasure is the joy of understanding.”
- Leonardo da Vinci

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This thesis research was conducted on Treaty 6 territory, traditional lands of First Nations and Metis people.

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List of Symbols & Abbreviations

AACE-ACE	American Association of Clinical Endocrinologists – American College of Endocrinology
ACR	Albumin-creatinine Ratio
AHA	American Heart Association
ATC	Anatomical Therapeutic Classification
BMI	Body Mass Index
BP	Blood Pressure
C-CHANGE	Canadian-Cardiovascular Harmonized National Guidelines Endeavour
CCHS	Canadian Community Health Survey
CHHS	Canadian Heart Health Survey
CHMS	Canadian Health Measures Survey
CPCSSN	Canadian Primary Care Sentinel Surveillance Network
CVD	Cardiovascular Disease
dBP	Diastolic Blood Pressure
EMR	Electronic Medical Record
FBG	Fasting Blood Glucose
GDM	Gestational diabetes mellitus
HbA1c	Glycated Hemoglobin
HDL-C	High Density Lipoprotein-Cholesterol
ICD9	International Classification of Disease 9
IDF	International Diabetes Federation
MetS	Metabolic Syndrome
NAFLD	Non-Alcoholic Fatty Liver Disease
NAPCReN	Northern Alberta Primary Care Research Network
NCEP-ATPIII	National Cholesterol Education Program – Adult Treatment Panel III
NHLBI	National Heart, Lung, & Blood Institute
NIH	National Institutes of Health
PCOS	Polycystic Ovarian Syndrome
sBP	Systolic Blood Pressure
SD	Standard Deviation
T2D	Type 2 Diabetes
TG	Triglycerides

WC	Waist Circumference
WHO	World Health Organization

– Chapter 1 –

Introduction

Metabolic syndrome (MetS) is a growing public health concern and is defined as the clustering of biochemical and clinical abnormalities including central obesity, dyslipidemia, hypertension, and insulin resistance [1–4]. The pathophysiology of MetS can be explained by chronic low-grade inflammation brought about by the impairment of lipid and glucose homeostasis within the body, increasing the risk of type 2 diabetes (T2D), and cardiovascular disease (CVD), amongst other conditions [5]. Traditionally, MetS and its constituents were considered to manifest in older adult populations. Due partly to the increases in obesity rates in childhood and adolescence, we are now seeing children and younger adults affected by MetS [6]. The rates of chronic disease is often predicated on early manifestations of MetS. The global prevalence of obesity has doubled in the last 40 years, with 39.0% of the world's population (1.9 billion) classified as overweight and obese [7]. Approximately 425 million people worldwide are living with diabetes, and this is projected to increase to 629 million by 2045 [8]. Evidence has shown that the risk of CVD doubles in the presence of MetS [9], and CVD is the number one cause of mortality with an estimated 31% of global deaths [10].

Global estimates for MetS prevalence have varied given the evolving criteria throughout the last 30 years [11]. Metabolic syndrome is approximately three times as common as many chronic diseases such as diabetes and the global prevalence of MetS has been estimated by some, to be about one-quarter of the world's population or more than 1 billion people [11]. A pooled analysis of data from multiple studies from 17 countries with varying definitions suggested that approximately 5-7% of young adults aged 18-30 years have MetS [12]. Emerging evidence also

suggests that younger adults (defined as aged 18-29 years) are among the highest risk groups for measures of increased waist circumference (WC) and low high-density lipoprotein cholesterol (HDL-C) leading to a lifetime risk burden for chronic disease [13].

The age of onset for the development of MetS and related diseases is now being recognized at an earlier age [14,15] suggesting that earlier identification and intervention of MetS risk factors are required [16,17]. Over the last 50 years, the lifestyles of younger adult populations have changed, with increases in sedentary inactivity and screen time, more accessible heavily processed foods, and reduced active transportation [18–20]. The most effective strategies for prevention and treatment of MetS have included dietary modification and an increase in physical activity [17,21,22]. The consumption of low glycemic index and less processed foods are essential to maintaining good metabolic health [21,23,24], yet are increasingly difficult to access due to modern food industrialization.

Physical activity also plays an important role in energy expenditure and the prevention and management of MetS. Regular exercise promotes positive structural changes to muscles, increasing glucose homeostasis and therefore reducing muscle related insulin resistance and lipogenesis [25]. Many studies have shown the positive effects that physical activity has on lowering the odds of MetS [26], its partial association between MetS and depressive symptoms [27], and reducing overall sedentary and screen times [28]. A diminishing knowledge in necessary life skills, lack of interest in long term consequences, and barriers in access to health care in early adult years contribute to poorer health outcomes and progression of chronic disease [20]. A change in lifestyle to include healthier eating and increased physical activity is not restricted to age and is perhaps the most beneficial and cost-effective treatment for chronic disease.

Purpose & Rationale

Primary care clinicians are faced with challenges in the early detection and treatment of MetS. A shift in the focus to primary prevention can lead to prevention of downstream morbidity and mortality [29,30]. Thus far, the public health focus in assessing the burden of MetS has either been on adolescents under 18 years of age or adult populations over 40 years of age [6,9,16,31–34]. The gap in knowledge and management of young-adult onset MetS is particularly alarming given the highest rate of diabetes incidence in Canada is among young women developing gestational diabetes [8]. Young-adult onset MetS (18-40 years) is a growing burden amongst the Canadian population.

We have taken a pragmatic approach to evaluating the prevalence of MetS in a convenience sample of younger adults attending primary care clinics in Northern Alberta. Specifically, we have used the Northern Alberta Primary Care Research Network (NAPCReN), part of the Canadian Primary Care Sentinel Surveillance Network (CPCSSN), to capture the state of young-adult onset MetS within the Northern Alberta region.

Therefore, this research aims to achieve three objectives:

1. Develop a case definition and case-finding algorithm inclusive for young-adult onset MetS using electronic medical record (EMR) data from the NAPCReN-CPCSSN primary-care setting.
2. Identify and describe the overall patterns and prevalence of young-adult onset MetS within a sample from the NAPCReN-CPCSSN primary care setting.
3. Describe the sex differences of those with MetS and the patterns of co-morbidity within a sample from the NAPCReN-CPCSSN primary care setting.

Literature Review

Metabolic Syndrome

Over the last one hundred years there have been several terms put forward for what is now known as MetS. The idea of co-occurring metabolic risk factors related to T2D and CVD have existed in the literature since at least 1923, when Eskil Kylin, a Swedish physician and researcher, first noted a syndrome defined by the collection of hypertension, hyperglycemia, obesity, and hyperuricemia [35]. In the early 1920s, other observed clustering of metabolic factors, such as hypertension, diabetes, elevated blood uric acid and hypertension [35–40]. During this same time, the distinction between insulin-sensitive and resistant phenotypes among people with diabetes was also identified, which contributed to the growing body of knowledge surrounding MetS [41].

Kylin (1923) referred to it as a syndrome of hypertension, which later was defined as elevated blood pressure [35]. Camus (1966) called it the 'trisyndrome' to denote the triple combination of gout, diabetes, and hyperlipidemia [42]. Avogaro & Crepaldi (1967) identified it as plurimetabolic syndrome [43]. Menhert and Kuhlmann (1968) referred to MetS as the Syndrome of Affluence [44]. It was not until 1981 when the term 'metabolic syndrome' was first suggested by Hanefeld and Leonhardt [45].

Among the terms developed, those most debated in last 30 years have been 'Syndrome X', mentioned in Reaven's seminal 1988 Banting Lecture [46], 'Deadly Quartet' by Kaplan (1989) [47], and 'Insulin Resistance Syndrome' by DeFronzo & Ferrannini (1991) [48]. Reaven hypothesized that Syndrome X, consisting of the presence of impaired glucose tolerance, elevated very low-density lipoprotein (LDL-C), elevated triglyceride (TG), low HDL-C, hyperinsulinemia, and hypertension, exacerbates the development of insulin resistance, which then leads to other disorders [46]. Kaplan later stressed the importance of including abdominal

obesity with Reaven's combination of hypertension, hypertriglyceridemia, and impaired glucose tolerance, referring to MetS as the Deadly Quartet [47]. DeFronzo and Ferannini [48] and Haffner et al. [49], illustrated that insulin resistance was sufficient in the development of disorders from the clustering of metabolic factors. Throughout the evolution of MetS, many have demonstrated the deleterious effect of insulin resistance on multiple organ systems, yet much work remains to be done in terms of adequately identifying, preventing, and managing its growing worldwide prevalence [50,51].

Defining Metabolic Syndrome

The definition of MetS has been evolving as various scientific groups have put forward differing guidelines and criteria over the years. The first formal definition for MetS was established by the World Health Organization (WHO) in 1998, as part of a report classifying and defining diabetes mellitus [52]. Within the WHO report, the committee identified the diagnostic and therapeutic challenges of persons living with "hypertension, central (upper body) obesity, and dyslipidemia, with or without hyperglycemia", who are at particular risk for the development of CVD and T2D [46,52]. They proposed a working definition of dysglycemia (as defined by a diagnosis of T2D, impaired glucose regulation, or reduced insulin sensitivity) plus two of the following: elevated blood pressure (BP) $\geq$140/90 mmHg, hypertriglyceridemia $\geq$1.7 mmol/L and/or low high-density lipoprotein cholesterol (HDL-C) <0.9 mmol/L in men and <1.0 mmol/L in women, abdominal obesity as defined by waist-to-hip ratio (WtHR) >0.9 (males) and >0.85 (females) and/or a body mass index (BMI) >30 kg/m^2, and albumin-creatinine ratio (ACR) $\geq$30 mg/g^{-1} [51,52].

The European Group for the Study of Insulin Resistance suggested that insulin resistance be at the core of the definition in identifying risk for T2D, suggesting that a diagnosis of T2D be dropped from the criteria given that insulin resistance is considered to be a risk factor for T2D

[53]. They also indicated that in order for an individual to be considered as having MetS, they must first have 2 of the following: fasting plasma glucose (FPG) ≥ 6.1 mmol/L; dyslipidemia as defined by TG ≥ 1.7 mmol/L or HDL-C < 1.0 mmol/L or receiving treatment; hypertension defined as ≥140/90 mmHg or receiving treatment; and central obesity as defined by (WC) ≥ 94 cm (men) and ≥ 80 cm (women) [53]. Notably, this definition placed a stronger focus on using waist circumference (WC) by removing measures of BMI from the definition altogether [53,54].

In 2001, the American National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines were developed with an emphasis on assessing risk for CVD as well as the diagnosis and treatment of high cholesterol [55]. The NCEP ATP III guidelines were updated in 2005 by a joint statement from the American Heart Association (AHA) and National Heart, Lung, and Blood Institute (NHLBI). They included diabetes in the definition of hyperglycemia, the use of lipid-lowering medications for the control of hypertension and dyslipidemia, and a decrease in the clinical cut point for an abnormal fasting blood glucose from 6.1 mmol/L to 5.6 mmol/L [4,56]. The definition put forward identified individuals with MetS and therefore at risk for coronary heart disease (CHD) who met any of three of five criteria as follows: presence of central obesity defined by a WC of > 102 cm in men or > 88 cm in women; hypertension as defined by an elevated BP ≥130/85 mmHg; hyperglycemia using a FPG cut point of ≥ 6.1 mmol/L; a presence of hypertriglyceridemia indicated by TG ≥1.7 mmol/L; and low HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women [4]. Diabetes was considered a replacement for insulin resistance within the AHA/NHLBI definition, given that most with diabetes have insulin resistance.

In 2003, the American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE), released a position statement in an *Endocrine Practice Report* on

first defining MetS as 'Insulin Resistance Syndrome' (IRS). They characterized IRS by a loss in tissue sensitivity to insulin leading to increased secretion, resulting in the clustering of metabolic abnormalities [57]. They defined MetS as meeting two or more abnormalities of plasma glucose 6.1-6.9 mmol/L or 120 minute 75g oral glucose tolerance test 7.8-11.1 mmol/L; hypertriglyceridemia defined by TG ≥1.7 mmol/L; hyperlipidemia defined by HDL-C <1.0 mmol/L in men and <1.3 mmol/L in women; and an elevated BP >130/85 mmHg [57]. Though BMI/ WC were not considered critical components of IRS, it was suggested that its presence increased the likelihood of IRS [54,57]. Among the other risk factors, a diagnosis of hypertension, polycystic ovarian syndrome (PCOS), non-alcoholic fatty liver disease (NAFLD), acanthosis nigricans, gestational diabetes mellitus (GDM), non-Caucasian ethnicity, sedentary lifestyle, age of 40 or above, and family history of CVD were also considered [57].

Despite differing criteria across the definitions of MetS, they all share a common goal in identifying individuals at higher risk for the development of cardiometabolic disease. The public health and scientific communities are tasked with reaching consensus on clear definitions of MetS. Not only does assessing MetS using various definitions among different populations pose a challenge but the sources of data also contribute to a greater variation in the estimates of prevalence. A systematic review of data from 26,609 young adult individuals (18-30 years of age) across 17 countries, showed definition dependent estimates of prevalence for MetS to be 4.8% (NCEP-ATP III), 5.2% (AHA/NHLBI), 7.0% (IDF), and 6.5% (harmonized) [12]. The most prevalent factor for MetS amongst these studies was low HDL followed by elevated BP, abdominal obesity, and elevated TG, irrespective of the definition [12]. Evidence in US longitudinal data on a representative sample from the National Health and Nutritional Examination Survey (NHANES) III (1988-1994) found that based on the NCEP ATP III guidelines, the overall unadjusted prevalence of MetS within the general adult US population was 21.8%, ranging from 6.7% to 15% in those 20-40 years [33]. In Canada, epidemiological

investigation of MetS is less studied amongst younger adults [1,32,34,54,58–60]. The prevalence of young-adult onset MetS in Canada has increased with estimates of 6.5% in those 18-39 years from a 2011 report of the Canadian Health Measures Survey (CHMS) [34], to just under 13% as reported by Statistics Canada and CHMS in 2013 [61].

Pathophysiology of Metabolic Syndrome

Our understanding of the roles of adiposity and insulin resistance in MetS has changed in the last 10-20 years. Adipose tissue is now recognized as having complex endocrine functions and categorized into multiple types such as white, brown, and pink fat [11]. Excess adiposity as manifested by central obesity and insulin resistance, is thought to be a main driver of many of the pathophysiological changes that lead to the development of MetS [39].

Insulin is a hormone that plays a role in multiple mechanisms including adipose tissue lipolysis, protein synthesis, glucose homeostasis and conversion to glycogen, and the uptake of amino acids [39]. The insulin-sensitive individual possesses phenotypical characteristics of someone who is generally physically active with little presence of central obesity however, the opposite is seen in the insulin-resistant individual [62]. It is now understood that insulin resistance and hyperinsulinemia contribute to a myriad of chronic disease and metabolic derangement, much of which can be prevented or controlled through modification to lifestyle. With the consumption of food, there is an increased secretion of insulin that aids in the storage of glycogen in the liver and upon reaching storage capacity, any remaining carbohydrates are converted into fat by way of hepatic de novo lipogenesis [63]. During lipolysis, adipose tissue contributes to the development of insulin resistance as the growth of adipocyte size increases the production of FFA [64]. Under normal physiological conditions, insulin regulates adipose tissue lipolysis and synthesis of FFAs however, FFA production is increased in the insulin resistant person from a dysregulation in insulin secretion [3,65]. A release of FFAs by enlarged and stressed adipocytes

paired with reductions in FFA clearance, has an inhibitory effect on insulin's antilipolytic action and therefore increases adiposity [66]. Elevated FFA levels in obese individuals are thought to produce low grade inflammatory effects that contribute to an increased atherogenic lipid profile [67].

An increase in visceral adipose tissue (VAT) specifically, causes a vicious cycle where the production of FFAs leads to insulin resistance and therefore an increased presence of insulin once again results in increase FFAs [39]. The hypothesized "portal theory" suggests that because VAT originating FFAs are drained directly into the portal system, the liver is therefore exposed to a high presence of FFAs leading to the development of insulin resistance [68]. If not oxidized and stored, the presence of FFAs in the liver inhibit insulin production causing an increase in the output of glucose as well as synthesis of proinflammatory cytokines and elevated TGs [39]. This hypertriglycemic state contributes to the reduction in HDL-C by way of clearance of smaller more efficient HDL-C particles converted from triglyceride-rich lipoproteins and secreted through the kidney [69]. In skeletal muscle, peripheral insulin resistance occurs in the downregulation of glucose transport by an increase in FFA uptake and the accumulation of TGs [67]. The role of FFA mediated insulin resistance and its presence among a myriad of chronic diseases, highlight the importance of understanding the pathophysiological mechanisms underlying MetS.

In young adults, MetS is shown to be associated with subclinical atherosclerotic risk factors in otherwise healthy adults [70]. Findings from the Bogalusa Heart study have shown the association between MetS and the increased risk of atherosclerotic burden in young adults through B-mode ultrasonography of the carotid arteries [70]. Furthermore, this study showed that increased BP and low HDL-C are particularly strong predictors of increased carotid intima-media thickness in younger adults, showing a 3.4 fold increased likelihood of MetS under NCEP

ATP III criteria. Given that factors for MetS are modifiable, these results show the potentially reversible nature of atherosclerotic burden in younger adults emphasizes the need for greater awareness and intervention of MetS at a younger age.

In persons with hypertension, insulin resistance is known to cause a reduction in vasodilatory action in the blood vessels and an increase in reabsorption of sodium in the kidney [71]. Further alterations in the delivery of insulin to skeletal muscle by way of the sympathetic nervous system effects the uptake of glucose leading to insulin resistance [72]. Though vascular remodelling and the activation of the sympathetic nervous system is strongly associated with hypertension, obesity, and insulin resistance, it also plays an important role in the rise of BP and impaired glomerular kidney filtration [73]. The relationship between a rise in BP and obesity is almost linear although there are still individuals who are obese without hypertension, and has been hypothesized that genetic predisposition contributes to fat distribution and therefore a greater prevalence of hypertension in some overweight or obese individuals but not all [73].

The atherogenic burden has also been shown to be more aggressive in younger adults, with patients having a 14-times higher risk of myocardial infarction in the presence of diabetes before the age of 45 [74,75]. Young adults are also less aggressively managed than those who are older and has been suggested to be the result of clinical inertia and hesitation in prescribing drugs at such an early age [76]. The prevention of vascular complications should be considered an important goal, especially in those with existing metabolic derangement. Although MetS is a constellation of risk factors, this current evidence highlights the importance of targeting the atherogenic nature of MetS among young adults and how this can help reduce the risk and prevent the burden of chronic disease and organ damage later in life.

Canadian Primary Care Sentinel Surveillance Network (CPCSSN)

The CPCSSN was established in 2008 following a need to provide resources and infrastructure support to practice-based research networks across Canada [77]. The primary care-based network is the first pan-Canadian multi-disease EMR surveillance system consisting of 12 practice-based research networks spanning 8 provinces and 1 territory with participation from over 1,262 family physicians and nurse practitioners contributing data from approximately 1.8 million patients [78]. All CPCSSN EMR data is de-identified and consent is provided from all participating CPCSSN primary care clinicians and data custodians using the data for research. Patients are provided an opportunity to opt out of the CPCSSN database. The data that is collected within CPCSSN includes patient demographics, validated disease diagnoses, physical exam, laboratory results, medications, medical procedures, referrals and physician billings. There is an institutional data sharing agreement between CPCSSN and Queen's University in Kingston, Ontario where data is stored in the Centre for Advanced Computing using multiple layers of cyber security.

There are 8 validated disease definitions that have been developed by CPCSSN specifically for the primary care setting based on the International Classification of Diseases and Health Related Problems version 9 (ICD9) codes as well as numeric and text data within the EMR that includes problem and encounter diagnoses, billing, referrals, laboratory and physical exam tests, and medications specific to the treatment of each disease [79,80]. All validated CPCSSN definitions are listed in Table 1.1 of which hypertension and diabetes are used within the case-finding algorithm for MetS, and we evaluated the prevalence of depression and osteoarthritis for estimates of MetS related co-morbidity.

Northern Alberta Primary Care Research Network (NAPCReN)

The NAPCReN consists of family physicians and a multidisciplinary collaboration of researchers and clinicians within primary care that use evidence to drive and inform action within network clinic practices. The NAPCReN consists of 18 active sites with a total of 77 primary care providers representing a population of 91,525 patients in Northern Alberta [81]. Data generated in real world primary care settings is collected within the NAPCReN network and represents a sample derived from a population of patients attending a primary care clinician. Participating clinicians within the NAPCReN are eligible for participation in the CPCSSN. Data that is generated within the NAPCReN is contributed to CPCSSN in an effort to better understand the epidemiology of disease in the primary care setting and improve the health system and patient outcomes [81].

Table 1.1 Validated CPCSSN disease definitions

Disease	Definition
Diabetes Mellitus	1. At least two ICD9 250 codes for billing within two years. 2. Any ICD9 250 code on the problem list. 3. Anti-diabetic medications (Table A-1.1). 4. Lab result of an HbA1c ≥7 mmol/L or two occurrences within one year of an FBG > 7 mmol/L. Sensitivity 95.6%, PPV 87.0%, Specificity 97.1%, NPV 99.1%
Hypertension	1. At least two ICD9 codes 401-405 for billing within two years. 2. Any occurrences of ICD9 codes 401-405 on the problem list. 3. Anti-hypertensive medications (Table A-1.2). Sensitivity 84.9%, PPV 92.9%, Specificity 93.5%, NPV 86.0%
Depression	1. Any occurrence of ICD9 codes 296 and 311 within two years on the billing or problem lists. 2. Anti-depressant medications (Table A-1.3). Sensitivity 81.1%, PPV 79.6%, Specificity 94.8%, NPV 95.2%
Osteoarthritis	1. Any occurrences of ICD9 codes 715 and 721 on the billing or problem lists. Sensitivity 77.8%, PPV 87.7%, Specificity %, NPV 86.0%

**ICD9 International Classification of Diseases 9, PPV = positive predictive value, NPV = negative predictive value.*

– Chapter 2 –

Establishing a case definition and describing the burden of young-adult onset metabolic syndrome in a Northern Alberta primary care setting using electronic medical record data: A cross-sectional study

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Introduction

Metabolic syndrome (MetS) is a constellation of interconnected metabolic factors that contribute to the development of obesity, cardiovascular disease (CVD), type 2 diabetes (T2D) and other related chronic conditions [2,4,48]. The main components of MetS are widely considered to be elevated blood pressure (BP), low high-density lipoprotein cholesterol (HDL-C), hypertriglyceridemia, dysglycemia, and excess visceral adiposity [82]. The pathogenic mechanisms of MetS are thought to be driven by the presence of chronic low-grade inflammation due to the hormonal effects of excess adiposity [5]. The causes of MetS are still under investigation and reviews of this have been published elsewhere [1,82,83]. To date, findings from the Canadian Heart Health Survey (CHHS) data demonstrated the prevalence of MetS among the overall adult population to be 19.0%, with an increase in prevalence with age, as high as 39.0% in persons older than 60 years [34]. A slightly higher MetS prevalence has been reported in the US with 23.0% of the adult population having MetS, likely driven by the increasing prevalence of obesity and diabetes [84]. Given that rates of obesity continue to climb, and treatments remain largely ineffective, early detection of MetS is essential to preventing the development of irreversible organ damage [5,85].

Challenges in consistently reporting estimates of MetS prevalence are driven by the ambiguity of multiple definitions created by different organizations [4,51–53,86,87]. The most widely used criteria in the literature for identifying individuals with MetS comes from the US National Cholesterol Education Program Adult Treatment Panel III (NCEP- ATP III) guidelines, where MetS are defined by the presence of at least three of the following:

- Large waist circumference (WC) ≥ 102 cm (men) or >88 cm (women)
- Elevated triglycerides (TG) ≥ 1.7 mmol/L
- Low HDL-C <1.0 mmol/L (men) or <1.3 mmol/L (women)

- Elevated BP of ≥130/≥85 mmHg
- Elevated fasting blood glucose (FBG) ≥5.6 mmol/L [86].

Further guidelines have suggested differences in ethnic specific WC cut points, given the predisposition of certain non-white ethnicities to developing MetS at significantly slimmer WC's than white ethnicities [8]. Current estimates of prevalence for MetS worldwide are highly dependent upon the definition being used and the specific population being studied among other factors.

Since MetS is typically more prevalent in older populations, its characterization in younger adult populations is less studied. Two Canadian based studies both using cycle 1 Canadian Health Measures Survey (CHMS) data 2007-2009, showed population prevalence estimates for young-adult onset MetS 18-40 years to be 6.5% and 7.8%, respectively [9,34]. The difference between these two studies was the use of ethnic-specific cut points for measures of abdominal obesity (WC), resulting in a higher overall estimated prevalence in the second study. To date, there has been little investigation of the prevalence of young-adult onset MetS in Alberta. Existing reports are either based on smaller cohorts of older adults, minority ethnic groups, or overall population estimates based on self-reported data [9,88,89].

There is a growing interest in addressing the increase in childhood obesity and the development of related chronic disease as children mature into adulthood [7,90]. Patterns of infant and childhood weight gain strongly predict the development of MetS later in life [88]. There are also transgenerational effects, where genetic predisposition and family history of disease strongly influencing MetS health outcomes [91,92]. A prospective study of a cohort from the Princeton Lipid Research Clinic showed that children with a cluster of factors for MetS were more likely than their peers to develop T2D 25-30 years later and were also affected by the presence of

parental T2D [15]. Growing evidence on the genetic inheritance and fetal programming for metabolic risk factors leading to the early development of obesity, substantiates the importance of assessing MetS in younger adults, especially in women of childbearing age where the rates of gestational diabetes continue to climb [3,8,15,51,93–95].

In recent years, health organizations have advocated for health promotion and metabolic disease prevention in children and young-adult Canadians [96–98]. However, many MetS criteria set forth were developed with considerations that MetS is more prevalent in older populations and thus cut points were assigned appropriately. Unfortunately, this also means that the historical definitions put forward for identifying MetS were created without the younger demographic in mind. To make matters more challenging, the use of multiple definitions creates confusion for clinicians tasked with identifying MetS with no clear actionable guidelines. Assessing the presence of young-adult onset MetS in the primary care setting is critical to understanding the scope of the problem and initiating systems-based strategies for improving care to this vulnerable group.

The main objectives of this study were to identify, assess, and report on the prevalence of young-adult onset MetS in Northern Albertan young-adult patients 18-40 years of age, using a harmonized criterion for use within the Northern Alberta Primary Care Research Network (NAPCReN) primary care electronic medical record (EMR) data. Using a case-finding algorithm, we identify MetS cases and examined the patterns of MetS factors and disease using a three-year catchment window. This is the first large-scale epidemiological study to assess the prevalence of young-adult onset MetS within the NAPCReN primary care setting in Alberta.

Methods

Data Source

This study uses Alberta-based data collected from the NAPCReN, which contributes data to the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) [78]. The EMR data is representative of 18 active clinics consisting of 77 participating primary care providers across Northern Alberta representing 91,525 patients[81]. Custodians, family physicians and other primary care providers, provide the NAPCReN with access to their EMR data. The data is extracted, cleaned, and entered into the NAPCReN regional repository, and then processed further for entry into the CPCSSN national data repository (http://cpcssn.ca). The data provided for this research is the NAPCReN regional data, a Northern Alberta subset of the Alberta primary care practice population. Our sample was de-identified and filtered *a priori* for the age range of 18-40 years, and consists of patient demographics, physical examination data, laboratory investigations, CPCSSN defined diagnosis of disease, medications, and referrals. This study utilizes patient demographics, physical exams, laboratory tests, and CPCSSN defined disease data. Physical exam data that was used includes body mass index (BMI), systolic blood pressure (sBP), and diastolic blood pressure (dBP). The laboratory diagnostic data that was used includes high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and triglycerides (TG).

Study Design

This is a descriptive cross-sectional study evaluating the most recent measures of physical examination, laboratory investigations, and disease diagnosis data to ascertain the prevalence of MetS in a sample of primary care practices in Northern Alberta, Canada. The study denominator included all alive persons between the ages of 18 to 40 years who had an

encounter with a participating NAPCReN primary care clinic between July 29, 2015 and July 29, 2018 with data for sex, birth year, and Alberta postal code.

Establishing a Population Practice Denominator

The estimation of a population practice denominator is essential for epidemiological study as it allows the comparison of prevalence or incidence of disease as well as various other measures [99]. Those who exist within the NAPCReN clinics who seek health care are considered to form the basis of the denominator. Study subjects must have had at least one physical exam, laboratory investigation, or disease diagnosis between the specified date range. This sample was limited to those patients residing in Northern Alberta who attended a participating NAPCReN-CPCSSN primary care clinic. A list of physical examination data, laboratory investigations, and disease diagnoses were then merged with patient demographics based on patient ID. Subjects were excluded if they were outside of the prespecified date range, were missing sex data, they had a non-Albertan postal code (i.e., not starting with T), or were deceased. Data received by the researcher is cleaned and filtered *a priori* by the NAPCReN data management team. As illustrated in Figure 2.1, the denominator was determined by filtering the physical exam, laboratory investigation, and disease data tables for the specified date ranges and selecting each subject based on their most recent measures. This study was approved by the Research Ethics Board, University of Alberta (Pro. 00073600).

Measures

Given that there are variations and controversies in the criteria used in establishing MetS [82], we based our criteria on available evidence used within young-adult populations [16,100] and available parameters within the NAPCReN EMR data. MetS was defined through a harmonized case definition using criteria based on NCEP ATP III [86], the World Health Organization

(WHO)[101], Diabetes Canada (DC) [51], Canadian-Cardiovascular Harmonized National Guidelines Endeavour (C-CHANGE)[102], and CPCSSN[80].

As outlined in Table 1.2, a subject was classified as having MetS if they met a minimum of three of five criteria. Recognizing the concerns and limitations of body mass index (BMI) as a measure of excess central adiposity, we chose to take a pragmatic approach and use BMI as virtually all (98.5%) individuals within this data did not have measures for WC and there is reasonable evidence to consider BMI an equally viable measure where WC data is unavailable [103]. We did not distinguish between those who are overweight and obese given that the minimum cut point in the established MetS definitions in the literature use a BMI of at least 25 kg/m^2 [86]. Physical exam data contained measures for BMI beyond the highest values seen clinically and were more likely to be entered incorrectly as body weights. Therefore, outliers were removed using cut points for BMI less than 15 kg/m^2 and above 55 kg/m^2.

Dysglycemia was present if a subject had a CPCSSN diagnosis of diabetes or HbA1c ≥6.0% or FBG ≥5.6 mmol/L. To identify dysglycemia, we used validated CPCSSN diagnosis of diabetes if they had an ICD9 250 code either in the billing or problem list, they were taking an anti-diabetic medication as well as having a previous laboratory value of elevated HbA1c or FBG. It should be noted that within the CPCSSN diagnostic criteria, an HbA1c ≥7.0% or two occurrences within a year of FBG >7.0 mmol/L were used, whereas we used the criteria cut points within the standardized MetS definitions (HbA1c ≥ 6.0% or FBG ≥ 5.6 mmol/L). A more stringent cut point was applied given that we are assessing the presence of dysglycemia and not diabetes.

We used the validated CPCSSN diagnosis of hypertension or an office sBP or dBP to establish the presence of elevated BP to be the most inclusive. Based on clinical judgement, we removed outliers for office BP that were outside the range of 60-300 mmHg for sBP and 30-200 mmHg

for dBP. A CPCSSN diagnosis uses information from medical billing and the problem list to identify hypertension related ICD9 codes (Table A-1.2). Further, it takes into consideration the use of anti-hypertensive medications. Had we only included those individuals with elevated office sBP/dBP, we would have missed those who had a diagnosis of hypertension and had their BP treated and under control. Conversely, office BP is highly dependent on lifestyle behaviour at the time of the measurement. There is no way to ascertain within the current EMR data whether or not BP was measured using proper technique or whether the patient had been exposed to other factors that could raise blood pressure e.g. consumed caffeine or engaged in physical activity prior to measurement. We acknowledge that this is a limitation and consider it a reasonable assumption since we aim to capture as many possible cases, given MetS is not considered unless at least two other risk factors are present.

To assess the presence of atherogenic dyslipidemia, we followed NCEP ATP III criteria which includes measures for HDL-C and TG in establishing MetS. Women were identified as having low HDL-C at <1.3 mmol/L and men at <1.0 mmol/L. Secondary lipid targets for low density lipoprotein cholesterol (LDL-C) are no longer considered in the criteria for MetS in all current definitions and therefore we have not included measures of LDL-C. Hypertriglyceridemia was determined using a TG cut point of ≥1.7 mmol/L. Notably, our data did not distinguish whether TG was fasting or random, but there is evidence that the use of non-fasting TG is acceptable for the purposes of identifying MetS [104].

MetS Case-finding Algorithm

A linear search algorithm was developed to ascertain prevalent cases of MetS in subjects who met a minimum of three of the five criteria listed in Table 2.1. The process of identifying MetS cases in the algorithm (Figure 2.2) begins with the first of ten possible combinations. Each eligible patient within the sample is computationally assessed for each combination. If a patient

meets the criteria in all three factors for a given combination, they are identified as having MetS and added to the capture pool (detailed algorithm in Appendix III). It is important to note that it is possible for a patient to have MetS based on more than one combination. As such, a patient is counted only once in establishing the prevalence, regardless of the number of combinations they meet.

CPCSSN Disease Definitions

CPCSSN investigators have created and validated case definitions for common conditions based on amalgamations of billing diagnoses, problem lists, medications, and laboratory investigations with details described below. The diagnosed diseases used in this study include hypertension, diabetes, depression, and osteoarthritis and can be found in Appendix I.

The CPCSSN validated disease definition for diabetes includes both type 1 and type 2 diabetes (Table 1.1) [80]. The diabetes definition consists of a minimum of two billing codes within two years, or any occurrence of an ICD9 250 code on the problem list, or a presence of an anti-diabetes ATC drug code, or a laboratory diagnostic of HbA1c $\geq$7% or two occurrences of FBG >7 mmol/L within a single year (Table A-1.1) [80]. Hypertension was identified using the CPCSSN validated disease definition (Table A-1.2) which is based on a minimum of two occurrences of hypertension billing codes 401-405 within two years, any occurrence of hypertension related ICD9 codes on the patient's problem list, medication based on anatomical therapeutic classification (ATC) code (subjective to diagnosis of migraines, coronary heart failure, myocardial infarction, diabetes, arrhythmia, tremor, and esophageal varices), or laboratory diagnostic results [80]. Elevated BP readings alone are not sufficient for a diagnosis of hypertension.

The CPCSSN validated disease definition for depression (Table A-1.3) includes any occurrences of a billing code for episodic mood disorders or depressive disorder, or any occurrence of ICD9 codes 296 or 311 on the problem list, or a listing of an anti-depressant medication (Table A-1.2) [79,80]. The CPCSSN disease definition for osteoarthritis (Table A-1.4) includes any occurrence of a billing or problem list entry for osteoarthritis or spondylosis [79,80].

Statistical Analysis

Statistical analysis was conducted using RStudio version 1.1.453, RStudio Inc., under Affero General Public License for data manipulation, univariate and bivariate analysis, and linear search algorithm development. The analysis was restricted to subjects who met at least three of the five MetS criteria. The variables studied included age (calculated from year of birth), sex, disease status, BMI, BP, FBG, HbA1c, HDL, and TG measures. Continuous variables are reported as mean ± standard deviation (SD). Categorical variables are expressed as counts with proportions. The period prevalence of MetS was defined as the ratio between those having MetS and the total number of subjects included in the denominator.

Results

There were 22,765 patients available for analysis within this study between July 29, 2015 and July 29, 2018. After excluding patients that were deceased, had a non-Alberta postal code, were missing data for sex/birth year, had outlier for physical examination data, or had duplicate data, a total of 15,766 individual patient records were evaluated for the presence of MetS (Figure 2.1). Using our linear search algorithm, we identified 695 participants with MetS, corresponding to a prevalence of 4.4%. The most common 3-factor MetS syndrome included measures of BMI ≥25 kg/m^2, elevated BP, and hypertriglyceridemia (Table 2.3).

Those with MetS had a higher mean BMI than those in the non-MetS group (35.13 ±7.00 kg/m^2 vs. 27.26 ±6.19 kg/m^2), though it is notable that the mean BMI in the non-MetS group was well within the overweight range. Those with MetS had higher measures of dysglycemia (FBG 5.74 ±1.68 mmol/L vs. 4.95 ±1.11 mmol/L; HbA1c 5.94 ±1.36% vs. 5.33 ±0.70%) than those without MetS. Triglycerides were twice as high in the MetS group compared to those without MetS (2.39 ±1.18 mmol/L vs. 1.28 ±0.77 mmol/L). The average HDL-C was lower in the MetS group (mean 1.09 ±0.24 mmol/L vs. 1.44 ±0.36 mmol/L) (Table 2.2).

Among physical exam measures, nearly all (91.2%) individuals in the MetS group had a BMI of ≥25 kg/m^2 (Figure 2.3 A) and elevated office sBP and dBP was higher in the MetS group (75.1%). Dyslipidemia was more prominent in the MetS group compared to the non-MetS group with a greater presence of hypertriglyceridemia (70.6% vs. 2.2%) and low HDL-C (59.1% vs. 2.3%). Of MetS individuals, 38.7% had dysglycemia. Depression represented the most prevalent comorbidity in the MetS group (16.5%) and the non-MetS group (13.5%). Diabetes was higher in the MetS group (15.2%) compared to the non-MetS group (1.7%), and hypertension was more prevalent among MetS individuals compared to the non-MetS group (14.2% vs. 0.8%). Though absolute values were small, 2.5% of the MetS group had a CPCSSN diagnosis of osteoarthritis compared to 1.0% in the non-MetS group (Figure 2.3 B).

Missing Data

In those with MetS, regardless of weight status, half (50.9%) were missing an FBG measurement and a fifth (21.9%) were missing measurements for HbA1c. Regarding measures of dyslipidemia and hypertriglyceridemia, 13.2% were missing laboratory investigations for HDL-C and 9.6% were missing TG. Physical examination data were measured more frequently in this group as only 7.2% were missing BMI and 3.2% were missing an office BP reading (Figure 2.4 A). Within the overall sample of young adults 18-40 years old, 25.5% were missing a BMI.

Moreover, among those who were missing a BMI measure, 65.0% met two factors for MetS and therefore could have been considered as having MetS if they had a BMI measurement recorded that was over the 25 kg/m^2 cut point. Of all those with a recorded BMI ≥25 kg/m^2 (n=7133), the vast majority were missing measures for FBG (84.0%), HDL-C (80.4%), TG (79.0%), and HbA1c (66.9%) (Figure 2.4 B). We examined the proportions of missing data by the number of MetS factors among all individuals 18-40 years of age and found that among those with zero, one, and two factors for MetS, there was a higher proportion of missing data compared to those with greater than two factors (Figure 2.5).

Discussion

We have established an EMR case definition and case-finding algorithm for MetS within the age group of 18-40 years and found a prevalence of 4.4% of younger onset MetS in Northern Alberta primary care EMR data. We harmonized MetS criteria guided by NCEP ATP III, WHO, Diabetes Canada, C-CHANGE, and CPCSSN definitions to allow for pragmatic use of available data given that most clinicians are not routinely recording waist circumference data [105–107]. We have focused on younger adults because of the rising prevalence of obesity in this population [108], and the worsening metabolic burden in those diagnosed younger [76,109].

The demographics in our study bear similarities with other CPCSSN based studies in that subjects tend to be female and of older age compared to the general practice population [110–115]. The patterns of health care utilization in North America show that females frequent the doctor's office more often than men, indicating that men may be underrepresented in this analysis [116–119]. Canadian epidemiological investigations vary greatly in prevalence estimates for MetS between 2% and 13% in most studies with the most reliable estimates being 6.5% and 7.8% based on CHMS data [9,34], it is important to note that our data provide only an estimation of MetS prevalence within the CPCSSN primary care setting in Alberta. An

investigation using CHHS 1986-1992 data, and a harmonized MetS definition based on NCEP ATP III criteria, suggested the prevalence of MetS amongst those between the age groups of 20-29 was 6% and 30-39 was 13% [120]. A second study using cycle 1 CHMS data (2007-2009) combining physical exam, laboratory investigations, and demographic characteristics for age, sex, education, and income, showed a prevalence of 6.5% amongst those 18-39 years [34]. A similar study using the CHMS cycle 1 (2007-2009) data showed MetS prevalence estimates of 7.8% for those 20-39 years based on assessments using dietary and sociodemographic assessments with clinical markers of MetS [9]. These findings suggest that our data underestimate the true prevalence of MetS in the primary care setting, given that the prevalence of obesity has not reduced since those studies were carried out [108], and that the metabolic health of those seeking primary care are possibly worse than the population not seeking any medical care [60,114].

One of our key findings indicate that the patterns within young-adult onset MetS are similar compared to other studies looking at older populations [33,89]. The 3-factor MetS syndrome was shown in a non-CPCSSN based family practice study among individuals 40-60 years where being overweight, having elevated BP, and hypertriglyceridemia was also their most common combination [89]. Although there may be an age-dependent increase in the prevalence of MetS, the distribution of MetS features remains relatively the same, where over half with MetS had the 3 criteria of being overweight, having elevated BP, and having hypertriglyceridemia despite previous evidence of the physiological differences in MetS by age [13].

With obesity being one of the main drivers and components of MetS [58,105,121–124], we acknowledge that we did not use ethnicity-specific cut-points or measures of WC and that considerably more patients may have excess adiposity given that Asian cut-points for BMI are >23kg/m^2, and that over 10% of Albertans come from Asian backgrounds [125]. Unrecorded

ethnicity is common within CPCSSN data where less than 3.0% of ethnicity is recorded within the EMR[126]. An increased recording of ethnicity would likely better illustrate the burden MetS given Canada's ethnically diverse population, yet is difficult given barriers in time, standardization of surveys, and the politically and socially sensitive nature of recording this information.

Importantly, we found a large proportion of missing data in this younger adult sample for laboratory and physical exam tests. We therefore suspect that our findings considerably underestimate the true prevalence of MetS given that one-quarter did not have a BMI recorded, and of those meeting the overweight BMI threshold, the vast majority (80%) were missing lipid and/or glucose testing. It is important to note that to meet the criteria for MetS in our study, a patient has to have a minimum of three factors and could still satisfy the MetS criteria even if missing physical exam or laboratory measures. The proportion of those missing a BMI measure with at least two other factors for MetS are important to consider in underestimations, since overweight and obesity is so prevalent in this sample. Regardless, it is difficult to know how missing data would potentially bias the true clinical prevalence given that those who have a physical exam or laboratory investigation were likely measured under clinical suspicion and therefore represent an enriched sample [114].

Given that the Canadian Obesity Clinical Practice Guidelines for primary care contain a Grade A recommendation to evaluate glycemic and lipid measures in those with elevated BMI [127], our findings suggest that incomplete clinical investigation for risk markers in younger adults with MetS or over the BMI threshold, may pose a greater risk for earlier lifetime burden of related chronic disease. This lack of investigation likely represents a combination of both patient and clinical inertia where physicians might be less likely to order laboratory tests for several reasons, including that these patients are younger and therefore are presumably in good health or not

following through in fulfilling laboratory requisitions. Furthermore, there are barriers to guideline adherence given variation in definitions for identifying MetS [128]. Missing data can be further explained by physician reluctance on placing the MetS label on a patient, as this could potentially cause distress or influence the ability for an individual to obtain health insurance. The WHO recommends that screening for any test take place where there is a clear benefit to a person's health, the test in question is reliable without subjecting further harm, and there must be an effective evidence-based treatment that proves beneficial prior to disease onset [129]. Considering that younger adult patients are conceivably healthy, physicians may feel that it is unnecessary to requisition physical and laboratory investigations.

We suspect that a significant proportion of MetS cases are simply not being detected given that 45% of our sample met the overweight threshold alone but the vast majority did not have additional risk factors investigated and documented [130]. However, physicians report difficulties addressing MetS in the presence of multiple definitions and the recognition that just identifying clinical risk factors is insufficient to appropriately address MetS [131]. Underlying problems often include broad social challenges requiring significant resources that may lie outside the scope of conventional medicine [132,133]. The Canadian Health Advanced by Nutrition and Graded Exercise (CHANGE) program is a good example of efforts to mitigate MetS related morbidity. The CHANGE program addresses social barriers and incorporates behavioural coaching in healthy eating and physical activity in all ages, however these strategies remain largely untranslated into standard clinical practice [134].

Unsurprisingly, there were higher rates of depression in those with MetS than in the overall sample [135], consistent with a recent meta-analysis of 17 different studies which showed a significant bidirectional relationship between MetS and depression (OR 1.52; CI95% 1.38, 1.67) [136]. Other forms of mental illness have also been associated with MetS, such as bipolar

disorder [137]. Individuals with mental illness face difficulty in being able to effectively self-manage their physical well-being, which leads to greater risk for the progression of metabolic derangement and the development of chronic disease [27,135]. A recent Canadian study consisting of a population of 65,000 people within eight cycles of the Canadian Community Health Survey (CCHS) data showed depression to be amongst the highest in those 18-39 years of age [138]. Given the prevalence and strong associations between MetS and mental illness, further investigation into improving mental health screening, prescribing of less obesogenic medications, and access to appropriate resources would be beneficial among all young-adults, MetS notwithstanding.

There are several strengths in this study. This is the first instance in which large-scale epidemiological data have demonstrated the prevalence of MetS in a younger adult practice population attending primary care clinics in Northern Alberta. Using robust and validated CPCSSN definitions for hypertension and diabetes in the case-finding for MetS adds to our study beyond the conventional measures for elevated BP and dysglycemia. The NAPCReN data are point-of-care EMR data allowing for a practical understanding of the patterns of disease and the diagnostic gaps in the primary care setting. Our harmonized case-finding algorithm for MetS will further assist the CPCSSN network in establishing and validating a case definition for use in future surveillance, research, and quality improvement projects.

Our study also has several limitations. Firstly, the generalizability of this sample is limited because the NAPCReN-CPCSSN primary care clinics are over-represented by a higher proportion of patients who tend to be older and female compared to the primary care practice population[116,126,139]. Though the proportion of female family physicians have continued to rise, the Canadian Institute for Health Information 2019 February Physician Report identified that there were slightly less female family physicians (45.5%) compared to males (54.5%) in

Canadian primary care practice [140]. The demographic of family physicians within the NAPCReN-CPCSSN however consists of physicians whom are female and younger [126]. Given that female physicians tend to see more female patients, this may have also contributed to the higher proportion of females patients within this sample [141]. With regards to our harmonized case definition, we acknowledge the criticism that BMI does not distinguish between lean body mass and fat mass and that it is being used as a measure of excess adiposity [114] and can overestimate the prevalence of obesity [90,114]. However, we took a pragmatic approach given the lack of 'gold standard' waist circumference EMR data [103]. We also recognize that the use of office BP can over-estimate the prevalence of elevated BP in the absence of a diagnosis of hypertension given it is highly subject to error in measurement [142]. The use of office BP in the assessment of MetS is less favourable given that the Canadian Hypertension Education Program (CHEP) guidelines recommend the use of at-home BP monitors as a preference for the diagnosis of hypertension [142]. Lastly, one of the major limitations of real-world practices is that of insufficient clinical documentation and the challenges of imperfect EMR data. In many instances, fields will be missing information, or worse incorrectly entered into the EMR. Attrition is also not always known and therefore not captured in the EMR when patients leave the network as a result of relocation or death [126]. Recording measures completely and accurately requires sufficient clinical reasoning and manpower. The processes of obtaining and recording clinical measurements are affected by many factors such as clinic processes, physician professional judgment, social desirability or strategic recording behaviours of the provider, practice habits, monetary incentives, and design of the EMR. Negative findings are less likely to be reported, or an assumption is made that no result is a negative result, resulting in a selective non-reporting bias [143].

Conclusion

This cross-sectional study suggests that one out of every twenty-five persons between 18-40 years of age attending a Northern Alberta primary care clinic has MetS. It is likely, however, that this is underestimating the prevalence due to large proportions of missing data, driven by the sub-clinical nature of MetS, the high prevalence of overweight and obese patients, and the competing priorities of both patient and physician. Further work is required to understand whether missing data is clinically informed, rather than an omission due to lack of time or resources. Ultimately, we hope that this pragmatic MetS case definition allows for earlier identification of cases and more targeted clinical resources to prevent and manage MetS-related comorbidities. Future iterations of this work will include a formal validation of the case definition. These observations provide a basis for engaging with primary care teams to consider the current recommendations for screening of young-adult onset MetS and develop actions to earlier detection and management of MetS.

Table 2.1 Harmonized criteria for defining metabolic syndrome: ≥ 3 factors to make a diagnosis

Metabolic Syndrome Criteria	Cut Point
Overweight and Obese	BMI ≥ 25 kg/m^2
Elevated Blood Pressure (BP)	CPCSSN diagnosis of hypertension or systolic BP ≥ 130 mmHg or diastolic BP ≥ 85 mmHg
Dysglycemia	CPCSSN diagnosis of diabetes or HbA1c ≥ 6.0% or FBG ≥5.6 mmol/L
Hypertriglyceridemia	TG ≥1.7 mmol/L
Low HDL-C	HDL-C <1.0 mmol/L in men <1.3 mmol/L in women

**BMI cut points for outliers at <15 kg/m^2 and ≥50 kg/m^2, if BMI is ≥30 kg/m^2, central obesity can be assumed. Body Mass Index (BMI), blood pressure (BP), glycated hemoglobin (HbA1c), fasting blood glucose (FBG), high density lipoprotein cholesterol (HDL-C), triglycerides (TG). Cut points are based on previously establish formal criteria for MetS, BMI* [101]*, elevated BP, HbA1c, and FBG* [51]*, HDL-C and TG*[86,102]*, CPCSSN disease diagnosis*[80].

Table 2.2 Baseline characteristics of study sample stratified by metabolic syndrome

Characteristic	MetS (n=695)			No MetS (n=15071)		
	N	**(%)**	**Mean ±SD**	***N***	**(%)**	**Mean ±SD**
Age (years)	695	(100.0)	34.29 ±4.84	15071	(100.0)	30.78 ±5.89
Sex (female, %)	342	(49.2)	-	9660	(64.1)	-
BMI (kg/m^2)	645	(92.8)	35.13 ±7.00	11111	(73.7)	27.26 ±6.19
Systolic BP (mmHg)	673	(96.8)	130.04 ±13.37	13512	(89.7)	118.66 ±12.75
Diastolic BP (mmHg)	673	(96.8)	84.15 ±9.31	13512	(89.7)	75.48 ±9.73
FBG (mmol/L)	341	(49.1)	5.74 ±1.68	1666	(11.1)	4.95 ±1.11
HbA1c (%)	543	(78.1)	5.94 ±1.36	3303	(21.9)	5.33 ±0.70
TG (mmol/L; median [IQR])	628	(90.4)	2.39 ±1.18	1940	(12.9)	1.28 ±0.77
HDL-C (mmol/L)	603	(1.1)	1.09 ±0.24	1800	(11.9)	1.44 ±0.36

*Physical exam and laboratory investigation measures are shown with counts, proportions, and mean ±SD/ median ±IQR and stratified by MetS. *Metabolic syndrome (MetS), body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high density lipoprotein cholesterol (HDL-C).*

Table 2.3 Prevalence of combinations meeting the minimum 3-factors for metabolic syndrome

Combinations of MetS Factors	MetS(n=695) N (%)	Hooven et al. 2006 (n=167) N (%)
Overweight + Elevated BP + Hypertriglyceridemia	288 (41.4)	73 (43.7)
Overweight + Reduced HDL-C + Hypertriglyceridemia	241 (34.7)	41 (24.6)
Overweight + Elevated BP + Reduced HDL-C	221 (31.8)	49 (29.3)
Overweight + Elevated BP + Dysglycemia	167 (24.0)	30 (18.0)
Elevated BP + Reduced HDL-C + Hypertriglyceridemia	159 (22.9)	66 (39.5)
Overweight + Dysglycemia + Hypertriglyceridemia	113 (16.3)	17 (10.2)
Overweight + Dysglycemia + Reduced HDL-C	97 (14.0)	15 (19.0)
Elevated BP + Dysglycemia + Hypertriglyceridemia	79 (11.4)	27 (16.2)
Dysglycemia + Reduced HDL-C + Hypertriglyceridemia	73 (10.5)	16 (9.6)
Elevated BP + Dysglycemia + Reduced HDL-C	67 (9.6)	23 (13.8)

Patients fit into multiple combinations. Blood pressure, (BP); high density lipoprotein (HDL-C). Elevated BP includes a CPCSSN diagnosis of hypertension or BP ≥130/85 mmHG, dysglycemia includes CPCSSN diagnosis of diabetes or FBG ≥5.6 mmol/L or HbA1c ≥6.0%. Overweight includes BMI≥25 kg/m^2. Comparison to a non-CPCSSN based family practice in Kingston, Ont. Based on FPG >6.1 mmol/L, TG ≥1.7 mmol/L, HDL-C <1.04 mmol/L men and <1.29 mmol/L women, BP ≥135/85 mmHg, WC >102 cm men and >88 cm women. Showing the most common combination of 3 factors to be obesity, hypertension, and hypertriglyceridemia [89].

Figure 2.1 Flow of data extraction and cleaning from the NAPCReN-CPCSSN data repository

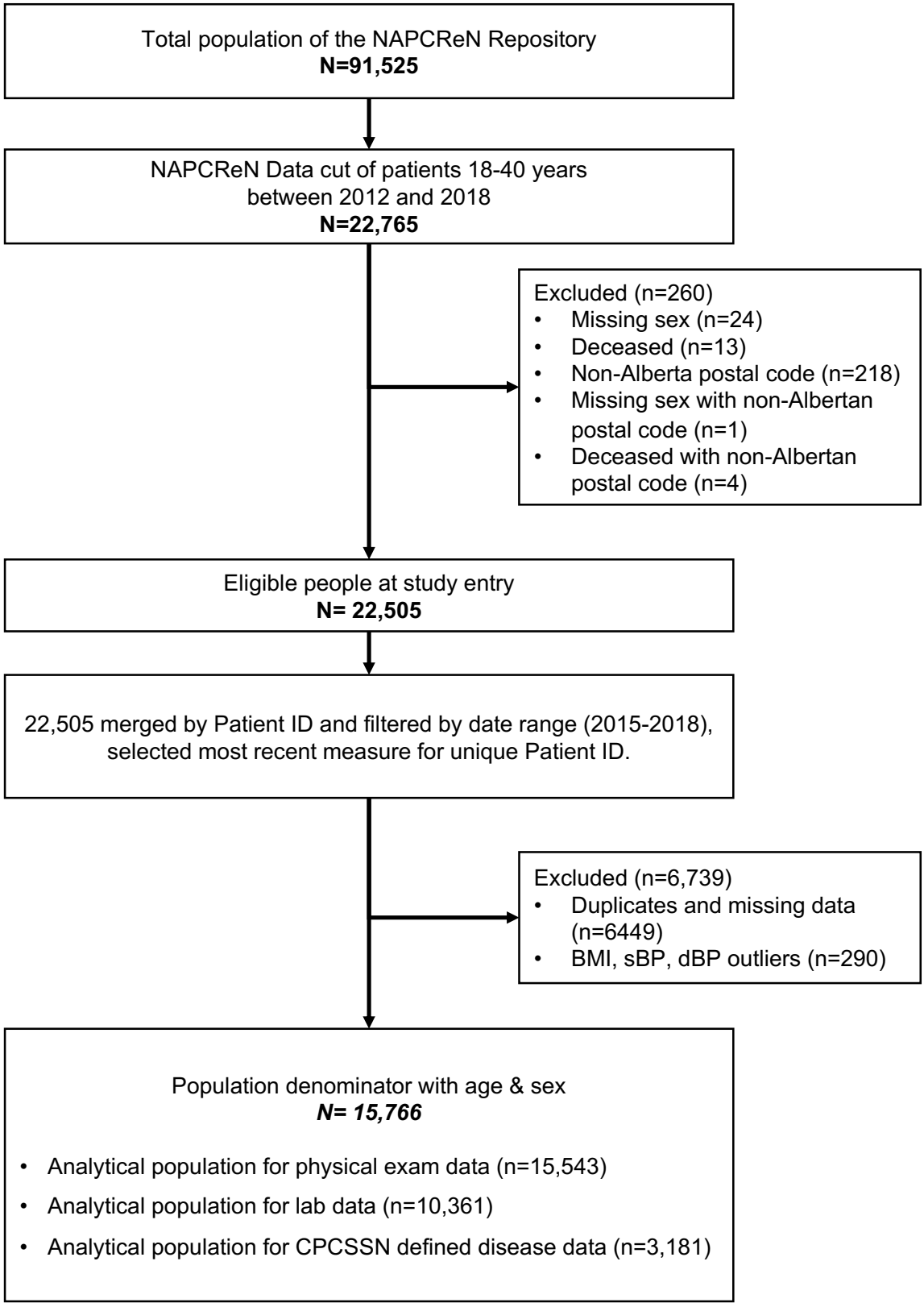
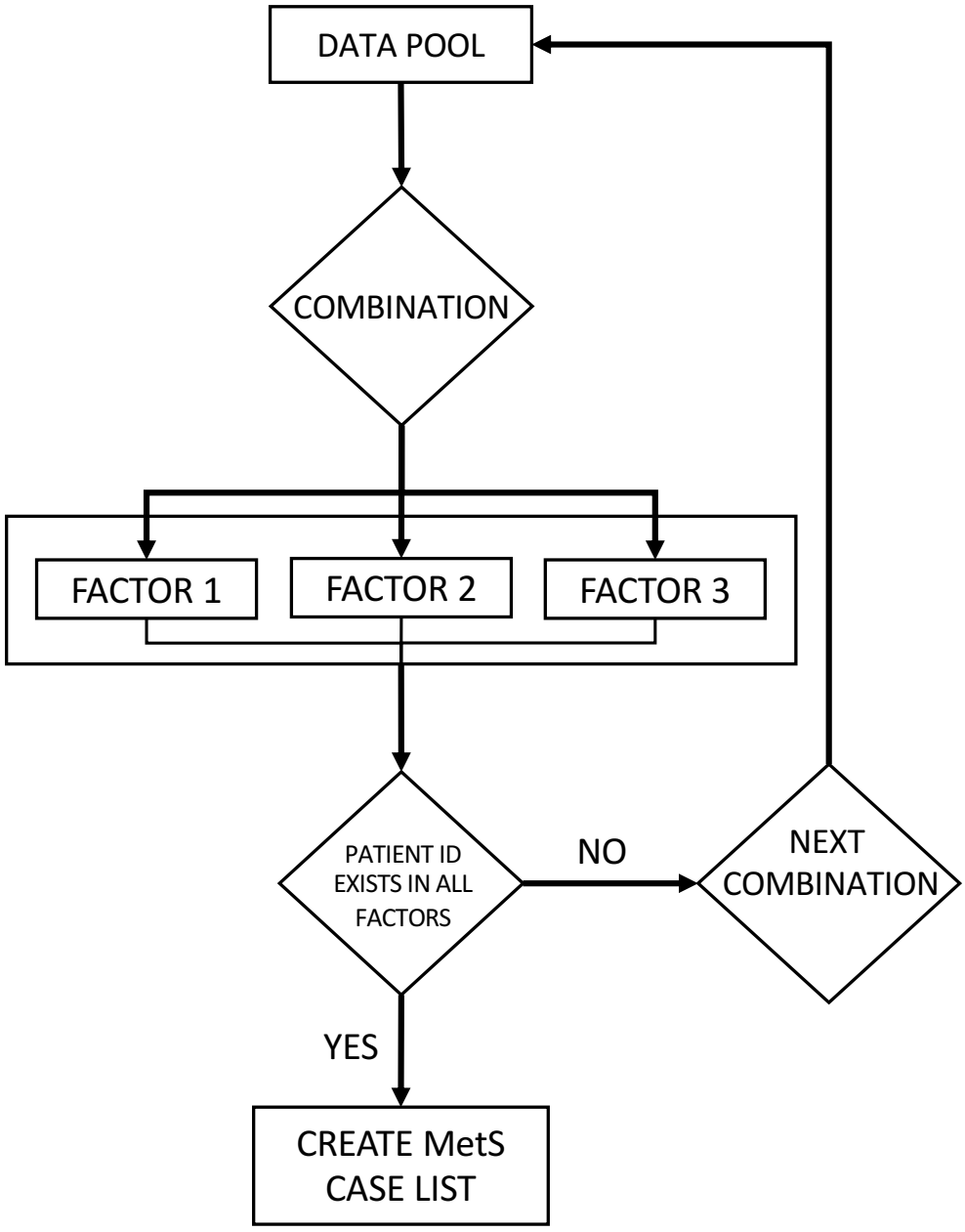


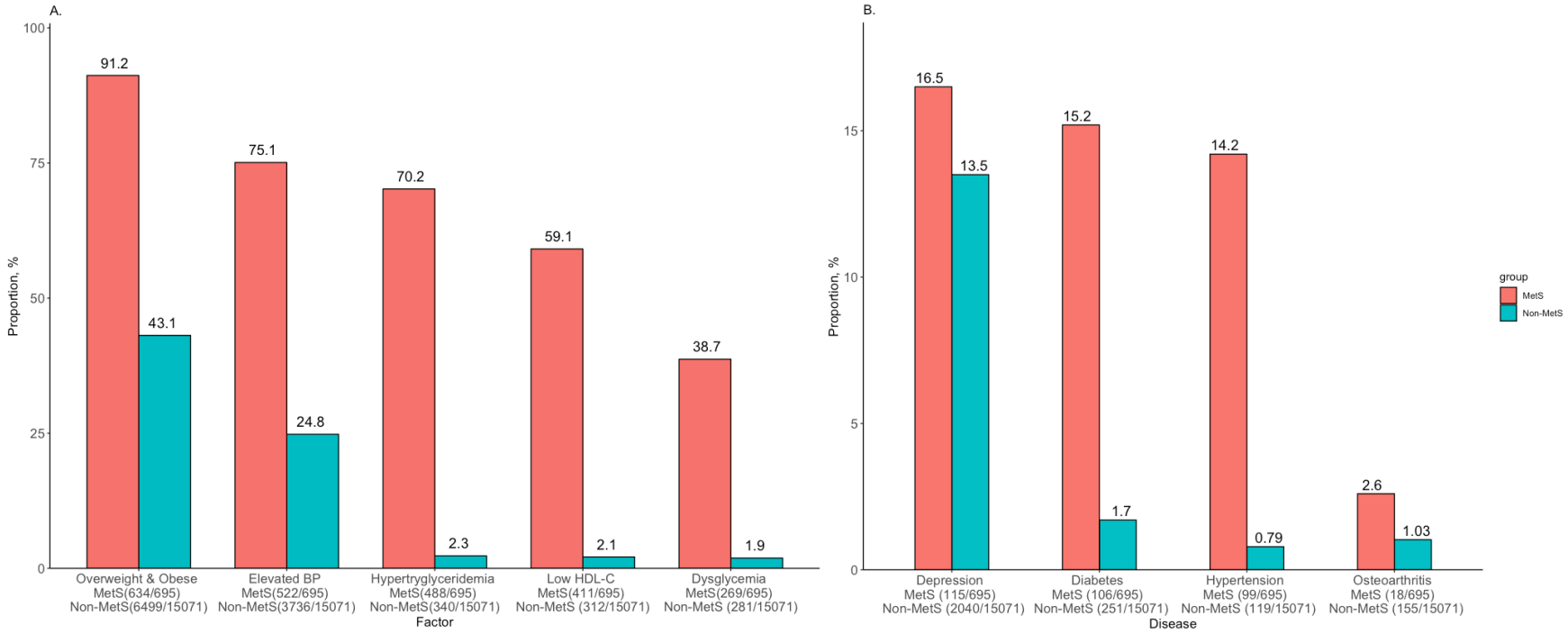
Figure 2.2 Metabolic syndrome case-finding algorithm



Demonstrating the path of a single combination consisting of three MetS components. The combination is first created and separated based on its factors. Three lists of patients meeting the MetS criteria for each factor are created. The lists are combined based on Patient ID, those patients which exist in all three lists fulfill the requirement for a positive MetS case according to the defined combination and are added to a MetS case list. Figure created in collaboration with C. Oliva.[1]

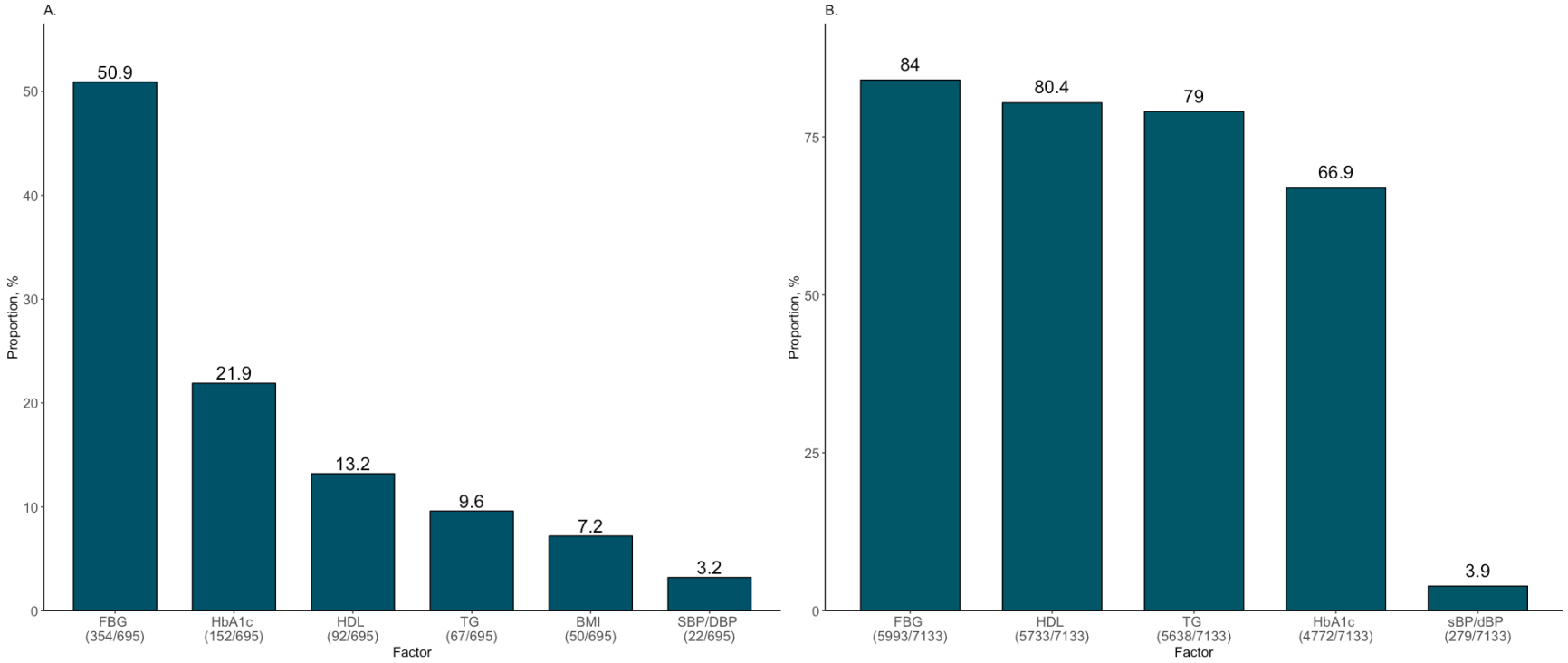
[1] For a more detailed diagram refer to Figure A-3 in Appendix IV.

Figure 2.3 Risk factors and disease proportions in individuals with and without metabolic syndrome



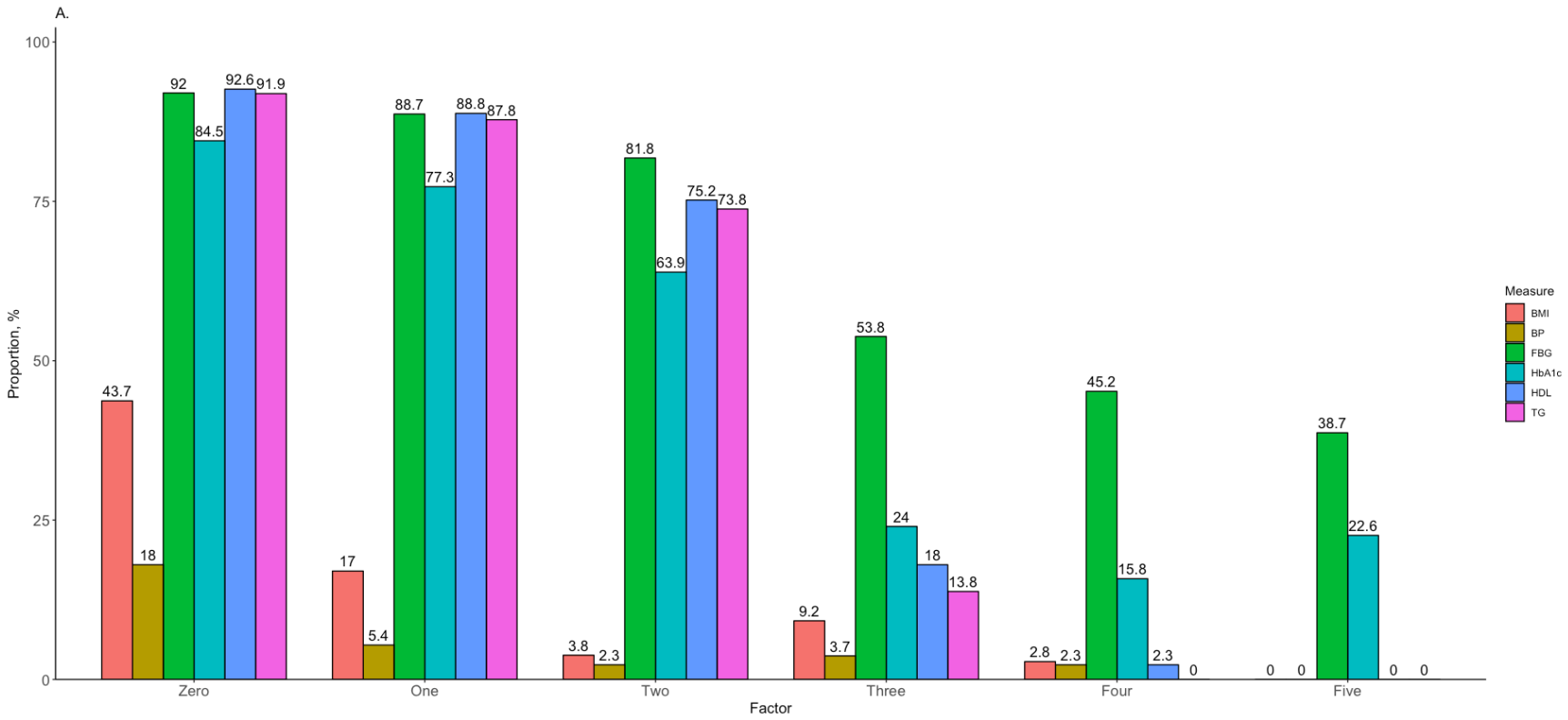
Data in parenthesis are the number of patients with MetS with valid data included in the analysis. Metabolic syndrome (MetS), blood pressure (BP), high density lipoprotein cholesterol (HDL-C), male (M), female (F). (A) Patients shown as proportion achieving MetS component cut points in individuals with and without MetS, (B) proportion of disease in individuals with MetS and without MetS.

Figure 2.4 Distributions of missing data in those with metabolic syndrome and those with a BMI ≥ 25kg/m^2.



*Data in parenthesis are the number of patients with MetS or who are overweight and obese. *Body mass index (BMI), triglycerides, (TG), high density lipoprotein (HDL), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), systolic/diastolic blood pressure (sBP/dBP).*

Figure 2.5 Proportions of missing physical exam and laboratory tests by number of metabolic syndrome factors for all individuals.



Metabolic syndrome (MetS), triglycerides (TG), high density lipoprotein (HDL), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), blood pressure (BP). Individuals meeting 3 or more factors are diagnosed as having MetS.

– Chapter 3 –

Describing the sex differences in young-adult onset metabolic syndrome using electronic medical record data from primary care settings in Northern Alberta

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Boisvenue et al. –Metabolic Syndrome

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Introduction

The prevalence of metabolic syndrome (MetS) in Western society continues to increase [2] with the parallel rise in sedentary inactivity, a lack of interest in long-term health outcomes, and barriers in access to health resources. Global estimates of MetS are difficult to obtain amidst varying definitions applied across diverse populations. However, given that MetS is approximately three times more prevalent than diabetes, the global prevalence is estimated to be present in approximately one-quarter of the world's population [11]. MetS is defined as the clustering of risk factors associated with the development of cardiovascular disease (CVD), type 2 diabetes (T2D), and obesity [2]. The recognized risk factors of MetS include a presence of abdominal obesity, elevated blood pressure (BP), dysglycemia, and dyslipidemia [144].

In Canada, the prevalence of MetS among young adults aged 18-39 years was 6.5% and the overall stratified estimates for all adults 18-79 years showed that women had a higher prevalence than men [34]. Moreover, the development of chronic disease is far greater amongst individuals with MetS, with differing patterns of co-morbidity between females and males [84]. The effect of sex and prevalence of chronic disease varies by as much as 10-fold between men and women, illustrating the importance of sex in all matters of biological functioning [145]. For instance, the risk of CVD in women with MetS is 14-fold higher than non-MetS women, whereas the risk is 4-fold higher when comparing men with and without MetS, according to the San Antonio Heart Study [146]. The physiological differences in sex influence the symptoms and treatments received and therefore are likely one of the most important components of precision medicine [147].

The sex difference in how MetS comorbidities manifest is partially dependent on the differences in adipose tissue accumulation [148,149]. Under normal physiological conditions, premenopausal women have more overall fat mass and men have higher lean body mass [149].

Men tend to accumulate two-fold higher visceral adipose tissue (VAT) which is typically found in the upper body deep abdominal regions and women are more prone to subcutaneous adipose tissue (SAT) accumulation in the lower thigh and hip regions [150]. The differences in VAT/SAT ratios between sex are thought to be evolutionary and specific to energy metabolism, with VAT being a stronger predictor of CVD outcomes and metabolic derangement [151]. Subcutaneous adipose tissue is suspected to have protective effects in CVD development, where increased SAT mass is associated with a lowering of circulating lipids and glucose [152]. Further, women and men lose weight differently, with men having a greater reduction in VAT and potentially greater improvement in metabolic profiles despite a similar loss in weight [151]. Sex specific differences in adipocyte size contribute differently to MetS, as size is closely linked with insulin resistance and lipid metabolism, with larger adipocytes having a higher rate of lipolysis [153]. In men, VAT/SAT adipocyte size are considered to be relatively similar with VAT being hypertrophied, whereas in women SAT adipocyte size is larger and likely attributed to estrogen-induced hyperplasia [154].

In general, healthy women have a less atherogenic lipid profile compared to men with differing particle sizes where women tend to have larger HDL particles and a lower concentration but larger particle size of LDL [155]. Dramatic changes in estrogen secretion post-menopause play a large role in the development of VAT accumulation in women and may further explain the accelerated worsening of CVD related events with age [156]. Visceral fat accumulation and the presence of insulin sensitivity, increases the concentrations of free fatty acids (FFA) and lipase activity leading to an increase in hypertriglyceridemia and overall reduction in HDL particles [157]. However in premenopausal women, it has been hypothesized that estrogen protects against insulin resistance [158]. In the presence of insulin resistance and obesity, there are changes in lipid homeostasis specifically with increased concentrations of TG, LDL, and decreased HDL [155].

Sex differences in BP have been well documented, with men having higher sBP and dBP compared to women [159]. In general, the rates of hypertension are much lower in younger women, where men show a steeper increase in BP throughout life, up until the fifth decade [156]. The relationship of sex and hypertension however, is reversed with older women over 65 having higher rates of hypertension [160], a phenomenon hypothesized to be associated with menopause [161]. Though this hypothesis is still a matter of debate as many studies are confounded by the fact that women consistently outlive men [156].

Glucose homeostasis is typically regulated through skeletal muscle by way of insulin-stimulated uptake of glucose [145]. The differences in accumulation of VAT in men and SAT in women can partially explain the sex differences in glucose homeostasis [157]. Women have more favourable glucose homeostasis than men and it has been hypothesized that this is due to the role that estrogen plays between puberty and menopause [93,162]. Better glucoregulation in women might also explain why the prevalence of diabetes is higher among men than women even though women tend to gain and carry greater amounts of weight [93]. A diagnosis of abnormal glucose homeostasis is made either through HbA1c, impaired fasting glucose (IFG), or impaired glucose tolerance (IGT). IGT is associated with insulin resistance in the skeletal muscle and is substantially more prevalent in women whereas IFG is more common in men as was shown in the DECODE/DECODA study [163]. It is also hypothesized that IGT may better predict diabetes in women, which highlights the importance of ordering oral glucose tolerance tests in women particularly. It has also been postulated that estrogen plays a protective role in whole body inflammation, suggesting that women may have greater resistance to metabolic derangement than men [164]. During pregnancy and postpartum, there is an increase in visceral adiposity to meet the energy demands of fetal development and lactation which generally dissipates after weaning however, this process is seen to differ between normal and overweight

women [165]. Fetal programming has shown that children born of mothers with T2D were more likely to develop T2D up to 30 years later in life [15]. Other research has demonstrated the impact of pregnancy complications on increasing the future risk of cardiovascular disease [166]. Among young women whom are overweight or obese, the risk of downstream chronic disease and organ damage should therefore be of great concern.

Many studies have demonstrated the different factors contributing to MetS and the prevalence by which they cluster are different between females and males [12,83,109,167]. Operationalizing a single definition may not be feasible given the ethnic and genetic variations in the manifestation of MetS factors [157]. For instance, the WC cut points are larger for Caucasians compared to Asian populations. The patterns of MetS characteristics between females and males are better reported in older populations and females are under reported in younger adults [168,169]. A close focus on the primary prevention of young-adult onset MetS is critical but especially so in young women of childbearing years. The main objectives of this study were to apply the aforementioned harmonized case definition and the established case-finding algorithm to a Northern Alberta-based primary care practice population to identify, assess, and report on the characteristics of MetS between young-adult females and males.

Methods

Data Source

The data used for this analysis have been described in more detail in chapter 2. Briefly, data were collected from EMR's within the Northern Alberta Primary Care Research Network (NAPCReN) primary care clinics. Within the NAPCReN, data consists of a repository of patient records of 18 active clinics consisting of 77 participating primary care clinicians across Northern Alberta representing 91,525 patients [81]. Physicians providing data have consented to have

their patient panel de-identified and submitted for secondary research [78]. Demographic data includes birth year, sex, and the first three characters of postal code. Physical exam data includes variables for office BP, and BMI measurements. Laboratory investigation data includes blood panel measures for FBG, HbA1c, TG, HDL-C. The clinical definitions for MetS have evolved over the last 50 years with more recent definitions distinguishing cut points specific to sex for WC and HDL-C [55,86,87]. Given the large proportion of missing WC measures within this data, BMI was used in its place. Specific cut-points for HDL-C are identified for females and males according to the NCEP-ATP III criteria [86]. Disease diagnostic data were provided based on the 8 validated CPCSSN diseases available which include diabetes, depression, hypertension, and osteoarthritis [80].

Study Design

We used a cross-sectional study design in a sample of Northern Alberta primary care clinics within the NAPCReN. All measures are stratified by sex as either female or male. Patients were recruited via a waiver of explicit consent with the option to opt out. We included all alive persons with characteristics for sex and birth year between 18-40 years who attended a primary care clinic between July 29, 2015 and July 29, 2018. The data were filtered to exclude anyone deceased, without sex, year of birth, or valid Alberta postal code. Physical exam, laboratory investigation, and disease data that were outside of the 3-year catchment period were excluded from the analysis. Younger primary care users are generally low-users as indicated in Albertan and Canadian health care utilization data [108,111,170]. Therefore, we included low-users who only had a single visit as well as the most recent measures of patients who had more than one encounter. This study was approved by the University of Alberta Research Ethics Board (Pro. 00073600).

Measures

We defined MetS using a harmonized case definition, based on definitions from NCEP-ATP III, WHO, C-CHANGE, CPCSSN, and Diabetes Canada [51,52,80,86,102].A detailed explanation of the harmonized definition for a diagnosis of MetS has been described in Chapter 2. A patient is identified as having MetS if they have any three of the following: overweight or obese BMI, elevated BP, dysglycemia, hypertriglyceridemia, or low HDL-C. To identify prevalent cases of MetS we used a linear search algorithm that first identified a specific combination followed by assessing the proportion of patients who met the criteria cut points for each factor in a single combination. A diagram of the algorithm can be found in chapter 2, Figure 2.2. Ten unique combinations were identified, and patients could classify as having MetS in more than one combination (Appendix II). The distinct number of patients having MetS is reported as well as the proportions for each combination. Outliers for BMI were identified in measures that fell below 15 kg/m^2 and above 55 kg/m^2 and for office BP measures of sBP 60-300 mmHg and dBP 30-200 mmHg.

CPCSSN Disease Definitions

Validated CPCSSN disease definitions for hypertension and diabetes were used in assessing elevated office BP and dysglycemia, respectively. We also included CPCSSN disease definitions for depression and osteoarthritis in the analysis. All disease definitions have been validated across multiple Canadian EMR systems [80]. A hypertension diagnosis was made if there was a minimum of two hypertension related ICD9 codes (401-405) in either the billing or problem list, a presence of anti-hypertensive medications based on ATC codes, or a physical exam result for office BP indicative of hypertension (≥130 or ≥85 mmHg). A diagnosis of diabetes was made where two ICD9 250 codes occurred in billings or any occurrence within the problem list, an anti-diabetes medication in the medication list was present, or a laboratory

investigation of HbA1c ≥7% or two occurrences of FBG > 7 mmol/L [80]. Diabetes included a diagnosis of type 1 or type 2, controlled or uncontrolled.

Statistical Analysis

Descriptive statistics were carried out to describe the sample, stratified by sex. Continuous variables are reported as counts with mean ± standard deviation (SD). The categorical variables are expressed as counts with proportions. The prevalence of MetS is measured as the proportion of individuals meeting at least 3 of the MetS criteria outlined in Table 2.1. A case-finding algorithm was developed to ascertain prevalent cases of MetS using a linear search technique. A chi-square test for independence was performed to assess any significant differences in sex amongst categorical variables. The statistical significance of all p-values is determined at α 0.05. The calculated mean difference between females and males with and without MetS is shown. Statistical analysis was conducted using RStudio version 1.1.453, RStudio Inc., under Affero General Public License for all data manipulation, analysis, and algorithm development.

Results

A total of 22,765 patients were available to assess sex differences in factors affecting MetS. Among those, 260 (1.1%) were excluded for having a non-Albertan postal code, being deceased, of missing data for the year of birth and sex. An additional 6,739 patients were excluded who were outside the prespecified date range of July 29, 2015 and July 29, 2018 or had outliers for BMI or BP. The remaining 15,766 patients who were eligible for the study were used to describe baseline demographics and assess differences in sex amongst MetS and non-MetS groups. A process diagram for data cleaning and mining is provided in chapter 2 (Figure 2.1). Using the linear search algorithm previously established in chapter 2 (Figure 2.2), the overall prevalence of MetS in this sample was 4.4% according to our harmonized criteria. We found no difference in the prevalence of MetS amongst females and males.

At baseline, we found that there were more females (63.4%) than males and there was no difference in age between sexes. Also, females had more favourable metabolic profiles than males for all physical exam and laboratory investigations (Table 3.1). When stratifying by MetS status (Table 3.2), we found the opposite; females with MetS had higher BMI (36.33 ±7.03 kg/m^2 vs. 33.98 ±6.79 kg/m^2) and lower HDL-C (1.15 ±0.25 mmol/L, <1.3 mmol/L cut-point) versus men (1.03 ±0.21 mmol/L, <1.0 cut point). When comparing the mean differences for MetS factors stratified between MetS and non-MetS groups and sex (Figure 3.3), we found that females had a higher mean difference than males for office BP, BMI, age, FBG, and HbA1c.

When evaluating patterns of MetS factors, the most prevalent MetS factor for both sexes was being overweight/obese (90.9% (F) and 91.5% (M)) (Figure 3.1 A). Males had significantly higher presence of elevated BP and TG measures compared to females who had significantly higher measures for low HDL-C and dysglycemia. The most prevalent MetS combination amongst females (37.4%) consists of being overweight/obese, hypertriglyceridemia, and low HDL-C, whereas the most prevalent combination in males was being overweight/obese, hypertriglyceridemia, and elevated BP (53.3%) (Table 3.3). The prevalence of depression was 20.2% for females, and 13.0% for males. Diabetes prevalence was more than twice as high amongst females as it was for males (21.6% vs. 9.1%) (Figure 3.2 B). The prevalence hypertension was lower in females compared to males (12.6% vs. 15.9%, $P < .001$). Osteoarthritis was found to be relatively low in both sexes (<3.0%). Among individuals without MetS, a higher prevalence of depression was preserved in females (14.2%) compared to males (10.8%).

Missing Data

Approximately half of the young adults in this study were missing laboratory investigations amongst both females and males for FBG, and approximately one-quarter of females and one-third of males were missing measures for HbA1c. Females were missing a higher proportion of HDL-C (17.8%) compared to males (9.1%) and TG (14.9% versus 4.5%) (Figure 3.2 A). Amongst those who were overweight and obese, the proportions of missing data were substantially higher in females (Figure 3.2 B). Overweight/obese females were more likely to have missing measures of HDL-C (83.8% vs 74.6%, $P < .001$), TG (82.8% vs. 72.9%, $P < .001$), and HbA1c (70.4% vs. 66.0%, $P < .01$) than males. The proportions of missing BP measures for both sexes was below 5.0%.

Discussion

The patterns of MetS between sexes in young adults have not previously been investigated in a Canadian primary care setting. While the overall prevalence of MetS was similar between females and males, the sex differences in the patterns of MetS suggest the need to screen sexes differently. A lack of difference in the prevalence of MetS between sexes likely represents an underestimation of both the overall and sex-specific prevalence due to large proportions of missing data.

The presence of being overweight/obese was consistently in the top four MetS 3-factor combinations, highlighting the foundational role that excess adiposity plays in metabolic derangement [81]. The differences in MetS 3-factor combinations between sexes are consistent with other studies, where women are more likely to have lower levels of HDL-C and men are more likely to have elevated BP [34,92,171]. Low HDL-C is also shown to be one of the strongest MetS factors associated with mortality risk in young women [171]. Females tolerate a higher percentage of body fat given the accumulation of SAT in the lower body regions

however, they also accumulate a greater overall proportion of fat compared to men which predisposes them to a higher risk of metabolic dysfunction, especially when excess weight is maintained during post-menopause [93]. The metabolic derangements of overweight and obese young women compared to men specifically for dysglycemia, in our study suggest that women with MetS have worse metabolic profiles compared to men with MetS.

We also found that the sex differences among MetS individuals for chronic diseases within our study are consistent with other CPCSSN based studies where women had higher rates of depression and diabetes and men had higher rates of hypertension [105,112–114]. Many theories have posited that women are more likely to experience more severe forms of depression and different metabolic profiles compared to men. It has been hypothesized that in the presence of increased adiposity, the metabolic worsening in women may be due to the greater hormone dysregulation, reproductive function, cognitive-affective symptoms, hypersomnia, and secretion of adipokines [172–174]. Further, evidence suggests that there is a bidirectional relationship between abdominal obesity and depression [136,175] suggesting an underlying relationship between metabolic derangement and depression in females within our study. The use of anti-depressants and other obesogenic medications could also contribute to the higher BMI measures among MetS individuals as has been previously established [176,177]. Though women exhibited double the rates of diabetes as compared to men in our study, men overall are typically more prone to the development of T2D [93]. It has been hypothesized that this is because men develop diabetes at both a lower age and BMI given a greater susceptibility to decreased insulin sensitivity through hepatic FFA exposure caused by increased VAT [93,144,178]. Women tend to have more factors associated with insulin resistance such as greater amounts of adipose mass, circulating FFA, and decreased skeletal muscle mass yet women are resistant to FFA induced insulin resistance, which illustrates the important protective role that sex hormones play in the sex differences of metabolic

derangement [93,162]. The higher prevalence of diabetes among young women with MetS in our sample suggests that metabolic derangement plays an important role in blunting the protective hormone related effects seen in women (perhaps explained by estrogen), on the development of insulin resistance and diabetes.

We have shown that males overall had higher proportion of hypertension and elevated BP than females, similar to what has been reported by the American Heart Association [179]. While hypertension is generally seen as a disease that comes with age, worryingly nearly half of young adults with MetS have hypertension [13]. Among younger adults, hypertension is more prevalent in men compared to women with or without MetS [13,156]. The protective effect of female hormone secretion on reduced cardiovascular outcomes in premenopausal women has been hypothesized as one of the reasons why hypertension is less prevalent in women [180]. Estrogen and other sex hormones play an important role, exerting its antihypertensive effects in tissues and vasculature [181]. This protective effect is lessened post-menopause, as the risk of elevated BP is shown to double, likely due to the dramatic decrease in the secretion of sex hormones [72,156,180].

Given that females in our sample represent young women of childbearing age and that pregnancy provides a unique opportunity to adopt healthier lifestyles, there are several important considerations for MetS and pregnancy. Women experience difficulties with post-pregnancy weight retention which influences reproductive health before and after conception, bringing a pregnancy to term, and complications with delivery [182]. Complications such as hypertensive disorders of pregnancy, GDM, and even mild glucose intolerance have been shown to increase the likelihood of developing MetS and cardiovascular disease later on in life [183,184]. Previous studies have suggested that hormonal responses in women lead to protective effects in arterial stiffness during childbearing years and that changes in menopause

may explain the sudden reversal where women are just as, if not more likely to be hypertensive later in life [180]. The implications of MetS should also be amplified for women planning for pregnancy, since women of childbearing age are rarely counselled or checked for dysglycemia prior to conception [185]. Increased clinical suspicion regarding MetS testing would further help identify the dimorphisms amongst sex in individuals at risk of MetS and help young women and families metabolically prepare for pregnancy.

A key finding of this study was the large proportion of missing data, illustrating that women were less likely to have available laboratory tests compared to men. The proportions of missing data are even more apparent amongst those overweight/obese women without MetS diagnosis, consistent with the well-documented bias that physicians perceive women to be at less cardiovascular risk than men [186]. Conversely, women are shown to have higher rates of CVD related mortality compared to men [176,183]. It is possible that the large proportions of missing WC measures, and the inability to differentiate lean from fat mass due to the use of BMI within this data, may have led to misclassification of overweight/obese diagnosis between women and men with MetS. There is also a potential for further misclassification since men are less likely than women to go to the doctor, as is representative of the proportions of men and women in our sample [189]. Regardless, these data show that the proportion of missing measures, especially among women, are indeed a barrier in adequately establishing prevalence estimates within this sample. The lack of blood testing in young adults who present as either overweight or hypertensive, may lead to greater unchecked risk factors and development of MetS and chronic disease. Regardless of sex, there is great advantage in efficiently and cost effectively measure physical parameters of BMI/WC and BP as an initial assessment of risk for MetS. A presence of both elevated BP and BMI/WC should prompt the clinician to order a lipid and blood panel.

This is the first large-scale epidemiological study assessing the prevalence and characteristics of young-onset MetS using EMR data in the primary care setting. A major strength of this study is the capture of granular clinical characteristics including anthropomorphics, labs, and medications to provide better estimation of variables that are lacking from many Canadian health administrative databases.

There are several limitations to consider in this study. The generalizability of this sample to the younger adult Canadian primary care practice population is limited by several issues previously described in Chapter 2. Limitations in the measurements of physical exam and laboratory investigations invite further study using measures of WC as a better estimation of central obesity. The inclusion of sociodemographic information would provide for richer description of the population. Given that the proportion of males was half that of females, it is likely that men are underrepresented in this cohort. There is a potential for bias in the assumption that the differences in patterns of MetS are due exclusively to sex when in fact they are due to the presence of other psychosocial and socioeconomic factors. Given that the prevalence of MetS is considered rare (<5.0%), reporting the probability of the observed differences within and between sex may not be sufficient to infer clinical significance.

Conclusions

Our results suggest there are important differences between females and males in the presentation of MetS, supporting the notion that MetS is a heterogenous condition in which the definition would benefit from being described differently, specifically for measures of WC and The proportions of missing physical exam and laboratory investigations further highlight the differences in clinical testing between females and males. Women prone to MetS appear to be investigated less than men, despite known and recorded risk factors. Further research with a

focus on understanding both the biological and behavioural factors that differ between sex, is critical to understanding MetS and chronic disease progression. Primary prevention programs that metabolically prepare and support younger adults may help improve health literacy, prepare young families for pregnancy and healthy child-rearing, and reduce the overall burden of chronic disease. This study is a necessary migration into understanding the epidemiological differences in females and males with MetS and how increased testing for and addressing clusters of risk factors is beneficial to the primary prevention of chronic disease in Alberta.

Table 3.1 Baseline characteristics of study sample stratified by sex

Characteristic	Female (n=10002)			Male (n=5764)		
	N	(%)	Mean ±SD	N	(%)	Mean ±SD
Age (years)	10002	(100.0)	30.94 ±5.83	5764	(100.0)	31.01 ±5.97
BMI (kg/m^2)	7771	(77.7)	27.48 ±6.69	3985	(69.1)	28.09 ±6.08
Systolic BP (mmHg)	9042	(90.4)	116.53 ±12.27	5143	(89.2)	123.51 ±12.88
Diastolic BP (mmHg)	9042	(90.4)	74.73 ±9.61	5143	(89.2)	77.91 ±10.03
FBG (mmol/L)	1091	(10.9)	4.85 ±1.03	575	(10.0)	5.15 ±1.22
HbA1c (%)	2071	(20.7)	5.29 ±0.66	1232	(21.3)	5.39 ±0.77
TG (mmol/L)	1078	(10.8)	1.16 ±0.63	862	(15.0)	1.44 ±0.90
HDL-C (mmol/L)	994	(9.9)	1.56 ±0.37	806	(14.0)	1.29 ±0.29

Body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), standard deviation (SD).

Table 3.2 Characteristics in individuals with metabolic syndrome stratified by sex

Characteristic	Female(N=342)		Male (N=353)	
	N **(%)**	**Mean ±SD**	***N*** **(%)**	**Mean ±SD**
Age (years)	342 (100.0)	34.36 ±4.92	353 (100.0)	34.22 ±4.76
BMI (kg/m^2)	316 (92.4)	36.33 ±7.03	329 (93.2)	33.98 ±6.79
Systolic BP (mmHg)	326 (95.3)	128.35 ±13.33	347 (98.3)	131.64 ±13.22
Diastolic BP (mmHg)	326 (95.3)	83.51 ±9.80	347 (98.3)	84.75 ±8.80
HbA1c (%)	253 (74.0)	6.15 ±1.59	290 (82.2)	5.75 ±1.10
FBG (mmol/L)	175 (51.2)	5.71 ±1.47	166 (47.0)	5.77 ±1.88
TG (mmol/L)	291 (85.1)	2.25 ±1.19	337 (95.5)	2.52 ±1.16
HDL cholesterol (mmol/L)	281 (82.2)	1.15 ±0.25	322 (91.2)	1.03 ±0.21

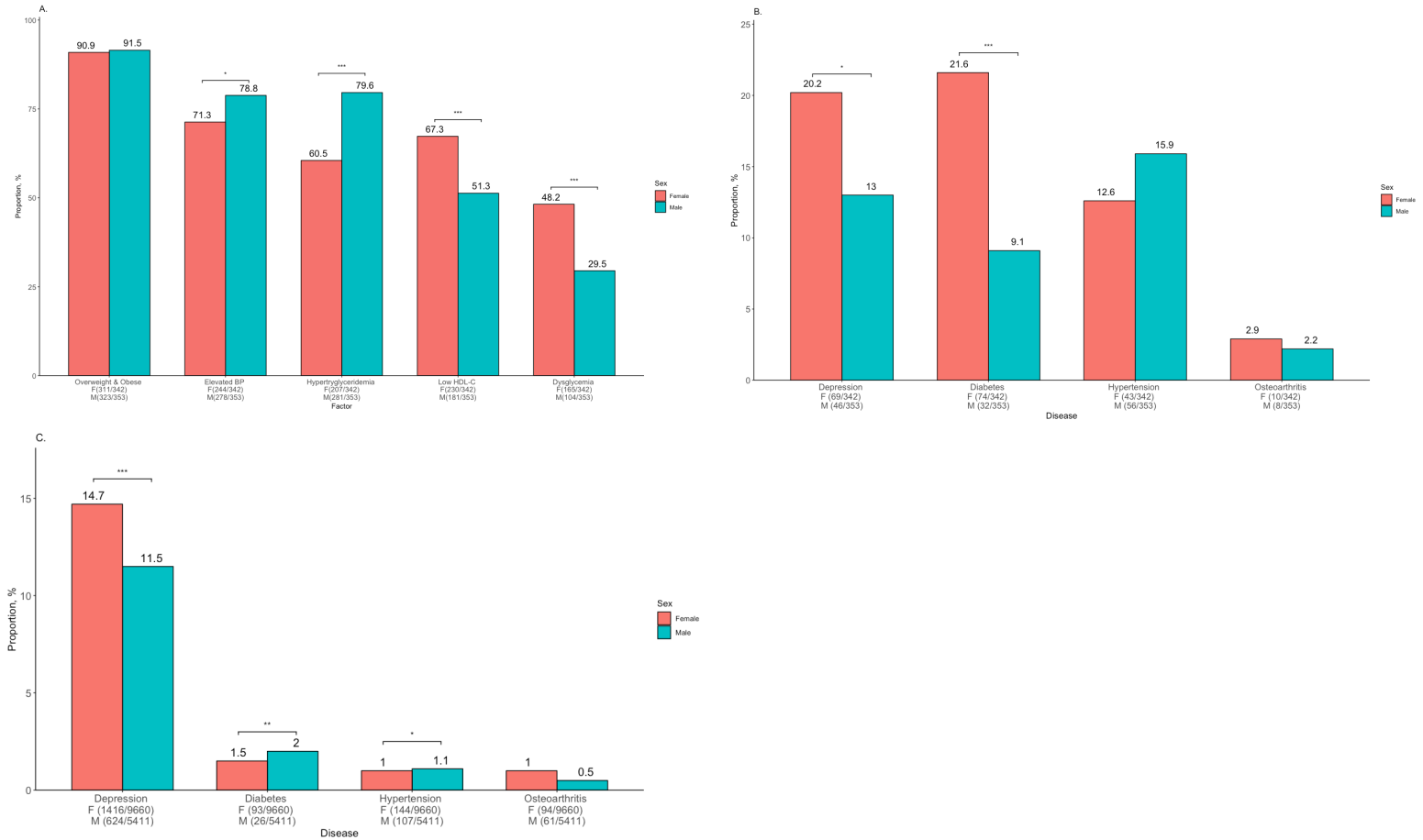
Body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high density lipoprotein cholesterol (HDL-C).

Table 3.3 Sex stratified prevalence of combinations meeting the minimum 3 factors for MetS

Combinations of Surrogate Criteria	Female (n=342) N (%)	Males (n=353) N (%)	P-Value*
Overweight + Elevated BP + Hypertriglyceridemia	100 (29.2)	188 (53.3)	<0.001***
Overweight + Elevated BP + Low HDL-C	120 (35.1)	101 (28.6)	0.067
Overweight + Elevated BP + Dysglycemia	106 (31.0)	61 (17.3)	<0.001***
Overweight + Low HDL-C + Hypertriglyceridemia	128 (37.4)	113 (32.0)	0.134
Elevated BP + Low HDL-C + Hypertriglyceridemia	80 (23.4)	79 (22.4)	0.369
Overweight + Dysglycemia + Hypertriglyceridemia	60 (17.5)	53 (15.0)	0.366
Elevated BP + Dysglycemia + Hypertriglyceridemia	43 (12.6)	36 (10.2)	0.324
Overweight + Dysglycemia + Low HDL-C	70 (20.5)	27 (7.6)	<0.001***
Elevated BP + Dysglycemia + Low HDL-C	48 (14.0)	19 (5.4)	<0.001***
Dysglycemia + Low HDL-C + Hypertriglyceridemia	49 (14.3)	24 (6.8)	0.001

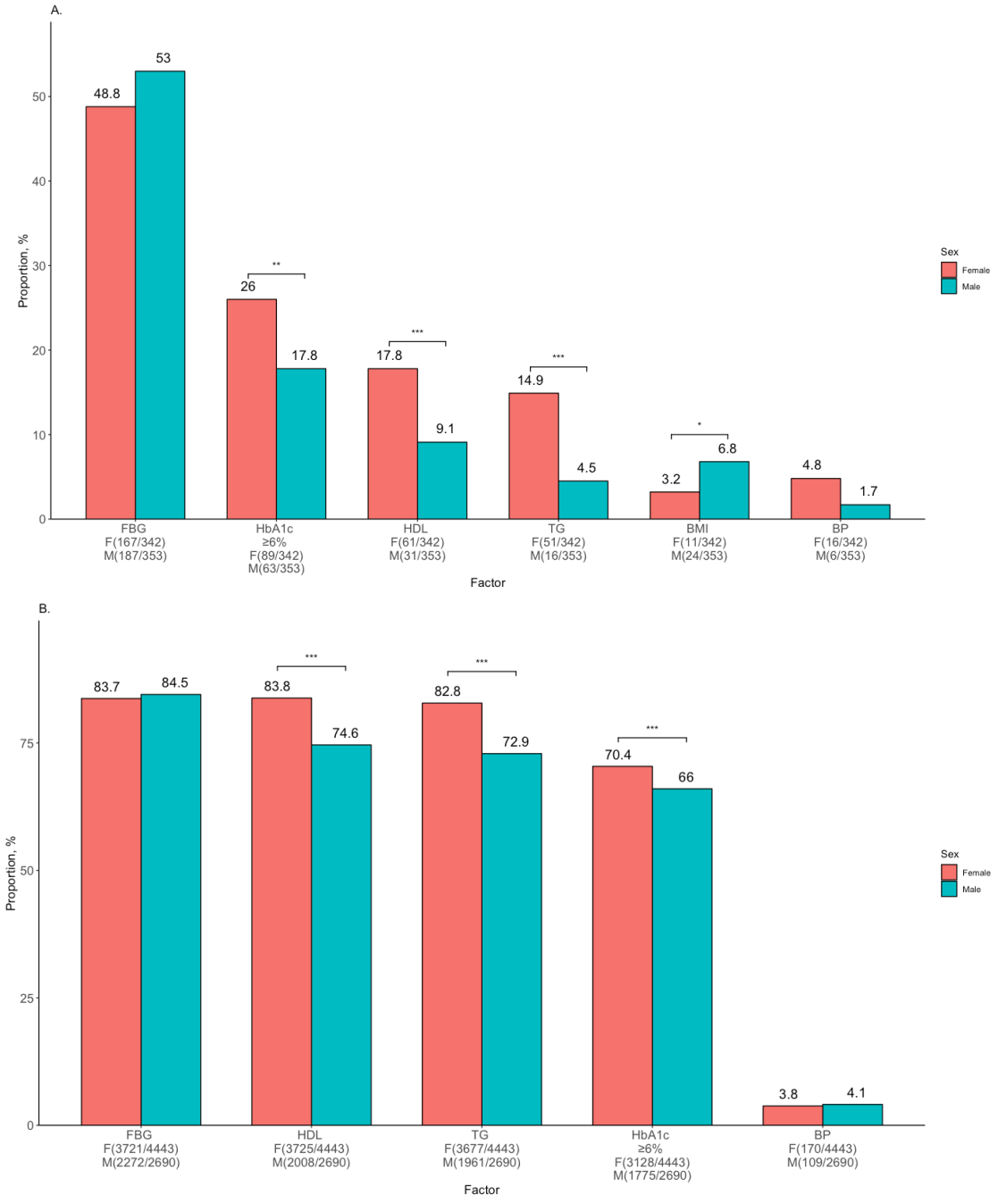
*Patients fit into multiple combinations. Blood pressure (BP), high density lipoprotein cholesterol (HDL-C). Elevated BP includes a CPCSSN diagnosis of hypertension or BP ≥130/85 mmHG. Dysglycemia includes a CPCSSN diagnosis of diabetes or FBG ≥5.6 mmol/L or HbA1c ≥6.0%. Overweight or obese includes a BMI≥25 kg/m^2. Hypertriglyceridemia includes a TG ≥1.7 mmol/L. Low HDL-C inclused HDL <1.3 mmol/L women, <1.0 mmol/L men. *p<0.05, **p<0.01, ***p<0.001.*

Figure 3.1 Proportions of risk factors and disease in individuals with metabolic syndrome by sex



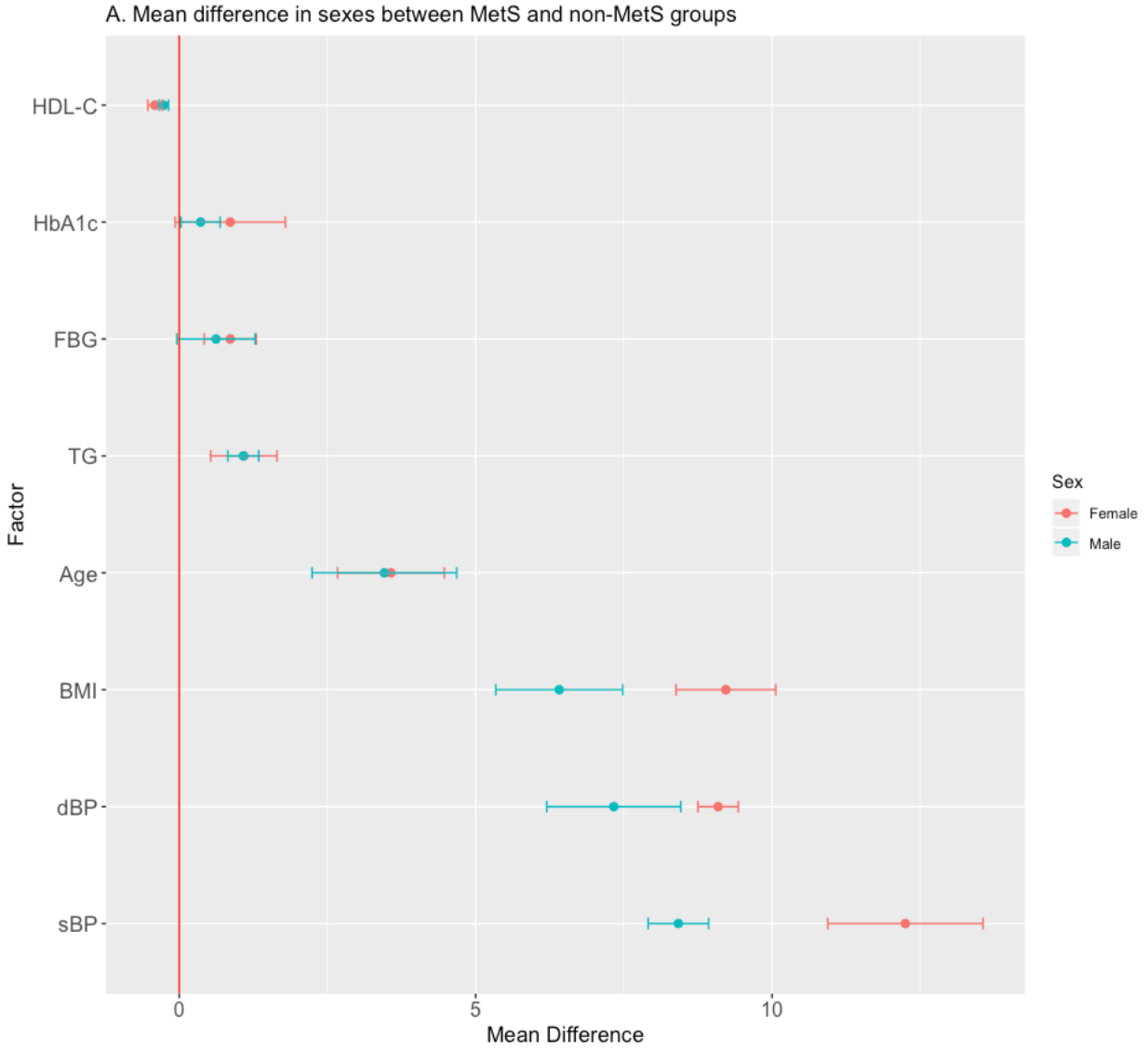
*Metabolic syndrome (MetS), blood pressure (BP), high density lipoprotein cholesterol (HDL-C) male (M), female (F). (A) proportion of physical exam and laboratory investigation tests among MetS by sex. (B) proportions of disease among individuals with MetS by sex. (C) proportion of disease among individuals without MetS by sex. Diagnoses based on CPCSSN disease definitions. Elevated BP includes a CPCSSN diagnosis of hypertension or BP ≥130/85 mmHG. Dysglycemia includes a CPCSSN diagnosis of diabetes or FBG ≥5.6 mmol/L or HbA1c ≥6.0%. Overweight or obese includes a BMI≥25 kg/m^2. Hypertriglyceridemia includes a TG ≥1.7 mmol/L. Low HDL-C inclused HDL <1.3 mmol/L women, <1.0 mmol/L men. *p<0.05, **p<0.01, ***p<0.001. *Body mass index, (BMI); triglyceride, (TG); high density lipoprotein, (HDL); fasting blood glucose (FBG); hemoglobin A1c (HbA1c), systolic/diastolic blood pressure (sBP/dBP).*

Figure 3.2 Sex stratified proportions of missing physical exam and laboratory investigations



*Body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), male (M), female (F). (A) proportion of missing physical exam and laboratory investigation tests among MetS by sex, (B) proportions of missing physical exam and laboratory investigation tests among BMI ≥ 25kg/m^2. *p<0.05, **p<0.01, ***p<0.001.*

Figure 3.3 Sex stratified mean differences comparing individual with and without metabolic syndrome



Showing the mean differences between MetS and non-MetS by sex. Metabolic syndrome (MetS), Body mass index (BMI), blood pressure (BP), fasting blood glucose (FBG), glycated hemoglobin (HbA1c), triglycerides (TG), high density lipoprotein cholesterol (HDL-C).

– Chapter 4 –

Thesis Discussion

The global burden of obesity in children and younger adults is contributing to the increased prevalence of young-adult onset MetS [11,108]. The majority of epidemiological investigations within Canada have demonstrated the growth and patterns of MetS through the use of publicly funded data repositories such as the Canadian Community Health and Canadian Health Measures Survey(s) [16,34,59]. The 2012-2013 CHMS estimated that just under 13% of Canadians adults aged 18-39 years have MetS, with WC, triglycerides, and HDL-C being significantly higher in younger adults [61]. Our aim was to develop a case definition applicable to younger adults attending a Northern Alberta primary care clinic participating in the NAPCReN, develop a case-finding algorithm for MetS using the definition created, and characterise MetS as an entity in the younger adult NAPCReN primary care practice population in Alberta.

Through our case-finding algorithm we show that the prevalence of MetS in the CPCSSN primary care space within Northern Alberta was 4.4%, equating to approximately 1 out of every 25 younger adults. The common 3-factor combinations of MetS that we have demonstrated are consistent with many other studies [19,89,124]. Importantly, the large proportions of missing laboratory investigation data, especially amongst individuals who are overweight and obese, illustrate a greater need for the screening of clinical markers and their clustering in the development of MetS[190–193]. Incorporating measures of both BMI and WC in the assessment of MetS would further help to characterize the differences seen between sexes and younger compared to older populations.

Our findings indicate that the relationship of MetS to sex is heterogeneous. Despite the differences in metabolic profiles for women and men, the prevalence remained the same which is likely attributed to under-representation in both sexes in this sample [171]. Though both females and males showed similar factors of obesity and elevated BP among MetS 3-factor combinations, the most common third factors in females was a low HDL-C measure whereas in males the presence of hypertriglyceridemia was most common. A worsening of metabolic profiles in females with MetS for dysglycemia and low cholesterol especially among those overweight or obese, indicates a need to metabolically prepare young women for childbearing years. The patterns of favourable laboratory testing for overweight and obese men indicate a greater need for laboratory investigations in women who are overweight or obese especially given that they are of childbearing age and that this provides a unique opportunity to metabolically prepare women for pregnancy [193].

Treatment of MetS generally involves the treatment of its constituents such as hypertension, dysglycemia, and dyslipidemia [3,51,57,86,101]. Since MetS is classified as a syndrome and not a disease, many clinicians prefer to target specific factors to mitigate any risk of stroke, CVD, and diabetes. Treatments are often target specific (eg. BP and dyslipidemia) and there are interventions for pre-diabetes such as diet and treatment with metformin however, if clinicians are unaware of the risks for pre-diabetes, these factors will not be targeted. This is also done at the cost of strategies for prevention that address the root causes of chronic disease predicated on lifestyle behaviours [130,194]. Evidence on the Mediterranean diet is growing and is shown to be associated with a lower the risk of CVD and MetS [195]. In fact, it has become so widely used in practice that Dieticians Canada have endorsed the use of the Mediterranean diet, leading to the creation of a Mediterranean Diet Toolkit for use with at-risk patients [196]. The gut microbiome also plays an important role as was shown in a dietary intervention combined with education in food literacy among college students. The study showed that increase in fruit and

vegetable intake on the gut microbiome had an overall decrease in the number of MetS specific components in young adults [197]. Beyond modifying food choices towards healthy meal decisions, making time to prepare and enjoy meals with others at regular intervals is integral to healthy eating behaviours. Significant cultural and familial barriers play a role in food choices and consumption. One study showed that young adults will often choose to eat foods consistent with the rest of their family or feel that they are unable to refuse offerings as it would be a sign of disrespect to the family member who prepared the meal [198].

Behavioural change regarding dietary and physical activity habits are among the most difficult interventions [199]. The recommendation to "eat less and move more" has historically been used as a blanket statement encouraging patients to improve health overall, but has been largely ineffective [200,201]. Efforts are underway in Canada through the Canadian Health Advanced by Nutrition and Graded Exercise (CHANGE) program by Metabolic Syndrome Canada (MetSC) (*https://www.metabolicsyndromecanada.ca/)* to help individuals with MetS focus on long term goals for overall well-being [134,202]. The causes of chronic disease are further explained not just by lifestyle behaviours but a complex web of causation with many factors at play that go beyond the individual [194]. Early detection of MetS in young adults may be a vital prevention strategy for the progression of chronic disease [203, 204].

Other studies have combined sociodemographic information with clinical metabolic markers to provide a richer estimation of the prevalence of MetS in Canadian young-adult populations [16,34]. Inclusion or better reporting of sociodemographic characteristics in EMR's such as education, income, and lifestyle behaviours, would help to better characterize the prevalence of MetS in all age groups. Other studies have added important evidence on nutrition patterns in the development of MetS and should not go unnoticed when addressing underlying co-morbidities and the development of chronic disease [9,27].

Implications for Research

The current definitions used to identify MetS are nuanced and raise some important issues. First, there is ambiguity in adequately identifying and characterizing MetS in the young adult population given the use of varying criteria across multiple definitions. For instance, the WHO uses measures of glucose tolerance for fasting glucose and BMI in assessing MetS whereas the NCEP ATP III and IDF definitions use impaired fasting glucose and measures of WC [82]. Even among similar definitions (NCEP ATP III and IDF), the parameters for fasting glucose are different [11]. Second, the current rationale for clinical cut points are set for the older adult population over 40 years of age. Also, sex specific cut points are used for some MetS criteria but not all, raising the question of whether or not other measures of MetS would benefit from sex stratification, given the substantial physiological differences between hormonal function and fat accumulation and in men and women. Further research is needed to clarify the phenotypes of MetS to better understand the age and sex variability and the best therapeutic approaches to screening and managing various phenotypes.

The use of EMRs in clinical practice is now widespread and though many EMRs have the ability to accurately capture measures of health status. In Alberta, the rates of EMR adoption are 85% and continuing to increase [16]. Despite the increasing uptake, EMRs are often not used to their full potential. Firstly, there remain many technological, economic, knowledge-based, and behavioural challenges to effective utilization of EMRs into practice [205]. Standards for recording health data continue to evolve, and clinician continue to struggle with EMRs that often lack the desired flexibility and functionality needed in practice [206]. Furthermore, clinicians are faced with limited time to manage pressing clinical issues, while also tasked with providing

increasingly detailed reporting and thus much information is simply not recorded. The EMRs in NAPCReN is not immune to these issues, as demonstrated by the large proportion of labs that were not ordered in this sample. It is clear from this study that many more efforts are required to understand the challenges in accurate clinical documentation in EMRs to ensure that they provide reliable epidemiological conclusions. Many studies have addressed the need for measures of ethnicity and behavioural risk factors into the definitions of MetS [207]. There are challenges in adequately recording ethnicity and other social characteristics into existing EMRs due to time constraints and a lack of standardized way to collect this information [208].

The question of how MetS should be defined remains to be delineated and may vary by population and on the intention and impact of diagnosing such individuals. The responsibility of intervening on MetS should not only fall to primary care physicians. However, since primary care is the entry point for the majority of patients, especially young-adults, there is a unique public health opportunity for educating clinicians and the public on important matters regarding strategies for healthier living. On taking a population-based approach, Rose's prevention paradox best describes that in understanding the burden of disease, the focus on identifying high risk individuals does an injustice to society as a whole [209]. Since exposure and disease occur as a function of society, placing an emphasis on a larger number of individuals of lower risk such as young adults, may result in the greatest benefit in shifting the population risk distribution and prevention of chronic disease [209]. Given the high rates of obesity in our study, there is a research opportunity to see how best to develop relationships and infrastructure between primary care clinicians and community-based health programs like the Diabetes Prevention Program (DPP) that support healthier habits in young adults who are susceptible to MetS [204].

In order to have acceptance of this preliminary case definition, further validation is needed to accurately assess and operationalize it into practice. The use of a retrospective chart reviews paired with prospective studies using this preliminary case definition in multiple EMR settings would provide a better understanding of the clinical utility of this definition in practice. Chart audits may also reveal the clinical nuances of recording in the EMR. Though MetS has an ICD9 code 277.7, it is not being used since physicians are not looking for MetS due to a lack of awareness and a consistent case definition for screening populations at risk. Physicians instead screen for specific risk factors and forget about the clustering subclinical nature of MetS. Interviews and focus groups with clinicians would be helpful in understanding why there is a paucity of missing data within the existing EMR and provide insight into ways to meaningfully capturing the clinical characteristics of MetS.

Implications for Practice

When physicians are trained to take the social history portion of the medical history, questions include smoking status, occupation, alcohol consumption, and drug use. However, physicians often miss inquiring about important social and behavioural determinants of metabolic health, such as physical activity and nutrition habits, as traditional medical teaching does not include these components [210]. Social and behavioural characteristic if collected, are recorded as free-form text in the EMR making analysis difficult for research. Given the subclinical nature of MetS factors, most patients seeking care have other clinical concerns, and making time for discussion of social determinants and metabolic conditioning often does not take precedence. There are also concerns of over-medicalization of MetS into practice since placing the MetS label creates its own barriers and social challenges for patients. The ambiguity of defining MetS in practice leads to patients being labelled as having MetS by some physicians and not others.

The variation in definitions have posed challenges for primary care physicians to properly address MetS across patient panels. Without a clear and actionable definition, patients are less likely to be detected and receive clinical intervention to improve health. A clear definition would have a positive impact on practice by helping clinicians intervene and address MetS on an episodic visit and practice management level. Clinicians would also be able to evaluate the care provided to these MetS patients and implement practice level interventions to monitor and assess treatment appropriately.

Conclusion

Our study provides the first epidemiologic investigation of the prevalence of young-adult onset MetS in a Northern Alberta using primary care EMR data. Though the prevalence in this population is lower than other national estimates, the proportions of missing data particularly amongst those with MetS or who are overweight and obese highlight the importance of capturing the appropriate clinical evidence that is necessary for MetS surveillance. The low health service utilization rates further demonstrate the challenges facing clinicians in providing care to younger adult populations at risk for developing MetS. The lack of clear actionable diagnostic criteria also poses barriers for clinicians to address MetS in the younger adult population. The fundamental biological and phenotypical characteristics of MetS between sexes should be considered for further investigation within this sample. Considerations should also be made in the treatment of metabolic clusters as a more efficient method of action to preventing the development of young-adult onset MetS. Efforts to prevent, treat, and diagnose young-adult onset MetS are critical to preventing the development of chronic disease. The MetS case definition and case-finding algorithm demonstrated in this study will help CPCSSN primary care

physicians identify younger adults with MetS, generate new hypotheses, and improve overall quality of care.

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Appendices

Appendix I

Table A-1.1 CPCSSN Disease Definition for Diabetes

Diabetes Mellitus (Occurrences of any of the following indicators is enough to index the disease.)						
Billing	**OR**	**Problem List**	**OR**	**Medication**	**OR**	**Lab Result**
Minimum Two occurrences of the following codes within two years: 1. 250, Diabetes mellitus		Any occurrence of the following codes: 1. 250, Diabetes mellitus		DrugName — ATC Code ACARBOSE — A10BF01 GLIBENCLAMIDE — A10BB01 GLICLAZIDE — A10BB09 GLIMEPIRIDE — A10BB12 INSULIN (HUMAN) — A10AB01 INSULIN (HUMAN) — A10AC01 INSULIN (HUMAN) — A10AD01 INSULIN (HUMAN) — A10AE01 INSULIN ASPART — A10AB05 INSULIN ASPART — A10AD05 INSULIN DETEMIR — A10AE05 INSULIN GLARGINE — A10AE04 INSULIN LISPRO — A10AB04 INSULIN LISPRO — A10AD04 METFORMIN — A10BA02 METFORMIN AND ROSIGLITAZONE — A10BD03 SITAGLIPTIN — A10BH01 TOLBUTAMIDE — A10BB03 INSULIN (PORK) — A10AC03 The following diagnosis if exist in patient's problem list make **the medication criteria alone insufficient**: • 256.4, Polycystic Ovarian Syndrome • 648.8, Gestational Diabetes • 249, Secondary (chemical induced) Diabetes • 790.29, Hyperglycemia NOS • 775.1, Neonatal diabetes mellitus		1. Any HbA1C >= 7 2.Two occurrences within one year of Fasting Glucose >7

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Table A-1.2 CPCSSN Disease Definition for Hypertension

Hypertension (Occurrences of any of the following indicators is enough to index the disease.)						
Billing	**OR**	**Problem List**	**OR**	**Medication**	**OR**	**Lab Result**
Minimum Two occurrences of the following codes within two years: 1. 401, Essential hypertension 2. 402, Hypertensive heart disease 3. 403, Hypertensive chronic kidney disease 4. 404, Hypertensive heart and chronic kidney disease 5. 405 , Secondary hypertension		Any occurrence of the following codes: 1. 401, Essential hypertension 2. 402, Hypertensive heart disease 3. 403, Hypertensive chronic kidney disease 4. 404, Hypertensive heart and chronic kidney disease 5. 405 , Secondary hypertension		DrugName — ATC Code ACEBUTOLOL — C07AB04 ALISKIREN — C09XA02 AMILORIDE — C03DB01 AMLODIPINE — C08CA01 ATENOLOL — C07AB03 ATENOLOL AND OTHER DIURETICS — C07CB03 BENAZEPRIL — C09AA07 CAPTOPRIL — C09AA01 CARVEDILOL — C07AG02 CHLORTALIDONE — C03BA04 CILAZAPRIL — C09AA08 ENALAPRIL — C09AA02 ENALAPRIL AND DIURETICS — C09BA02 EPROSARTAN — C09CA02 EPROSARTAN AND DIURETICS — C09DA02 FELODIPINE — C08CA02 FOSINOPRIL — C09AA09 HYDROCHLOROTHIAZIDE — C03AA03 HYDROCHLOROTHIAZIDE AND POTASS — C03EA01 INDAPAMIDE — C03BA11 IRBESARTAN — C09CA04 IRBESARTAN AND DIURETICS — C09DA04 LISINOPRIL — C09AA03 LISINOPRIL AND DIURETICS — C09BA03 LOSARTAN AND DIURETICS — C09DA01 METHYLDOPA (LEVOROTATORY) AND I — C02LB01 METOLAZONE — C03BA08 TELMISARTAN — C09CA07 TIMOLOL — C07AA06 TRANDOLAPRIL — C09AA10 TRIAMTERENE — C03DB02 VALSARTAN — C09CA03 VERAPAMIL — C08DA01 The following diagnosis if exist in patient's problem list make **the medication criteria alone insufficient**: • 346, Migraines • 428, CHF • 410, Myocardial Infarction • 412, Myocardial Infarction • 250, Diabetes • 427, Cardiac Arrhythmia • 333.1, Tremor • 456.0, Esophageal Varices • 456.1, Esophageal Varices		**N/A**
				• 413, Angina • 592, Kidney Stones • 572.3, Portal Hypertension		

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Table A-1.3 CPCSSN Disease Diagnosis for Depression

Depression						
Billing	**OR**	**Problem List**	**OR**	**Medication**	**OR**	**Lab Result**
Any occurrence of the following codes: 1. 296, Episodic mood disorders 2. 311, Depressive disorder not elsewhere classified		Any occurrence of the following codes: 1. 296, Episodic mood disorders 2. 311, Depressive disorder not elsewhere classified		AMITRIPTYLINE AND PSYCHOLEPTICS N06CA01 CITALOPRAM N06AB04 ESCITALOPRAM N06AB10 FLUOXETINE N06AB03 FLUVOXAMINE N06AB08 MIRTAZAPINE N06AX11 MOCLOBEMIDE N06AG02 SERTRALINE N06AB06 TRANYLCYPROMINE N06AF04 The following diagnosis if exist in patient's problem list make **the medication criteria alone insufficient**: • 300, Anxiety disorders		**N/A**

Retrieved online from http://cpcssn.ca/wp-content/uploads/2014/07/CPCSSN_DiseaseDefinitionsFINAL_July16-2014.pdf

Table A-1.4 CPCSSN Disease Definition for Osteoarthritis

Osteoarthritis					
Billing	**OR**	**Problem List**	**OR**	**Medication**	**Lab Result**
Any occurrence of the following codes: 1. 715, Osteoarthritis and allied disorders 2. 721, Spondylosis and allied disorders		Any occurrence of the following codes: 1. 715, Osteoarthritis and allied disorders 2. 721, Spondylosis and allied disorders		**N/A**	**N/A**

Retrieved online from http://cpcssn.ca/wp-content/uploads/2014/07/CPCSSN_DiseaseDefinitionsFINAL_July16-2014.pdf

Appendix II

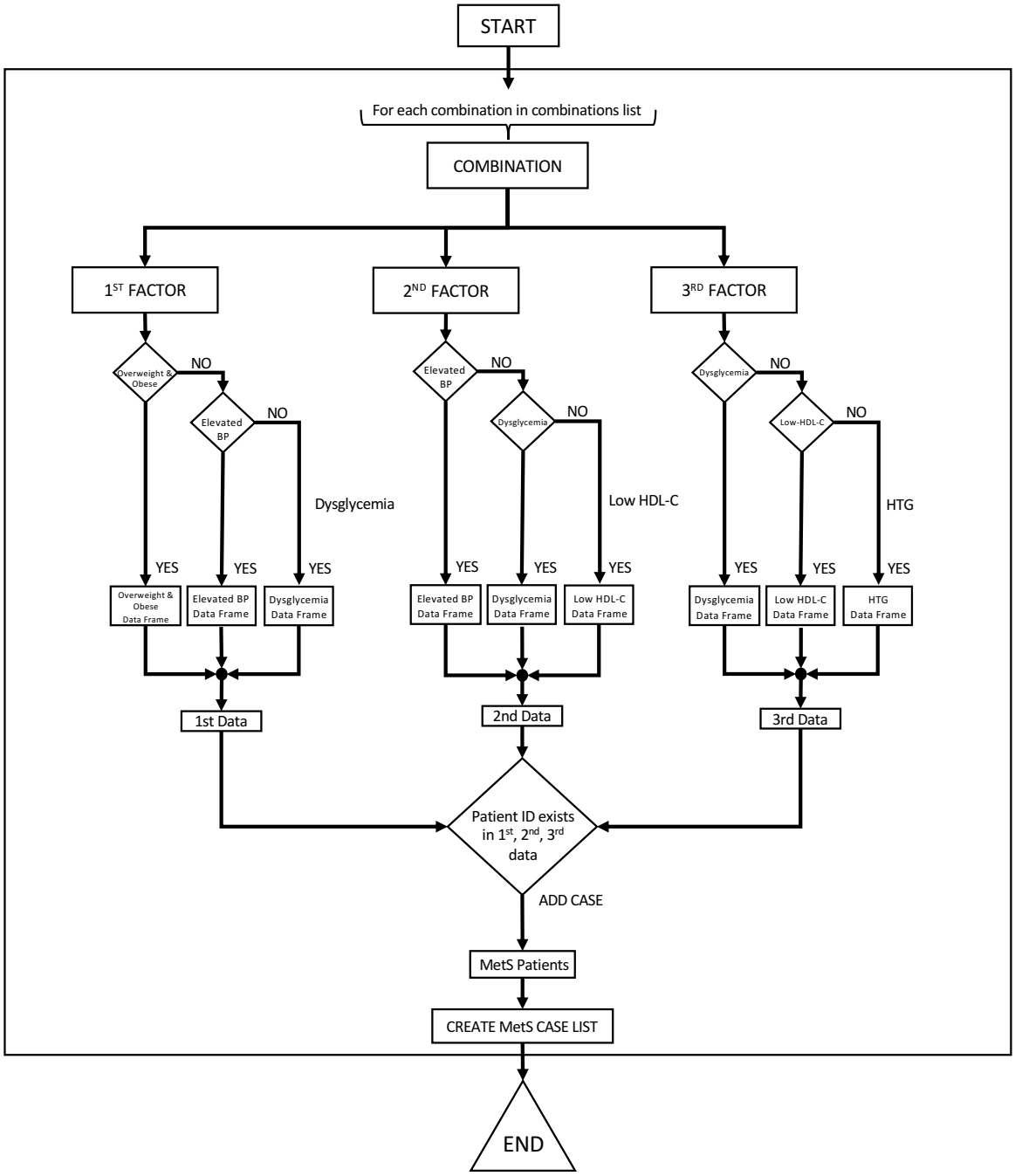
Table A-2. Metabolic syndrome 3-factor combinations

1. Overweight+ Elevated BP+ Dysglycemia
2. Overweight+ Elevated BP+ Low HDL-C
3. Overweight+ Elevated BP+ Hypertriglyceridemia
4. Overweight+ Dysglycemia+ Low HDL-C
5. Overweight+ Dysglycemia+ Hypertriglyceridemia
6. Overweight+ Low HDL-C+ Hypertriglyceridemia
7. Elevated BP+ Dysglycemia+ Low HDL-C
8. Elevated BP+ Dysglycemia+ Hypertriglyceridemia
9. Elevated BP+ Low HDL-C+ Hypertriglyceridemia
10. Dysglycemia+ Low HDL-C+ Hypertriglyceridemia

Blood pressure, BP. Low HDL-C include CPCSSN diagnosis of hypertension or BP ≥130 or ≥85 mmHG, Dysglycemia includes CPCSSN diagnosis of diabetes or FBG ≥5.6 mmol/L or HbA1c ≥6.0%. Overweight includes BMI≥25 kg/m^2. Hypertriglyceridemia include TG ≥1.7 mmol/L. Low HDL-C inclused HDL <1.3 mmol/L women, <1.0 mmol/L men.

Appendix III

Figure A-3. Linear search algorithm for identifying cases of metabolic syndrome



A combination consisting of three MetS components is first created and separated based on its values. Three lists of patients meeting the MetS criteria for each combination value are created. The lists are combined based on Patient ID, those patients which exist in all three lists fulfill the requirement for a positive MetS case and are added to a MetS case list. Figure created in collaboration with C. Oliva.

Appendix IV

Table A-4. Sex stratified population characteristics in individuals 18-40 years from 2015-2018

Characteristic	Female (n=10002)				Male (n=5764)			
	MetS		Non-MetS		MetS		Non-MetS	
	N (%)	Mean ±SD	N (%)	Mean ±SD	N (%)	Mean ±SD	N (%)	Mean ±SD
Age (years)	342 (3.4)	34.36 ±4.92	9660 (96.6)	30.79 ±5.82	353 (6.1)	34.22 ±4.76	5411 (93.9)	30.76 ±5.98
BMI (kg/m^2)	316 (3.2)	36.33 ±7.03	7455 (96.7)	27.11 ±6.19	329 (5.7)	33.98 ±6.79	3656 (94.3)	27.57 ±5.72
sBP (mmHg)	326 (3.3)	128.35 ±13.33	8716 (96.7)	116.10 ±12.02	347 (6.0)	131.64 ±13.22	4796 (94.0)	123.32 ±12.71
dBP (mmHg)	326 (3.3)	83.51 ±9.80	8716 (96.7)	74.42 ±9.46	347 (6.0)	84.75 ±8.80	4796 (94.0)	77.42 ±9.93
HbA1c (%)	253 (2.5)	6.15 ±1.59	2071 (97.5)	5.29 ±0.66	290 (5.0)	5.75 ±1.10	1232 (95.0)	5.39 ±0.77
FBG (mmol/L)	175 (1.7)	5.71 ±1.47	1091 (98.3)	4.85 ±1.03	166 (2.9)	5.77 ±1.88	575 (97.1)	5.15 ±1.22
TG (mmol/L)	291 (2.9)	2.25 ±1.19	1078 (71.0)	1.16 ±0.63	337 (5.8)	2.52 ±1.16	862 (94.2)	1.44 ±0.90
HDL-C (mmol/L)	281 (2.8)	1.15 ±0.25	994 (97.2)	1.56 ±0.37	322 (5.6)	1.03 ±0.21	806 (94.4)	1.29 ±0.29

*BMI, Body Mass Index; HbA1c, Glycated Hemoglobin; TG, triglyceride; FBG, fasting blood glucose; HDL-C, high density lipoprotein cholesterol. *Hypertension & diabetes are based on the validated CPCSSN disease definition, refer to Appendix I.*