The burden of young-adult onset metabolic syndrome in a Northern Alberta primary care setting using electronic medical record data

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Abstract

Background: The prevalence of metabolic syndrome (MetS) is growing worldwide, yet remains under-investigated in the Canadian adult primary care practice population. Given the preventable end-organ complications associated with MetS, we sought to describe the prevalence and metabolic burden of MetS in younger adults 18-40 years old.

Methods: Using electronic medical record data from the Northern Alberta Primary Care Research Network (NAPCReN), we developed a case definition and case-finding algorithm for the identification of MetS and performed cross sectional analysis on physical exam, laboratory, and validated electronic medical record derived disease diagnosis.

Results: In our sample of 15,766 young adults, the prevalence of MetS in this sample of young adults was 4.4%. The most frequent 3-factor combination (41.4%) of MetS consisted of being overweight/ obese, having elevated blood pressure (BP), and hypertriglyceridemia. Half of MetS cases (50.9%) were missing measures for fasting blood glucose and one-fifth were missing an HbA1c. Young adults with MetS showed a prevalence of diabetes (15.2%) and hypertension (14.2%). Notably, most young adults with a body mass index (BMI) ≥ 25kg/m2 were missing A1c (66.9%), fasting blood glucose (84.0%), and lipid testing (79.0%).

Interpretation: The proportions of missing data among young adults likely underestimates the true prevalence of MetS in this young adult sample. Further investigation is required to validate the case definition and determine whether appropriate intervention is being taken to identify young adults at higher risk of metabolic disease.

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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 [1–3]. 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 [4]. The pathogenic

mechanisms of MetS are thought to be driven by the presence of chronic low-grade

inflammation associated with the development of insulin resistance and excess adiposity [5].

The causes of MetS are still under investigation and reviews have been published elsewhere

[4,6,7].

Since MetS is typically more prevalent in older populations, its characterization in younger adult

populations is less studied. Recently, there has been little investigation of the prevalence of

young-adult onset MetS in Canada. Existing reports are either based on smaller cohorts of older

adults, minority ethnic groups, or overall population estimates based on self-reported data [8–

10]. Two Canadian based studies both using cycle 1 Canadian Health Measures Survey

(CHMS) data from 2007-2009 showed population prevalence estimates for young-adult onset

MetS 18-40 years to be 6.5% and 7.8%, respectively [8,11].

Challenges in consistently reporting estimates of MetS prevalence are driven by the ambiguity

of multiple case definitions created by different organizations [1,12–16]. The most widely used

criteria for identifying individuals with MetS were published in the US National Cholesterol

Education Program Adult Treatment Panel III (NCEP- ATP III) guidelines [12]. Moreover, the

use of multiple definitions has created confusion for clinicians tasked with identifying MetS with

no clear actionable guidelines. The main objectives of this study were to report on the

prevalence of young-adult onset MetS in Northern Albertan young-adult patients 18-40 years of

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age using a harmonized case definition for use within the Northern Alberta Primary Care

Research Network (NAPCReN) primary care electronic medical record (EMR) data.

Methods

Data Source

We used Alberta-based data collected from NAPCReN, which contributes data to the Canadian

Primary Care Sentinel Surveillance Network (CPCSSN) [17]. The data provided for this

research is the NAPCReN regional data, a Northern Alberta subset of the Alberta primary care

practice population. The EMR data is representative of 18 active clinics consisting of 77

participating primary care clinicians across Northern Alberta representing 91,525 patients[18].

Consenting family physicians and primary care clinicians provide NAPCReN with access to their

EMR data. We analyzed patient demographic, physical examination, laboratory investigation,

and CPCSSN defined diagnosis of disease data. Physical exam data included body mass index

(BMI), systolic blood pressure (sBP), and diastolic blood pressure (dBP). The laboratory data

included high-density lipoprotein cholesterol (HDL-C), hemoglobin A1c (HbA1c), fasting blood

glucose (FBG), and triglycerides (TG).

Study Design

This was a cross-sectional study evaluating the most recent measures of BMI, BP, laboratory

investigations, and disease diagnosis data to ascertain the prevalence of MetS in a sample of

primary care practices. The population 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 June 29, 2015 and June 29, 2018. In establishing the denominator, study subjects

must have had at least one measure between the specified date range and were excluded if

they were outside of this range, were missing sex data, had a non-Albertan postal code, or were

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deceased (Figure 1.1). This study was approved by the Health Research Ethics Board,

University of Alberta (Pro. 00073600).

Measures

We developed a harmonized case definition using criteria based on the National Cholesterol

Education Program Adult Treatment Panel III [12], the World Health Organization (WHO)[19],

Diabetes Canada [15], Canadian-Cardiovascular Harmonized National Guidelines Endeavour

(C-CHANGE)[20], and CPCSSN validated disease definitions [21]. As outlined in Table 1.2, a

patient was classified as having MetS if they met a minimum of three of five criteria. We used

BMI given that 98.5% individuals within this data did not have measures for waist circumference

(WC) and there is reasonable evidence to consider BMI where WC data is unavailable [22]. We

used a BMI value of $\geq$ 25 kg/m^2 and did not distinguish between those in overweight or obese

categories [12]. Outliers were removed using cut points < 15 kg/m^2 and > 55 kg/m^2 based on

clinical judgement.

Dysglycemia was present if a subject had a CPCSSN diagnosis of diabetes [21] or HbA1c $\geq$

6.0% or FBG $\geq$ 5.6 mmol/L. A diagnosis of diabetes was identified through an ICD9 250 code in

the billing or problem list, anti-diabetic medications, or a previous laboratory value of elevated

HbA1c or FBG.

We used the validated CPCSSN diagnosis of hypertension [21] or an office sBP or dBP to

establish the presence of elevated BP. 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

diagnosis of hypertension was made from medical billing, medications, and the problem list to

identify hypertension related ICD9 codes (Table A-1.2).

To assess the presence of dyslipidemia, women were identified as having low HDL-C at <1.3 mmol/L and men at <1.0 mmol/L. 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 [23].

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 1.1. The process of identifying MetS cases in the algorithm (Figure 2.1) begins with the first of ten possible combinations. Each eligible patient within the sample is assessed for each combination. If a patient met the criteria for three factors for a given combination, they were identified as having MetS. It is important to note that it is possible for a patient to have MetS based on more than one combination, and that a patient is counted only once in establishing the prevalence, regardless of the number of combinations met.

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 were reported as mean ± standard deviation (SD). Categorical variables were expressed as counts with proportions. The prevalence of MetS was defined as the ratio between those having MetS and the total number of subjects included in the denominator.

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Results

There were 22,765 patients available for analysis within this study between June 29, 2015 and June 29, 2018. After exclusion criteria were applied, a total of 15,766 individual patient records were evaluated for the presence of MetS (Figure 1.1). 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 representing 41.1% included measures of BMI, elevated BP, and hypertriglyceridemia.

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 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 1.2).

Among physical exam measures, 91.2% of individuals in the MetS group had a BMI of ≥25 kg/m^2 (Figure 1.3) and 75.1% had elevated office sBP and dBP. 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

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were small, 2.5% of the MetS group had a CPCSSN diagnosis of osteoarthritis compared to

1.0% in the non-MetS group (Figure 1.3).

Missing Data

In those with MetS, 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 1.4 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 would have been considered as having MetS if they had a BMI over the 25 kg/m^2 cut

point.

Notably, among all 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 1.4 B).

Discussion

We 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. Importantly, we found a large proportion of missing data in this

younger adult sample and therefore suspect that our findings underestimate the true prevalence

of MetS. 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 may represent an enriched sample [24].

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One of our key findings indicate that the patterns within young-adult onset MetS were similar compared to other studies looking at older populations [10,25]. Although there may be an age-dependent increase in the prevalence of MetS, the distribution of MetS features remains relatively the same, despite previous evidence of the physiological differences in MetS by age [26].

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 [8,11]. These findings reinforce the likelihood that our data underestimate the true prevalence of MetS in the primary care setting, particularly given that the prevalence of obesity has not reduced since those studies were carried out [27], and that the metabolic health of those seeking primary care are possibly worse than the population not seeking any medical care [24,28].

Our data might suggest that the lack of clinical investigation for risk markers in younger adults with MetS or over elevated BMI, represents a lost opportunity for chronic disease prevention. This lack of investigation likely represents a combination of both patient and clinical inertia where patients may be less inclined to obtain lab testing while young and asymptomatic, and physicians might be less likely to order laboratory tests for the same reasons. There may also be reluctance to place the MetS label on a patient, as this could potentially cause distress or influence the ability for an individual to obtain health insurance. There may also be considerable resource restraints given that 45.2% of young adults in this practice population had a BMI in the overweight/obese category. Physicians also report difficulties addressing MetS among multiple definitions and recognize that identification of individual clinical risk factors is insufficient to appropriately address MetS [29]. Lastly, the causes of MetS often involve broad social

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challenges requiring significant resources that may lie outside the scope of conventional

medicine or pose a challenge due to other conflicting clinical priorities in a patients care [30,31].

The NAPCReN data are point-of-care EMR data allowing for a pragmatic understanding of the

patterns of disease and the diagnostic gaps in the primary care setting. Using validated

CPCSSN definitions for hypertension and diabetes in the case-finding for MetS strengthens this

study beyond the conventional measures for elevated BP and dysglycemia. 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. A major limitation of real-world data is that of insufficient clinical documentation and

imperfect EMR data. In many instances, fields are missing information, incorrectly entered into

the EMR, and patient demographics such as home address and death are not always reported if

they moved out of province [32]. We recognize that recording complete health information

requires sufficient clinical reasoning and manpower and that measurements are affected by

factors such as clinic workflow, professional judgment, recording behaviours of the provider,

monetary incentives, and design of the EMR. Moreover, negative findings are less likely to be

reported, resulting in a selective non-reporting bias [33]. These limitations should be carefully

considered in the interpreting this study.

Conclusion

This cross-sectional study of real-world family practice data suggests that one out of every

twenty-five persons between 18-40 years of age has MetS. However, this is likely

underestimated 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 patients and physicians. Further work is required to validate this case definition, and better

understand whether missing data is clinically informed, rather than an omission due to lack of

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time or resources. These observations provide a basis for engaging primary care clinicians in considering the current recommendations for screening of young-adults at higher risk of metabolic disease, and actions to earlier detection and management of MetS and its associated morbidity.

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Table 1.1 Harmonized criteria for defining metabolic syndrome: $\geq$ 3 factors to make a diagnosis

Metabolic Syndrome Criteria	Cut Point
Overweight and Obese	BMI $\geq$ 25 kg/m^2
Elevated Blood Pressure (BP)	CPCSSN diagnosis of hypertension or systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mmHg
Dysglycemia	CPCSSN diagnosis of diabetes or HbA1c $\geq$ 6.0% or FBG $\geq$ 5.6 mmol/L
Hypertriglyceridemia	TG $\geq$ 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 $\geq$ 50 kg/m^2, if BMI is $\geq$ 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 [19], elevated BP, HbA1c, and FBG [15], HDL-C and TG[12,20], CPCSSN disease diagnosis[35].

Table 1.2 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/m²)	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	(86.8)	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).
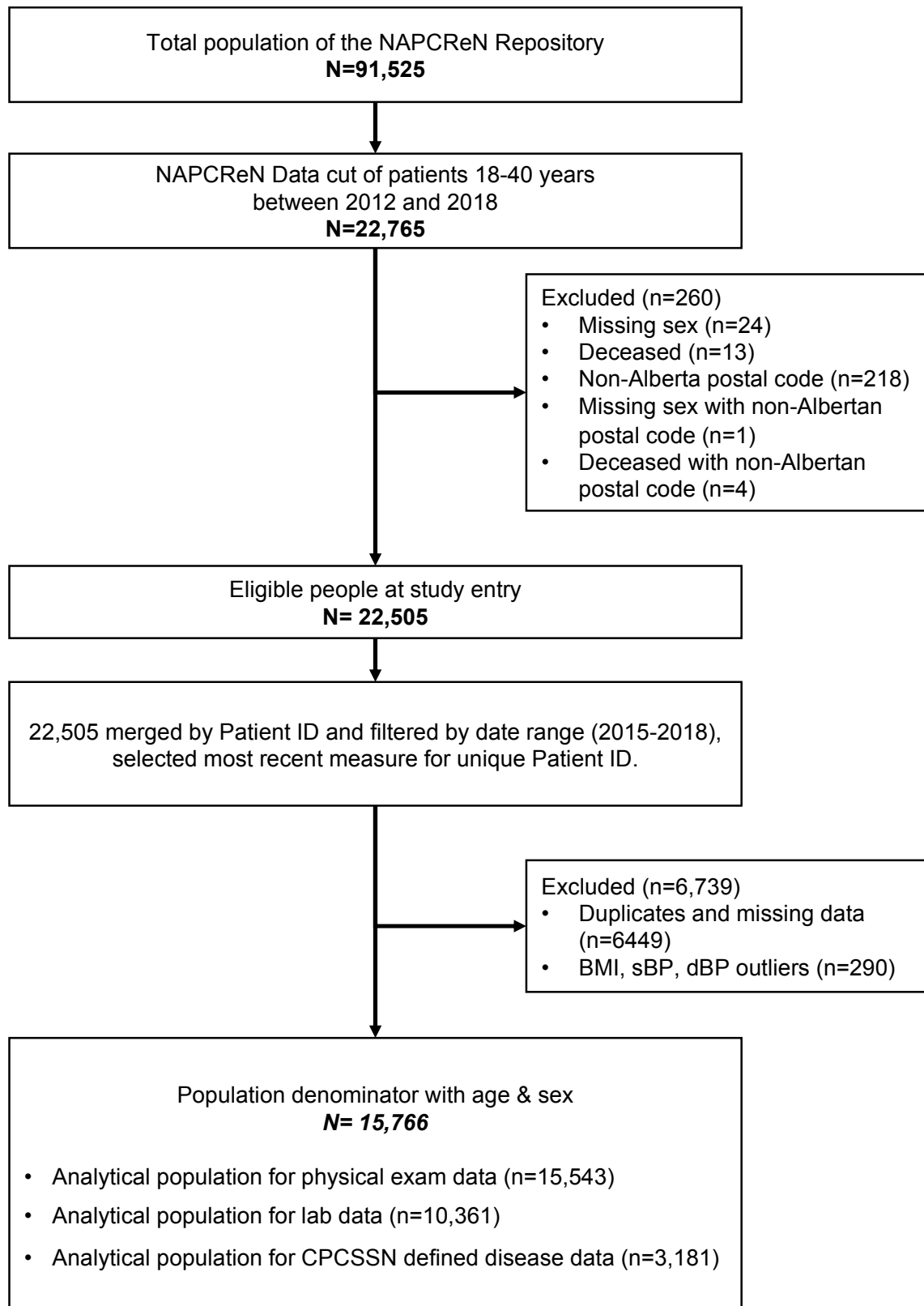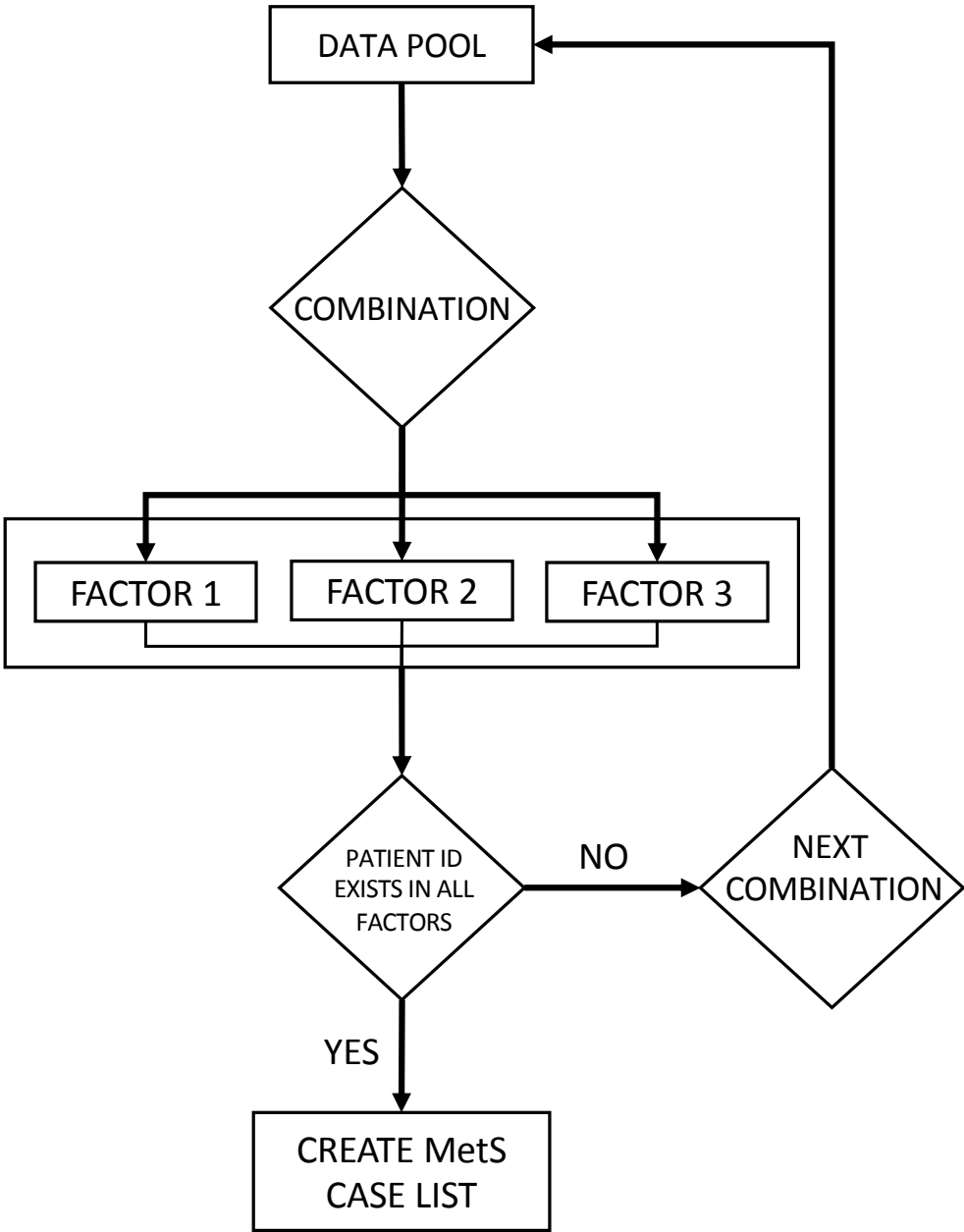
Figure 1.1 Flow of data extraction and cleaning from the NAPCReN-CPCSSN data repository

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Figure 1.2 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 and 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.

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Figure 1.3 Risk factors and disease proportions in individuals with and without metabolic syndrome
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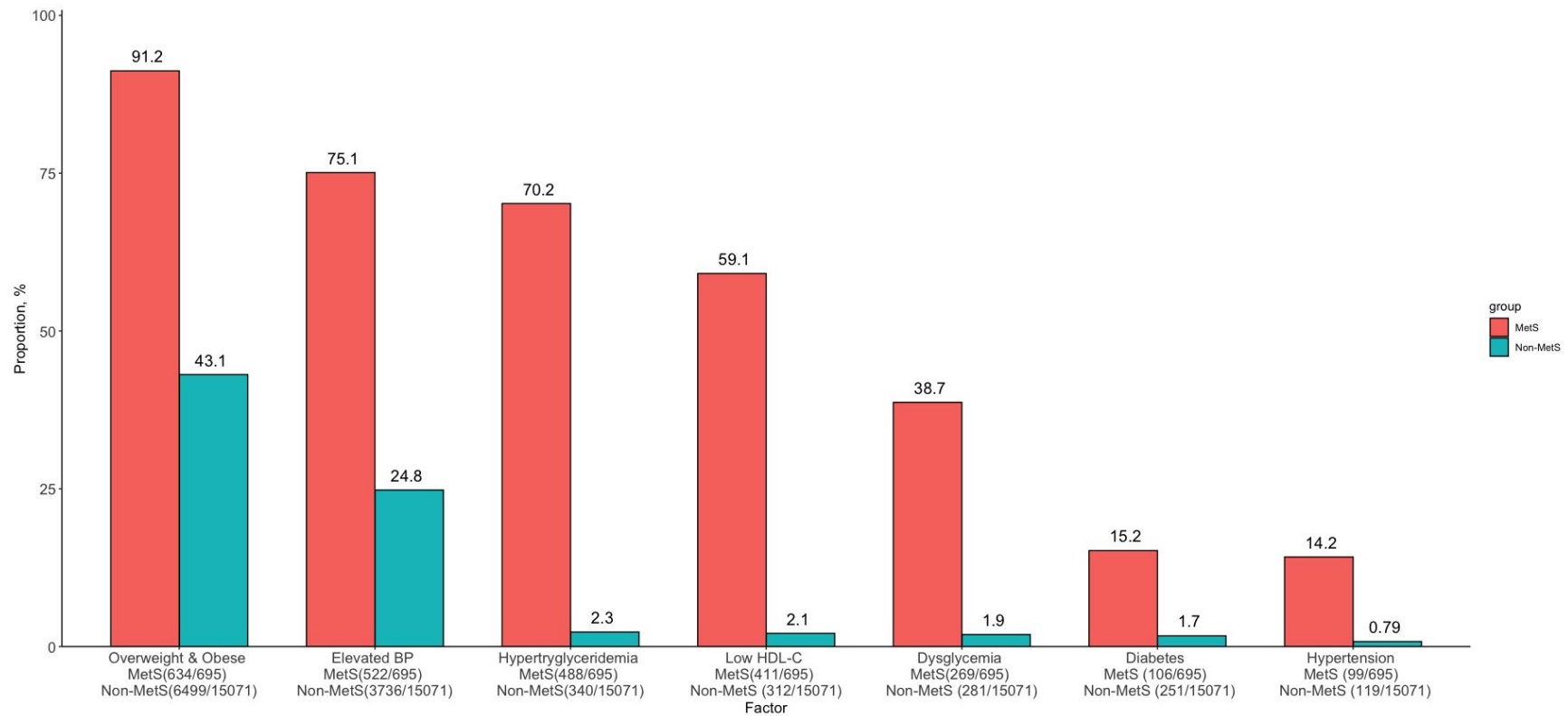
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32 *Patients shown as proportion achieving MetS component cut points in individuals with and without MetS, numerically represented in*
33 *parenthesis. Metabolic syndrome (MetS), blood pressure (BP), high density lipoprotein cholesterol (HDL-C).*
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Figure 1.4 Distributions of missing data in those with metabolic syndrome and those with a BMI $\geq$ 25kg/m^2
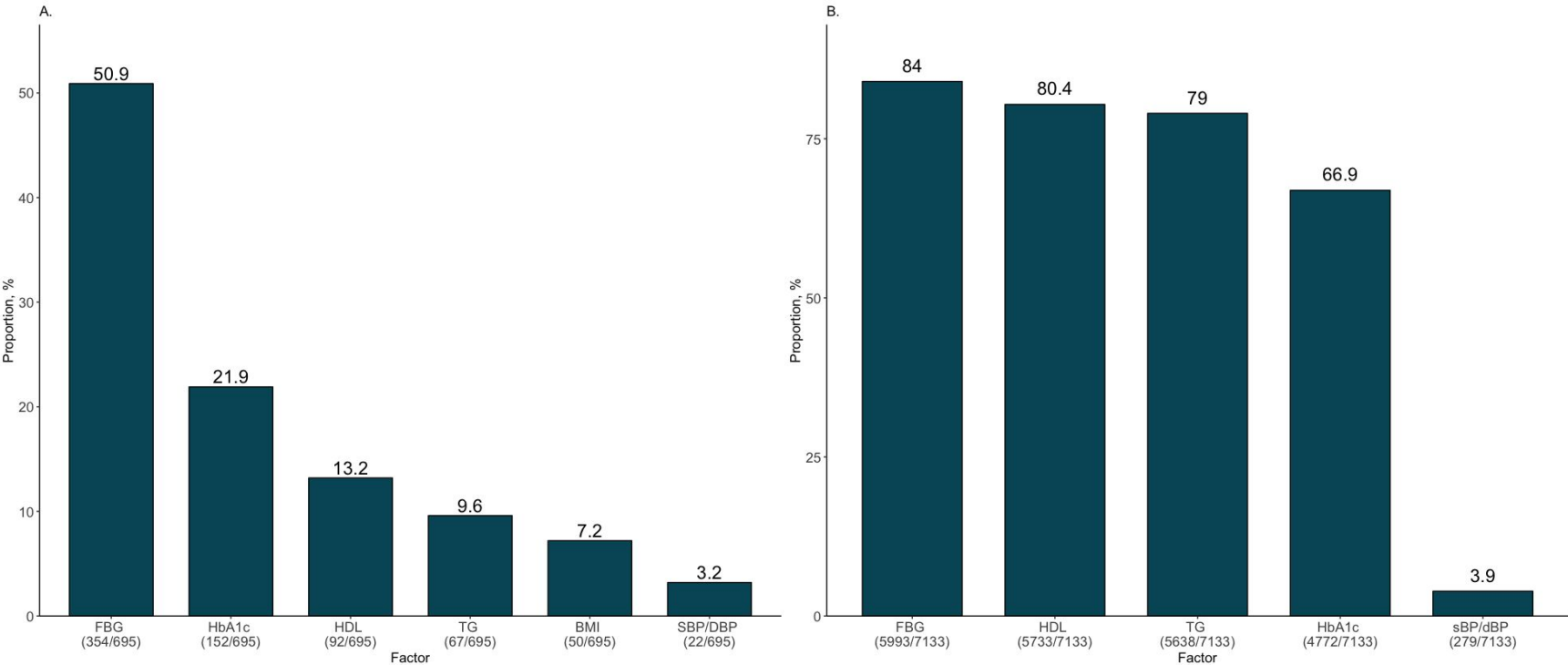
*Data in parenthesis are the number of patients with MetS or who are overweight and obese. *Body mass index (BMI), triglycerides, (TG), high density lipoprotein (HDL), fasting blood glucose (FBG), hemoglobin A1c (HbA1c), systolic/diastolic blood pressure (sBP/dBP).*