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# Preventive Health Care among Canadian Adults with Schizophrenia and Related Disorders

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# Preventive Health Care among Canadian Adults with Schizophrenia and Related Disorders

by

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## Abstract

**Objective:** To characterize cardiovascular disease risk factors (CVD-RFs) and preventive health services of people with schizophrenia and related disorders (SCZ) in a Canadian context.

**Methods:** This cross-sectional survey collected laboratory, physical examination, and interview data from 202 randomly selected Calgary outpatients with SCZ.

**Results:** There were high prevalences of several CVD-RFs. Metabolic syndrome was present in 30.0%. Mean 10-year general CVD risk was 8.8%. Many previously known CVD-RFs were inadequately treated, and several previously undetected CVD-RFs were discovered (e.g. 33.3% of diabetes). There was variable receipt of preventive services, and participants explained non-receipt by "Thought it was unnecessary" or "Didn't get around to it".

**Interpretation:** This study found substantial physical morbidity coupled with gaps in prevention, detection, and management, as well as patient factors that might be a target of interventions for improved care. Multifaceted strategies will be needed to make a difference in the health of people with schizophrenia.

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## List of Symbols, Abbreviations and Nomenclature

| Symbol | Definition |
|---|---|
| ATP III | Adult Treatment Panel III |
| AUDIT | Alcohol Use Disorders Identification Test |
| BMI | Body mass index; weight (kg) divided by height$^2$ (m$^2$) |
| BP | Blood pressure |
| CCHS | Canadian Community Health Survey |
| CDSS | Calgary Depression Scale for Schizophrenia |
| CHD | Coronary heart disease |
| CHHS | Canadian Heart Health Survey |
| CHMS | Canadian Health Measures Survey |
| Component A | Portion of the current study examining CVD risk factors |
| Component B | Portion of the current study examining preventive health services |
| CVD | Cardiovascular disease |
| DM | Diabetes mellitus |
| EPTS | Early Psychosis Treatment Service |
| FPG | Fasting plasma glucose |
| HDL | High density lipoprotein cholesterol |
| LDL | Low density lipoprotein cholesterol |
| K6 | A scale for measuring nonspecific psychological distress |
| MetS | Metabolic syndrome |
| NCEP | National Cholesterol Education Program |
| OSS | Outpatient Schizophrenia Service at Foothills Medical Centre |
| SMI | Severe mental illness |
| SMR | Standardized mortality ratio |
| TC | Total cholesterol |
| TG | Triglycerides |

# Chapter One: **Introduction**

## 1.1 Goal of the research project

There is a multifaceted interplay between mental and physical health that complicates the detection and treatment of physical disorders in individuals with mental illness, including schizophrenia.

Schizophrenia is a severe and persistent mental illness that causes significant disability, and is classically stated to affect one in a hundred persons worldwide (although estimates differ) [1;2]. In addition to suffering from a serious mental illness, these individuals have a high prevalence of physical medical illnesses, which often go undetected [3].

The goal of this study was to explore the relationships between physical health and schizophrenia and related disorders in a Canadian context, concentrating on preventive health care and cardiovascular risk factors.

For the purpose of this study, schizophrenia and related disorders was defined as nonaffective psychotic disorders including schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, and psychotic disorder not otherwise specified. At times in this document, for brevity, the term "schizophrenia" is used to represent this broader concept.

## 1.2 Current state of knowledge: Cardiovascular disease risk factors and schizophrenia

### *1.2.1 Mortality, cardiovascular disease mortality, and schizophrenia*

It has been recognized for decades that schizophrenia is associated with increased mortality rates [4;5]. A meta-analysis conducted by Saha and colleagues in 2007 identified 37

studies and found a median standardized mortality ratio (SMR) for all-cause mortality of 2.58, with a 10%-90% range of 1.18-5.76; moreover, they demonstrated that the mortality gap has worsened in recent decades [6].

The leading cause of death in schizophrenia has been reported to be ischemic heart disease or cardiovascular disease (depending on the study's breakdown of diseases), as in the general population [7-9]. Yet cardiovascular disease (CVD) mortality has been shown to be elevated in schizophrenia compared to the general population rates in most studies and meta-analyses (although there have been some studies with conflicting results) [5;7;10-12]. For example, Curkendall used Saskatchewan Health administrative data linked to vital statistics, and found an adjusted risk ratio of 2.2 (95%CI 1.7-2.8) for CVD mortality in schizophrenia compared to the general population [13]. In fact, it appears that this CVD mortality "gap" might be widening: it was demonstrated by Osby and colleagues (2000) that in Stockholm County the standardized mortality ratio (SMR) for CVD in schizophrenia had significantly increased over 25 years for both men and women, and other studies have suggested the same [8;14;15]. This increasing SMR for CVD may be at least partially related to a demonstrated decrease in CVD mortality in the general population, but it does imply a relative increase in the cardiovascular mortality among those with schizophrenia [16-18]. Not unexpectedly, cardiovascular disease morbidity has also been shown to be elevated in schizophrenia compared to the general population, both internationally and in Canada [3;13;19-21].

### *1.2.2 Cardiovascular disease risk factors and risk prediction*

Ischaemic heart disease has been known for decades be linked to "traditional" CVD risk factors including age, sex, hypertension, diabetes, hypercholesterolemia, and smoking [22-24].

Since many of the CVD risk factors are modifiable, their screening is suggested in clinical practice guidelines [25-28]. These guidelines suggest that multiple CVD risk factors should be considered in an integrated fashion, since risk factors act synergistically.

Several algorithms have been derived for prediction of cardiovascular events based on an individual's CVD risk factor profile [29-31]. Many of these algorithms are based on data from the Framingham Heart Study, a cohort study that has been continuing since the 1950s (www.framinghamheartstudy.org). The prediction results are frequently used to determine the aggressiveness with which risk factors should be treated (e.g. hypertension and elevated lipids) and screened for (e.g. diabetes) [25;26;32]. The most commonly used Framingham algorithms typically require information on age, sex, blood pressure, diabetes, smoking, total or low density lipoprotein (LDL) cholesterol level, and high density lipoprotein (HDL) cholesterol level [30;31].

Unfortunately, methods to calculate the risk of cardiovascular events from an individual's CVD risk profile are often unavailable in younger adults. For example, some risk algorithms based on the Framingham study results begin at age 30 because the study sample on which the algorithm is based ranged in age from 30 to 74 at baseline [29;31].

Two risk algorithms were of particular interest in the current study because they have been employed commonly in the literature or are used in current Canadian guidelines. First is the Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) calculation from 2001 predicting the risk of a hard coronary heart disease (CHD) event, meaning myocardial infarct or coronary death, over the next 10 years [30]. This algorithm made a modification to earlier approaches by considering diabetes to place individuals in a high CHD risk category (over 20% risk). This algorithm is valid for individuals aged 20 to 74 without diabetes or CHD; if individuals have diabetes or CHD they are assigned to the high risk category. The second

algorithm of interest was published by D'Agostino and the Framingham group in 2008, and predicts total or general CVD risk over the next 10 years, including coronary heart disease, stroke, peripheral artery disease, and heart failure [31]. This algorithm is valid for individuals aged 30 to 74 with no current cardiovascular disease. It includes a term for presence of diabetes and as such does not automatically assign high risk to those with diabetes. This algorithm is being suggested as more useful for general use as it gives a global sense of an individual's risk. For example, the current Canadian Cardiovascular Society guidelines suggest the use of this total CVD algorithm to determine targets for treatment of elevated cholesterol [25].

### *1.2.3 Schizophrenia and cardiovascular disease risk factors*

It can be postulated that the increased CVD mortality in schizophrenia is at least partly related to a higher frequency of traditional CVD risk factors. Indeed, Brown demonstrated in a cohort of 370 schizophrenia outpatients that CVD mortality was elevated in smokers but not in non-smokers [33]. It is known that a higher proportion of persons with schizophrenia smoke [34]. Moreover, many antipsychotic medications used to treat schizophrenia have been found to cause weight gain and worsen glucose and/or lipid metabolism [35;36].

In the past decade there has been increasing evidence that cardiovascular risk factors are more prevalent in schizophrenia than in the general population in many jurisdictions [37]. For example, Goff compared proportions with individual CVD risk factors at baseline in the CATIE Schizophrenia Trial (a US multisite antipsychotic trial in patients with SCID-diagnosed schizophrenia) to a randomly selected age-, sex-, and race/ethnicity-matched sample from the NHANES III, a general population survey [38]. In CATIE compared to NHANES, the proportion with smoking (68% versus 35%), diabetes (13% versus 3%), and hypertension (27% versus

17%) were significantly higher, while mean HDL was lower. There was no difference in total cholesterol. Although the CATIE trial provided a large sample compared to other relevant studies, it is important to remember that this was the baseline data from a trial, not a randomly selected sample. As such, results in this group might differ from those from the clinics as a whole.

In Canada, Bresee and colleagues used Alberta Health and Wellness administrative databases between 1995 and 2006 to examine the period prevalence of hypertension, dyslipidemia, and diabetes in those with and without schizophrenia in a population based study [39]. Defining schizophrenia as International Classification of Diseases, Ninth Revision (ICD-9) codes 295.x and using validated data definitions for the CVD risk factors, they reported that diabetes was significantly more common in the schizophrenia group (10.3% versus 5.6%), with unadjusted OR 1.94, particularly in women and young men [40]. Due to the large sample size small differences were significant, but point prevalences of hypertension (22.7% versus 21.1%) and dyslipidemia (23.0% versus 21.0%) did not differ noticeably for schizophrenia versus the non schizophrenia group. Of note, the administrative data definition of schizophrenia was not validated in this study, although the authors did report validity results from a Saskatchewan study of data from 1986 [41]. That report found only a 61.8% concordance for hospitalized schizophrenia patients between physician claims and primary hospital discharge diagnoses. Some aspects of their sample description might raise concern; for example, the schizophrenia group had a mean age that was older than the non schizophrenia group. Moreover, results on diabetes, hypertension and dyslipidemia in administrative data depend on individuals being screened for these disorders. Research suggests that screening is sometimes lower in individuals with schizophrenia, which might be expected to result in a bias toward lower detection in

schizophrenia. However, a potential bias toward increased detection might be suggested by the fact that the authors point out that those with schizophrenia were more likely to have seen a GP seven or more times in a year, which suggests that surveillance bias could have existed. It is unclear what effect these and other issues might have on the results.

The same group reported results on the presence of a number of self reported CVD risk factors based on data from Statistics Canada's nationally representative Canadian Community Health Survey Cycle 3.1 conducted in 2005[19] . Unadjusted analyses showed that the proportions with self reported diabetes, obesity, and current smoking were significantly higher with self-reported schizophrenia than without, whereas there was no statistically significant difference for hypertension. Interestingly, when adjusted for several sociodemographic and lifestyle variables as well as BMI and the number of chronic medical conditions, the difference in diabetes prevalence was no longer significant. One issue with this study relates to the validity of a self reported diagnosis of schizophrenia. Although many of the sociodemographic characteristics one would expect with schizophrenia exist in this sample (eg. Lower income and education, less likely to be married), other aspects were more questionable (eg. Less likely to use alcohol). Supina and Patten examined the use of this self report question for schizophrenia in another Statistics Canada survey, and concluded that the approach should be validated against a gold standard [42].

Cohn and colleagues in Toronto compared a group of 240 individuals with schizophrenia/schizoaffective disorder with an age and sex matched sample from the Canadian Heart Health Survey (CHHS) [43]. Their schizophrenia sample was two thirds inpatients and two thirds male, and had a mean age of 42.7 years and a mean of 19.4 years since first hospitalization. The schizophrenia group was recruited as a sample of convenience. Data were

collected in 1999 and 2000, and compared against the CHHS data from 1986 to 1990. They found rates of hypertension (BP≥ 140/90 mmHg or on antihypertensive drug) and total and LDL cholesterol levels were similar between groups, but that the schizophrenia group had significantly higher triglycerides and lower HDL levels and (not unexpectedly) higher smoking rates (74% of men and 66% of women). A subsample was tested for diabetes, and 18% were found to satisfy criteria; this was not tested in the CHHS. For BMI, both men and women with schizophrenia were elevated compared to controls, but there was an interaction between group and sex in that the difference was significantly more pronounced for women. It is important to note that this population had a very long duration of illness and severity was probably high in that two thirds were inpatients. Moreover, this was a sample of convenience, so their results might not necessarily have been representative of the entire group.

### *1.2.4 Schizophrenia and 10 year risk prediction*

Studies have computed 10 year risks of cardiovascular events in schizophrenia. For example, Goff compared the mean Framingham 10 year CHD risk at baseline in the CATIE Schizophrenia Trial to a randomly selected age-, sex-, and race/ethnicity-matched sample from the NHANES III, a general population survey [38]. The mean risk predictions in CATIE versus NHANES were significantly elevated in male (9.4% vs. 7.0%) and female (6.3% vs. 4.2%) schizophrenia patients compared to controls ($p<0.001$).

As noted above, Cohn and colleagues (Toronto) compared 240 individuals with schizophrenia/schizoaffective disorder with an age and sex matched sample from the Canadian Heart Health Survey (CHHS) [44]. They computed the 10 year Framingham risk for myocardial infarct in both groups; they refer to the NCEPATP III in their introduction, and one assumes this

is the algorithm they used. They found a mean Framingham 10 year risk of 8.9% in men (significantly higher than the control population at 6.3%) and 2.6% in women (not different from controls at 2.0%).

### *1.2.5 The concept of the metabolic syndrome*

"Metabolic syndrome" (MetS) describes a group of obesity-related metabolic abnormalities that cluster together in individuals and confer increased risk for diabetes and cardiovascular disease [45]. Although there is some debate as to the specific criteria that should be employed to define the syndrome, the features involved are disturbed glucose or insulin metabolism, hypertension, central obesity, and dyslipidemia (elevated triglycerides and lowered HDL cholesterol) [28;30;45;46]. A recent meta-analysis by Mottillo and colleagues from Montreal analyzed results from 87 studies and demonstrated that MetS is associated with approximately a two-fold relative risk for a number of CVD related outcomes, including CVD, CVD mortality, myocardial infarct, and stroke [47]. They also found that two different and commonly used definitions of MetS had similar results. Appendix A shows the criteria for diagnosis of the MetS as defined by the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) [30]. This definition has been used in a number of studies in schizophrenia [48]. Appendix A also includes the modified NCEP criteria (2008), and the current Canadian criteria, for comparison [28;46].

The definitions of MetS can be applied to individuals of any age. As such, individuals outside the age ranges for computation of 10-year risk of CHD or CVD events can still be assessed using the concept of the MetS.

In Canada, as part of a study on ethnic differences in MetS, Liu and colleagues examined

the prevalence of NCEP ATPIII-defined MetS in the non-aboriginal population, using data from the Manitoba Heart Health survey that took place between 1989 and 1990 [49]. They found the proportion of MetS was 25.3% in men and 23.7% in women, age-standardized to the 1991 census. MetS status was significantly associated with age but not sex. Riediger and colleagues were able to update these figures using data from Cycle 1 of the Canadian Health Measures Survey (CHMS), and found that using the NCEP ATPIII definition of MetS, the weighted proportion of Canadian men with MetS was 15.9% while that for women was 19.5% [50]. This survey occurred between 2007 and 2009. Although the authors did not present analytical results using the ATPIII definition of MetS, they found that for a slightly different definition age was the strongest predictor of MetS, and that men and women did not differ significantly in MetS prevalence.

### *1.2.6 Schizophrenia and metabolic syndrome*

MetS has been studied in a number of samples with psychosis. In the largest such study, McEvoy compared proportions with ATPIII MetS at baseline in the CATIE Schizophrenia Trial to a randomly selected age-, sex-, and race/ethnicity-matched sample from the NHANES III, a general population survey [51]. In CATIE, the proportion with ATPIII MetS was 40.9%, significantly higher in women (51.6%) than men (36.0%). Age was significantly and positively associated with MetS. Moreover, both men and women in CATIE were significantly more likely to have MetS than the general population sample, with odds ratios of 2.4 for men and 3.5 for women. Other studies have also shown high proportions with MetS in schizophrenia, as pointed out in a review article by Mitchell [48].

In Canada, Cohn and colleagues conducted a study of 240 participants with schizophrenia

and schizoaffective disorder (described above) in Toronto, and found an ATPIII MetS proportion of 42.6% in men and 48.5% in women, which was noted to be higher than the US adult population rates of 24% in men and 23% in women [43;52]. As noted above, this was a convenience sample with two thirds inpatients and with an average length of illness of close to 20 years.

### 1.3 Schizophrenia and preventive health services

Several studies have examined receipt of health care for physical illnesses among those with schizophrenia, and a number of these (though not all) have demonstrated decreased access to various aspects of care, even including end of life care [3;53-55]. Given this variable access to medical care, one might postulate that receipt of preventive health services might be decreased among those with schizophrenia. Yet, as pointed out by Lord and colleagues in their 2011 systematic review of this issue for patients with mental illness, the quality of preventive health services varies across studies [56]. In particular, there is incomplete information on access to preventive health care for those with schizophrenia in Canada. Since access to care varies across regions, and is related to a number of factors including availability of insurance, the use of preventive services by individuals with schizophrenia may be different in Canada from in other countries [57-59].

#### *1.3.1 Screening and treatment of cardiovascular risk factors in schizophrenia*

Since the recognition of the metabolic consequences of antipsychotic medications, there has been increasing interest in the appropriate screening and treatment of cardiovascular risk factors in persons with schizophrenia and related disorders, and various screening guidelines have been suggested [60-62].

1.3.1.1 Screening of CVD risk factors

Mitchell and colleagues performed a recent systematic review and meta-analysis of screening of metabolic risk that included studies between 2000 and 2011 of persons on antipsychotics, and reported separately on schizophrenia [60]. They found that in the 25 studies of schizophrenia (N=169,289), blood pressure was monitored in 57.9%, glucose in 40.0%, cholesterol in 33.3%, and weight in 38.6%. They noted that tested heterogeneity was high. Disappointingly, implementation of guidelines had only very modest effects in improving screening, and only in screening of BMI.

Since the dates included in the Mitchell study, Osborn and colleagues published a large cohort study that used United Kingdom (UK) data from the THIN Primary Care Database (in which 420 family practices record clinical data) to look at changes in screening over the years 2000 to 2007 [63]. The study examined 18,696 individuals with severe mental illness (SMI: 75.5% schizophrenia, schizoaffective disorder, or other psychosis) across the UK and compared them to patients without an SMI diagnosis for screening of BMI, blood pressure, cholesterol, and glucose. Prior to 2004, those with SMI had significantly lower rates of all types of screening. After 2004 there was an improvement only for individuals under age 60 with SMI, who no longer had significantly lower rates BMI, glucose, and cholesterol screening, but no change in blood pressure monitoring. This change had occurred in the context of newly implemented financial incentives in 2004 for general practitioners to keep a register of people with a severe mental illness diagnosis, and for offering them an annual review.

In Canada, Voruganti and colleagues examined receipt of screening for dysglycemia and other metabolic indices in a cross-sectional chart audit/study of 1123 community dwelling adults

aged 16 or above in five Ontario communities with recorded diagnoses of schizophrenia or schizoaffective disorder identified through a non-random "snowballing" technique with input from local community mental health facilities. Data were obtained in 2005 through chart review and from health care professionals. They found that fasting glucose levels were recorded for 78% while lipids, weight, height, waist circumference and blood pressure were available for 36.7% to 64.2%. They concluded that there were variable screening practices across centres. Of note, screening that occurred elsewhere (e.g. in a family physician's office) might not have been recorded in these mental health facility charts, thus potentially biasing Voruganti's results toward lower apparent screening rates.

In addition, Jennex and colleagues reported a Toronto study comparing monitoring of metabolic risk factors in 99 antipsychotic-treated patients in a mental health clinic (78.1% of which had schizophrenia, the rest bipolar disorder) to that of a control group from an HIV clinic [64]. The mental health clinic charts were significantly less likely to have documentation of screening for hypertension (70%), diabetes (61%), and dyslipidemia (40%) than the HIV group, and only 28% of mental health charts compared to 90% of HIV charts contained adequate information to compute the 10 year CHD risk. They chose the HIV clinic as the source of the control group as another example of a specialty clinic; however, one might wonder whether results might be different for another control specialty. Again (as for Voruganti's study above), it is possible that screening of these psychiatric (or HIV) patients might have been performed elsewhere and not recorded in the clinic chart.

#### 1.3.1.2 Treatment of CVD risk factors

De Hert's and colleagues' recent descriptive review describes disparities in treatment of

CVD risk factors in several settings [3]. For example, Nasrallah and colleagues reported on the rates of treatment of hypertension, elevated cholesterol, and diabetes in the CATIE trial sample at baseline [65]. Their definitions for each of these CVD risk factor conditions included presence of an abnormal test (blood pressure, lipids, or glucose) or current treatment for the condition. They found that 37.6% of those with hypertension, 12.0% with dyslipidemia, and 54.7% with diabetes were receiving pharmacological treatment.

In Canada, Bresee and colleagues used Alberta Physician Claims data to examine endocrinologist and internist visits for those with diabetes between 1995 and 2006 in a population based study [39]. Defining schizophrenia as ICD-9 codes 295.x and using a validated data definition for diabetes, they reported that among people with diabetes there was no difference in endocrinologist encounters for those with versus without schizophrenia (adjusted OR .93, 95%CI: .81-1.08), while internist encounters were more common among those with schizophrenia (adjusted OR 1.67, 95%CI: 1.48-1.88). As a higher proportion of those with than without schizophrenia in the study had coronary artery disease (and possibly other unmeasured illnesses) one might postulate that at least some of the excess internist visits were for disorders other than diabetes. As noted previously, the administrative data definition of schizophrenia was not validated in this study, and although the authors reported validity results from a previous 1986 study, that study reported only a 61.8% concordance for schizophrenia between physician claims and hospital discharge diagnoses [41].

### *1.3.2 Family physician and/or physical examination*

Since preventive health investigations are often performed by family physicians or general practitioners, it is important to know whether individuals with schizophrenia have access

to these health care providers.

In Canada, Bresee and colleagues used Alberta Physician Claims data to examine general practitioner (GP) visits between 1995 and 2006 [39]. This was part of the same study as was mentioned above under treatment for CVD risk factors. Defining schizophrenia as ICD-9 codes 295.x, they reported that people with schizophrenia were more likely to have visited a GP over that period (adjusted OR 7.75, 95%CI: 5.92-9.69), and more likely to have seen a GP at least four times per year (adjusted OR 3.60, 95%CI: 3.49-3.71). As noted above, the validity of the definition of schizophrenia was not evaluated in the study.

The same group reported results regarding having a regular medical doctor based on data from Statistics Canada's nationally representative Canadian Community Health Survey Cycle 3.1 conducted in 2005 [19]. There was no statistically significant difference in terms of having a regular medical doctor for those with self reported schizophrenia compared to without (adjusted weighted OR 1.23; 95% CI .65-2.35). This study was mentioned above, noting the concern regarding the validity of a self reported diagnosis of schizophrenia.

Of note, this finding of equivalent (or better) access to a family physician for individuals with schizophrenia versus without is consistent with what has been observed in other countries, e.g. Australia [66].

### *1.3.3 Other preventive health services*

In Canada, Chochinov and Martens used administrative data to examine women aged 50 to 69 living in Manitoba on December 31, 2003 and found that 44.8% of women diagnosed with schizophrenia and 58.3% without had had a mammogram in the past two years ($p<.001$). Of note, there was significant regional variation in the Manitoba data [67]. The same team examined

cervical screening using similar methodology, and found that a lower proportion of women living in Manitoba on December 31, 2002 with schizophrenia had had a Pap test (58.8% vs. 67.8%) in the past three years ($p<.001$) compared to those without schizophrenia [68]. These studies unfortunately would potentially suffer from the above-mentioned issues related to the validity of administrative data, and did not mention validating their case definitions.

With respect to dental services, it is well known that the oral health of individuals with schizophrenia is compromised [69]. On literature review, no Canadian information was found on receipt of dental services in those with schizophrenia.

In terms of eye examinations, Viertio and colleagues used data from visual acuity testing in the Health 2000 general population study in Finland and reported that measured visual impairment was more frequent among those with SCID-diagnosed psychosis than without [70]. In spite of this a literature review did not detect any Canadian studies of screening eye examinations or treatment of disorders of vision in schizophrenia.

For influenza immunization, current Canadian guidelines suggest that all individuals over age 6 should receive a flu shot annually [71]. A literature review did not produce any Canadian studies on rates of influenza immunization in individuals with schizophrenia.

### 1.4 Rationale for the study

There is evidence that individuals with schizophrenia have elevated CVD-related mortality and a higher prevalence of CVD compared to the general population [8;13]. Most studies have also shown that this group has higher rates of cardiovascular risk factors [38]. However, Canadian studies investigating this to date have either been done using administrative or survey data with their recognized measurement issues related to diagnosing psychotic disorders, or have

used convenience samples and/or less accurate measures [19;20;43].

Studies of preventive health services among individuals with psychosis and mental illness have had mixed results in comparison with the general population [56;63;72]. Of note, many of the relevant studies have been done in the United States or other countries without universal health care. It has long been known that access to health care is impacted by payer (eg. private versus public versus no insurance) [57;73]. Moreover, there is evidence that availability of insurance contributes to reducing disparities in access to care [74;75]. As such, it is of interest to study receipt of preventive services in a universal health care context, such as in Canada. Yet Canadian studies have had conflicting results regarding receipt of preventive services in this population, and have suffered from some of the same measurement issues mentioned above related to administrative and survey data [39;67;68].

It is necessary to know the Canadian prevalence of CVD risk factors and related prevention practices in schizophrenia to inform the development and provision of appropriate health services. It has been shown that preventive services can be improved for this population, but special programs targeting this group may be required to ensure universal access to care. For example, American studies in the Veterans Health Administration have demonstrated an improvement in preventive health services to patients with serious mental illness by providing integrated medical care at the mental health treatment site [76;77]. Another study has demonstrated ecological evidence that GP screening of CVD risk factors in severe mental illnesses increased with the introduction of specific remuneration for annual reviews of these patients [63]. The design of innovative preventive services for the schizophrenia population offers an exciting opportunity for further research. However, it will require adequate and valid Canadian data on the current levels of morbidity and preventive interventions in order to plan such innovations.

## 1.5 Objectives

This research had objectives concerned with the health of individuals with schizophrenia and related disorders that fell broadly into two categories: CVD risk factors and preventive health services. As such, the study was divided into two Components (A and B) with objectives and specific aims described below. Specific aims that were related to both categories, i.e. preventive health services for cardiovascular risk factors, were included with Component A.

### *1.5.1 Component A objectives and specific aims (CVD risk factors)*

The first objective of Component A was to describe the profiles of CVD risk factors, MetS, and 10 year predicted risk of cardiovascular events among adult outpatients with schizophrenia and related disorders. The second objective was to examine the relationships between the measured risk factors and previous screening, detection, and treatment of these risk factors.

The specific aims of Component A were to estimate the proportions in the Calgary outpatient schizophrenia/related disorders population and within sex-specific strata having:

1. Individual risk factors, including hypertension, elevated total cholesterol, elevated LDL cholesterol, elevated triglycerides, low HDL cholesterol, diabetes, impaired fasting glucose, smoking, elevated BMI, and elevated waist circumference. See Appendix B for operational definitions of these quantities.
2. MetS, as defined by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), or ATP III [30]. See Appendix A for

a detailed definition.

3. Ten-year risk of hard CHD event as defined by the NCEP ATP III [30].
4. Ten-year risk of general CVD event [31].
5. Preventive health services related to CVD risk factors, including:
    a. Previous screening and detection of hypertension, elevated cholesterol, and diabetes.
    b. Current pharmacological treatment of hypertension, elevated cholesterol, and diabetes.
    c. Previous counselling regarding smoking cessation.

### *1.5.2 Component B objectives and specific aims (Preventive health services)*

The objective of Component B was to describe the extent to which various preventive health services (not directly concerned with CVD risk factors) occur among adults with schizophrenia and related disorders in outpatient treatment.

The specific aims of Component B were to estimate the proportions in the Calgary outpatient schizophrenia/related disorders population and within sex-specific strata having:

6. A regular family physician.
7. Received the following preventive health care interventions, as appropriate to age and sex:
    a. Family physician visit
    b. Physical examination
    c. Mammogram
    d. Breast examination by a health professional

e. Pap test

f. Dental visit

g. Eye examination

h. Influenza immunization

For those not receiving certain of these services, the aim was:

8. To describe the reasons for lack of receipt of preventive health care interventions.

# Chapter Two: **Methods**

Although a number of variable definitions are provided in this chapter, these and others are included for reference in Appendix B, Operational Definitions.

## 2.1 Study Design

A cross-sectional survey design was used, in which data for both Components A and B were collected in a single integrated interview. This observational study design is ideal for providing estimates of point prevalence, especially in cases such as this where the prevalence of the outcome variable (cardiovascular risk factors) in the study population is high [78].

## 2.2 Population, Sample Selection, and Sample Size

The target population was adults with schizophrenia or related disorders receiving outpatient psychiatric care in Calgary. Randomly-selected men and women attending the Early Psychosis Treatment Service (EPTS) or the Outpatient Schizophrenia Service (OSS) were invited to sign informed consent and take part in the study if they were 1) aged 18 to 74 with 2) a recorded diagnosis of schizophrenia or related disorders (schizophrenia or schizoaffective disorder or, if in EPTS, psychosis NOS, schizophreniform disorder, or another psychotic disorder not felt to be secondary to mood, medical, or substance use disorder). Individuals were excluded if they 1) had insufficient English or 2) lacked the capacity to provide consent. Since family physicians and private psychiatrists in Calgary generally refer patients with psychosis to specialised clinics, this sample was expected to be representative of the target population. Moreover, the EPTS and OSS programs serve both early psychosis and chronic schizophrenia, so

the sample was expected to have a broad distribution of age and length of illness.

A sample size of 171 was determined (by a precision-based calculation) to be adequate to obtain 95% confidence intervals no wider than .15 (or 15%) around the estimated proportions having each risk factor and preventive health service. The target sample size was 200.

### 2.3 Recruitment and Consent

A list of patients with schizophrenia or related disorders was generated for each clinic from a clinical database that included the name, age, and primary psychiatric diagnosis for each patient seen in the clinics. These lists were randomly ordered and used to select potential participants. The psychiatrist of each selected individual was given a package containing an eligibility form and a preliminary consent form. The psychiatrist completed the eligibility form, indicating an initial opinion regarding their patient's satisfying each of the study inclusion and exclusion criteria (including age, diagnosis, language, and capacity), and invited eligible potential participants to sign a preliminary consent to allow contact by study staff. Individuals who provided preliminary consent met with the study investigator who explained the study and reviewed the study consent form, with an opportunity to ask questions. It was also emphasized that treatment in the clinic would not be affected by the individual's decision regarding participation in the study. During this interview potential participants' language and capacity were assessed by the investigator. Potential participants were given time to read the consent form and reflect prior to making a decision; if they decided to take part they were invited to indicate their provision of informed consent by signing the form. If they did so, a chart review was performed to ensure that the individual's age and recorded diagnosis were appropriate for study participation; if so, participants were enrolled in the study and were given a study

appointment and a detailed instruction sheet. They were telephoned to review fasting instructions the day before the appointment. At least three attempts were made to contact those who did not attend their appointment.

## 2.4 Measurement and data collection

Data were collected during a single study appointment. Participants were instructed to attend the appointment after fasting for 10 to 14 hours. During the study appointment, a physical examination and interview were conducted by the investigator (a psychiatrist) or a trained study nurse with a clinical mental health background and research experience. Participants attended an on-site laboratory for collection of blood samples; a small number warranted a second laboratory visit based on initial test results.

### *2.4.1 Examination and laboratory investigations.*

Blood pressure was measured using a e BpTRU™ automated electronic blood pressure device (BpTRU™ Medical Devices Ltd., Coquitlam, British Columbia) employing standardised Canadian protocols [79-81]. The BpTRU™ device takes six oscillometric measurements at one-minute intervals. The first measurement is used to check the function of the machine, and the mean of the last five measurements is calculated by the device. For this study, the interviewer left the room for these last five measurements to minimize "white coat effect" [82]. BpTRU™ measurements were taken twice for each participant (at the beginning and end of the study appointment) to minimize random error; guidelines for hypertension surveillance also suggest multiple readings per visit [80]. Anthropometric indices were measured using standardised protocols while still fasting. Waist circumference was measured to the nearest centimetre at the

level of the minimal waist, at the end of a normal expiration. Height was measured to the nearest centimetre using a square against a fixed vertical measuring scale. Weight was determined to the nearest 100 grams using the same balance beam scale for all participants, and zeroed before each use. .

Plasma glucose, total cholesterol, high-density cholesterol (HDL-C), and triglycerides were measured by Calgary Laboratory Services (CLS) employing a standard Hitachi assay; low-density cholesterol levels (LDL-C) was calculated by CLS from the total cholesterol, HDL-C, and triglycerides.

### *2.4.2 Interview*

Interview data including sociodemographic characteristics and past history of hypertension, elevated cholesterol, smoking, and diabetes and their treatment were collected, using standardized Statistics Canada questions where possible [83]. Participants were also screened for current alcohol use and depressive syndromes employing the Alcohol Use Disorders Identification Test (AUDIT) and Calgary Depression Scale for Schizophrenia (CDSS) [84-86]. The AUDIT has been validated in several studies for use in schizophrenia and first episode psychosis [87-89]. Its validated cut point for probable alcohol use disorder has varied from 7 to 10 in these studies; we chose to use the usual cut point in the general population, which is 8 or more. Lako and colleagues conducted a systematic review of instruments for assessment of depression in schizophrenia, and concluded that the CDSS correlated with other depression scales but more accurately differentiated symptoms of depression from those of schizophrenia [90]. The CDSS has a validated cut point of over 6 for probable depression, with a sensitivity of 85% and a specificity

of 82% [91]. Although the CDSS is copyrighted, it is available online (at www.ucalgary.ca/cdss) where it is noted that "The Scale may be used free by any student or non profit organization" [92]. The investigator (CB) had been previously trained in the use of the CDSS by Dr. Donald Addington, one of the developers of the scale. For training of study staff, interviewers reviewed CDSS training tapes with CB until they assigned scores for each of the CDSS items within ± 1 of CB's assigned score at least 80 per cent of the time. To obtain a sense of the current level of distress, both the "K6", a short psychological distress scale described by Kessler with a cut point of 13 or more for probable serious mental illness, and a single question concerning current stress employed by Statistics Canada in the Canadian Community Health Survey (CCHS) were used [83;93-95]. Data on receipt of preventive health services and time elapsed since these services were also collected using standard questions employed by Statistics Canada [83].

### *2.4.3 Chart review*

Data on each participant's diagnosis, date of onset of illness, current medications, and dates of starting antipsychotic and atypical antipsychotic medication were extracted from the chart by the investigator (a psychiatrist) using a piloted chart review data collection form.

The quality of the chart review data extraction was verified by a second psychiatrist who independently performed duplicate chart review in five per cent of cases (10 randomly selected participants). For diagnosis, the two reviewers agreed for all 10 participants, extracting a diagnosis of schizophrenia in nine cases and schizoaffective disorder in one case. Date of onset of psychotic symptoms agreed within 12 months in nine of 10 cases; for the case where there was disagreement, both reviewers agreed that psychosis had been present for over 10 years. Data for the starting date of antipsychotic medication agreed within 1 year in nine of 10 cases, while

for atypical antipsychotic medication starting date they agreed in 10 of 10 cases. Both reviewers extracted exactly the same data on current antipsychotic medications for all 10 charts, although there was disagreement on sedatives in one chart and on antidepressants in two charts.

## 2.5 Data management

Duplicate computer data entry was done using Epi-Info, which allowed the construction of study-specific data-entry menus in which prompts were provided for each item of data, with range checks of each variable at the time of data entry [96]. Data cleaning was performed in Epi-Info with the use of tabulations and plots prior to transferring into the statistical software (Stata) for analysis [97]. Further checking of the data integrity using graphical and tabular techniques was done in Stata before beginning analysis.

## 2.6 Data analysis

Data were analyzed with Stata 12.1 statistical software [97]. A significance level $\alpha=0.05$ was employed for statistical tests.

### *2.6.1 Sociodemographic and clinical characteristics of the sample*

Sociodemographic and clinical characteristics were described with counts and percentages for categorical variables and appropriate measures of central tendency and variability for continuous variables.

### *2.6.2 Component A: Cardiovascular risk factors*

The outcome variables were computed using the following definitions which are also

recorded in Appendix B for ease of reference. Hypertension was defined as a diastolic blood pressure of at least 90 mmHg or a systolic blood pressure of at least 140 mmHg according to Canadian guidelines, or current self reported drug treatment for hypertension [26]. Elevated triglycerides (TG), total (TC) and LDL cholesterol, and low HDL cholesterol were defined in mmol/L as TG≥1.7 mmol/L, TC≥5.2 mmol/L, LDL≥3.4 mmol/L, and HDL≤1.034 in men and ≤1.293 in women [30]. Current smoking was defined as either daily or occasional current smoking, to concur with the smoking definition used in the 10 year risk calculation (details below), which is "any smoking in the past month" [30]. Occasional smokers in this study were required to have smoked at least one cigarette in the past month. Of note, there is evidence that at least for men, occasional smoking confers elevated cardiovascular and total mortality risk [98]. Diabetes was defined as a fasting plasma glucose of at least 7.0 mmol/L on two days in accordance with current Canadian guidelines, or current self reported medication treatment for diabetes [28;32]. Impaired fasting glucose was defined as a fasting glucose of 6.1 to 6.9, which also follows Canadian guidelines [28]. High waist circumference was defined as over 88 cm in women and over 102 cm in men as in the definition of MetS (Appendix A) [99]. Body mass index (BMI) was computed as weight (kg) divided by height squared ($m^2$); overweight was taken as a BMI of at least 25 and below 30, and obesity was defined as a BMI of 30 or higher [30]. Metabolic syndrome was calculated as defined by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), or ATP III (Appendix A) [30;99]. The NCEP definition was employed for consistency with other reports in the literature, for example the CATIE study [51]. Moreover, two modifications from the revised NCEP criteria were also employed; namely drug treatment for hypertension and diabetes were taken to indicate the presence of those disorders.

This again is consistent with other studies [51].

The 10-year risk of hard coronary heart disease (CHD) event, defined as myocardial infarction or CHD death, was computed employing programmed risk tables based on the NCEP ATP III, and proportions falling into low risk (<10%), moderate risk (10-20 %) and high risk (>20%) groups were determined [30]. This calculation was not done for individuals who were under age 20, had diabetes, or had reported a history of CHD (self reported heart attack or angina in the current study) because the algorithm is not valid for these groups. Diabetes can be considered a CHD equivalent in that it confers a risk of hard CHD that is as high as the high risk group, as does known CHD, so a further calculation of 10 year risk groups was performed that included these individuals by placing them in the high risk group [30].

The 10 year risk of general cardiovascular event was also computed, using a Framingham based algorithm [31]. The Canadian Cardiological Society recommends estimating this 10 year risk of developing "total" cardiovascular events (including coronary heart disease, stroke, peripheral artery disease, or heart failure) as opposed to hard CHD [25].

Univariate descriptive analysis of the above outcome variables was performed. To address the first five Specific Aims (Section 1.5.1 above), the proportion of participants having 1) each individual CVD risk factor, 2) metabolic syndrome, 3) 10 year risk of hard CHD event that was less than 10%, 10% to 19%, and 20% or more, and 4) 10 year risk of CVD event that was less than 10%, 10% to 19%, and 20% or more, 5) current treatment for hypertension, diabetes, or dyslipidemia, and 6) previous CVD risk factor screening or intervention(s) was calculated, and exact 95% confidence intervals computed. Sex-specific rates were also computed. Regression methods were used to examine the relationship between BMI, age, and sex and between MetS, age, and sex.

### *2.6.3 Component B: Preventive health care activities*

To address Specific Aims 6) and 7) detailed in Section 1.5.2 above, the proportion of participants having 1) a regular family physician, 2) receipt of each of the preventive health interventions/activities was calculated, and exact 95% confidence intervals computed. Sex-specific proportions were also examined. The two most common reasons participants reported for not obtaining a blood pressure check, physical examination, dental visit, pap test, mammogram, breast examination by a health professional, or eye examination were determined for Specific Aim 8.

## 2.7 Funding

Funding for this project was received from the Carlos Ogilvie Memorial Fund, and from the University of Calgary and the Alberta Health Services. Dr. Beck was supported by a Clinical Fellowship from Alberta Heritage Foundation for Medical Research and a Fellowship from the Canadian Institutes for Health Research at times during the conduct of this research.

## 2.8 Ethical Considerations

Ethics approval was obtained from the Conjoint Health Research Ethics Board at the University of Calgary prior to initiation of the study. Reasonable reimbursement was offered to participants for their costs (e.g. parking and a snack after fasting) when they attended the interview; the amount was chosen not to be enough to act as coercion towards participation. The random selection of potential participants from clinic lists was done by clinic staff using a program provided by the investigator, to protect the privacy of non-selected patients. Preliminary consent was obtained by clinic staff from each selected individual before he/she was

contacted by the research team; full informed consent was then required before enrolment of each participant into the study. Of key importance, participants were informed of the results of their investigations and assisted to obtain timely medical services if indicated. Data regarding each participant were assigned a study-specific identification number (study ID). Computer data were identified only by study ID, and were kept on a password protected computer with a screen time-out that had regular maintenance including anti-virus and security software updates. All paper data were stored in a locked cabinet.

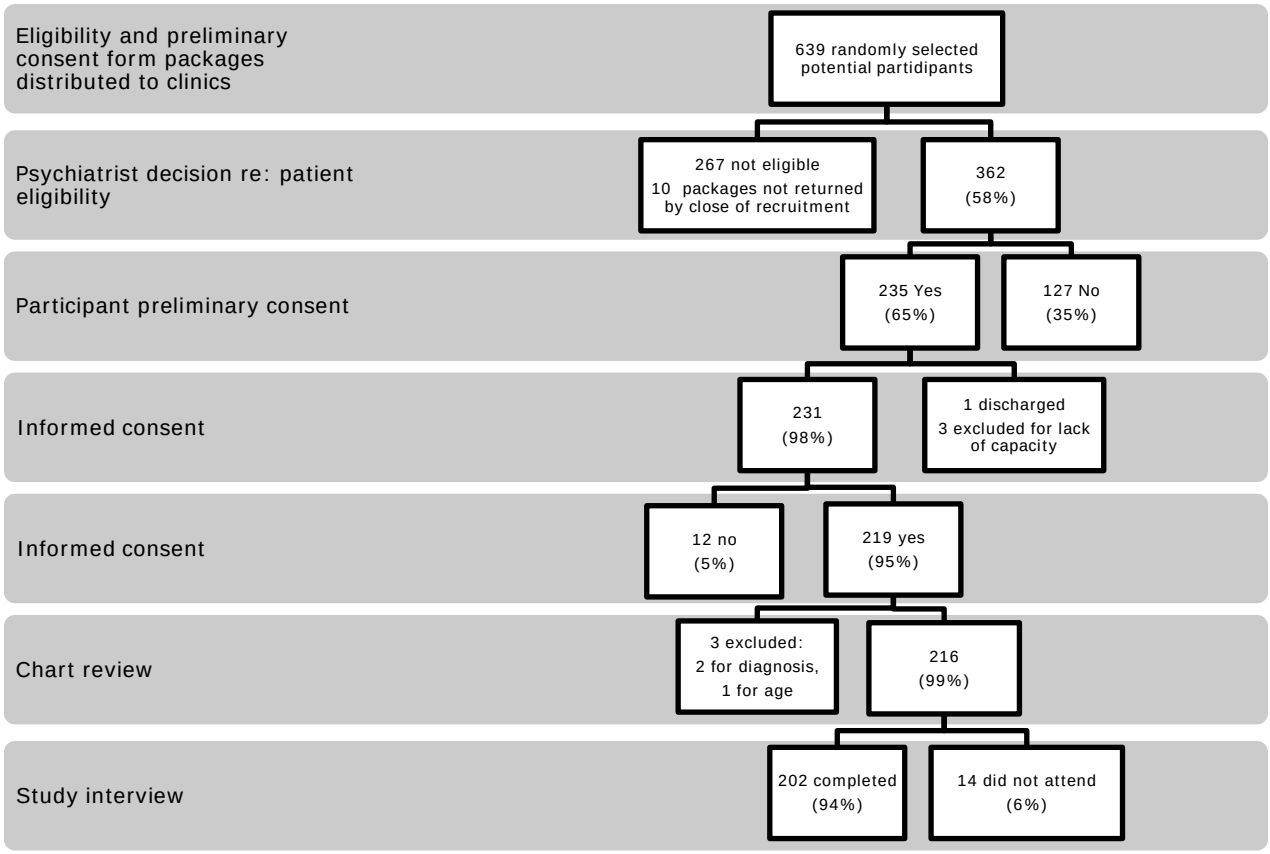
# Chapter Three: **Results**

## 3.1 Description of the sample

### *3.1.1 Recruitment and participation*

A total of 202 participants took part in the study between June 30, 2004 and September 7, 2005. Figure 3-1 depicts the recruitment process. Eligibility and preliminary consent packages were distributed to clinic staff for 639 potential participants who had been randomly selected from complete clinic lists for EPTS and OSS. Study recruitment closed prior to the return of 10 of the last 16 packages given to OSS clinic staff. Among the remaining 629 individuals, their psychiatrists felt that 362 were eligible for the study based on inclusion and exclusion criteria. The most common reasons for ineligibility were having been discharged from the clinic (N=94) and having the wrong diagnosis (N=70). Of the 362 eligible individuals, 235 (65%) agreed to meet and discuss the study, and 219 of these (95%) provided informed consent. A total of seven (3%) were excluded due to discharge from their clinic, lack of capacity, or ineligible diagnosis or age discovered either during the informed consent interview or the chart review. Of the 216 that remained, 14 (6%) cancelled or did not attend their interview, leaving 202 participants with interview and laboratory data. Although there are many ways to define response rates, this can be described as a participation rate of 202/(231-3)=90.2%, with a much lower conservatively defined response rate of 202/(362-7)=56.9% [100].

**Figure 3-1 Flowchart of sample recruitment and participation**




### *3.1.2 Table conventions*

The following conventions have been used for the tables in this chapter:

1. The full sample size (N) is displayed at the top of each results column
2. When the results presented have a sample size that deviates from that at the top of the column, for example in cases where there are missing values or when a subsample is being described, the sample sizes for each column are included in the left (descriptive) column, separated by slashes, e.g. N=134/66/200.
3. When results for a sample are presented in one row of the table, and further results for a subsample are given in the row below, the rows are separated by a dotted line ------- rather than the solid lines used elsewhere.
4. Most results are for categorical data, and are presented as counts and proportions in the format N (%). When other types of results are presented (e.g. means and standard deviations), this is indicated in the left column, and also the results are presented in italics and are separated by slashes / instead of parentheses.

### *3.1.3 Sociodemographic and clinical characteristics*

Table 3-1 presents the sociodemographic characteristics of the sample. As can be seen, there were almost twice as many men as women in the sample. Moreover, the mean age was younger for men (37.1 years) than for women (44.5 years). Figure 3-2 illustrates the age sex distribution graphically.

Further, Table 3-1 shows that women were more highly educated on average and more likely to be married. The most common major source of income was disability insurance (60.4%); while employment was the major income source for 27.2%. The mean number of hours worked in the previous week was 8, but the distribution was skewed and less than a quarter of the sample worked at all in the previous week.

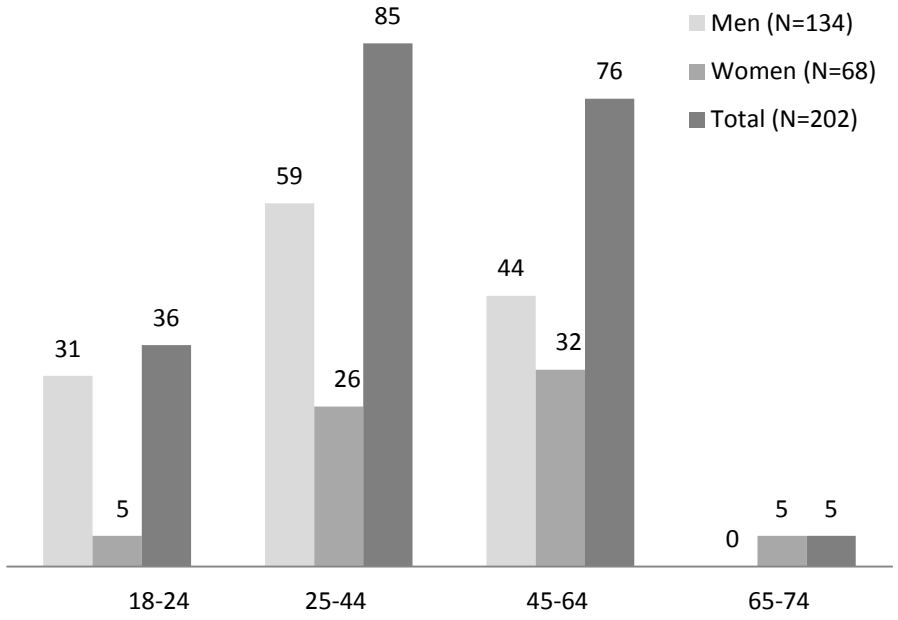
As shown in Table 3-2, the most common diagnosis was schizophrenia (79.7%), with a mean age at onset of psychois of 26.1 years. In addition, 9.9% of the sample had scores above the cutoff for probable depression on the Calgary Depression Scale for Schizophrenia, and 16.9% had scores of 8 or higher on the AUDIT, suggesting an alcohol use disorder [91] [87]. Only 13.4 % had a K6 Distress Scale score over the validated cutpoint for serious mental illness [94].

Almost all participants (98%) were being prescribed at least one antipsychotic medication (Table 3-3). The mean number of years since starting antipsychotic medications was 11.8, while for atypical antipsychotics it was 5.7 years. The most common class of concurrent psychotropic medications being prescribed at the time of the interview was antidepressants (32% of participants).

**Table 3-1: Description of the sample – Sociodemographic characteristics**

| | MEN (N=134) | WOMEN (N=68) | TOTAL (N=202) |
|---|---|---|---|
| Sex, N(%) | | | |
| Women | | | 68 (33.7) |
| Men | | | 134 (66.3) |
| Age | | | |
| *Mean /SD* | *37.1/13.0* | *44.5/13.0* | *39.6/13.4* |
| *Median/ Min-Max* | *35/ 18-63* | *46/ 18-72* | *40/ 18-72* |
| Race/ethnicity, N(%) | | | |
| White | 102 (76.1) | 49 (72.1) | 151 (74.8) |
| Other | 19 (14.2) | 14 (20.6) | 33 (16.3) |
| Two or more | 13 (9.7) | 5 (7.4) | 18 (8.9) |
| Marital Status, N(%) | | | |
| Married/ Common law | 12 (9.0) | 21 (30.9) | 33 (16.3) |
| Never married | 107 (79.9) | 30 (44.1) | 137 (67.8) |
| Widowed/Separated/Divorced | 15 (11.2) | 17 (25.0) | 32 (15.8) |
| Education (Highest achieved), N(%) | | | |
| < High school | 36 (26.9) | 13 (19.1) | 49 (24.2) |
| High school graduate | 14 (10.5) | 4 (5.9) | 18 (18.9) |
| Incomplete certificate/degree | 39 (29.1) | 16 (23.5) | 55 (27.2) |
| Postsecondary certificate/degree | 45 (33.6) | 35 (51.5) | 80 (39.6) |
| Work status (Age ≤ 65; N=134/63/197) | | | |
| Hours worked last week, *Mean/Median* | *8.0/0* | *8.0/0* | *8.0/0* |
| Worked > 8 hr last week, N(%) | 32 (23.9) | 15 (23.8) | 47 (23.9) |
| Didn't work last week, , N(%) | 90 (67.2) | 43 (68.3) | 133 (67.5) |
| Major source of income, N(%) | | | |
| Employment or employment insurance | 38 (28.4) | 17 (25.0) | 55 (27.2) |
| Disability insurance | 85 (63.4) | 37 (54.4) | 122 (60.4) |
| Pension or old age security | 0 (0) | 5 (7.4) | 5 (2.5) |
| Other | 10 (7.5) | 8 (11.8) | 18 (8.9) |
| None | 1 (.8) | 1 (1.5) | 2 (1.0) |

**Figure 3-2 Age sex distribution of the sample**



## Table 3-2: Description of Sample – Clinical characteristics

| | N=202 |
|---|---|
| **Diagnosis*, N(%)** | |
| **Schizophrenia** | **161 (79.7)** |
| **Schizoaffective disorder** | **17 (8.4)** |
| **Psychosis NOS** | **16 (7.9)** |
| **Schizophreniform disorder** | **6 (3.0)** |
| **Other psychosis** | **2 (1.0)** |
| **Clinic attended*, N(%)** | |
| **Early psychosis clinic** | **69 (34.2)** |
| **Schizophrenia clinic** | **133 (65.8)** |
| **Age of onset of psychotic symptoms†* (N=197‡)** | |
| ***Mean/SD*** | ***26.1/9.2*** |
| ***Median*** | ***23.3*** |
| **Duration of illness (psychosis) in years†* (N=197‡)** | |
| ***Mean/SD*** | ***13.8/11.8*** |
| ***Median*** | ***10.4*** |
| **Depression (CDSS>6), N(%)** | **20 (9.9)** |
| **Alcohol use disorder (AUDIT≥8), N(%)** | **34 (16.8)** |
| **Distress scale (K6)** | |
| ***Mean/Median*** | ***7.0/7*** |
| **Elevated distress scale score (K6≥13)** | **27 (13.4)** |
| **Feels stress most days (Extreme, quite a bit, or a bit), N(%)** | **143 (70.8)** |
| **Self rated health (excellent or very good), N(%)** | **68 (33.7)** |

* Based on chart review
† Date of first recorded psychotic symptoms
‡ Chart data were not found on date of first psychotic symptoms for 5 participants
CDSS: Calgary Depression Scale cut point for probable depression is >6 [91]
AUDIT:Alcohol Use Disorders Identification Test cut point for probable alcohol use disorder is ≥8 [88]
K6: Distress scale cut point for probable serious mental illness is K6≥13 [93;94]

**Table 3-3: Description of Sample – Medication treatment**

| | N=202 |
|---|---|
| **Total number of current medications*** | |
| ***Mean /SD*** | ***2.2/1.5*** |
| ***Range*** | ***0-10*** |
| **Years since first taking antipsychotic medication*; *Mean/SD*** | |
| **Any antipsychotic (N=202)** | ***11.8/11.0*** |
| **Any atypical antipsychotic (N=195)** | ***5.7/4.0*** |
| **Current antipsychotic medication*; N(%)** | |
| **≥ 1 antipsychotic** | **197 (98)** |
| **≥ 1 atypical antipsychotic (including clozapine)** | **172 (76)** |
| **Clozapine** | **43 (21)** |
| **Other current psychotropic or side effect medication*, N(%)** | |
| **Antidepressant** | **65 (32)** |
| **Anticholinergic/antidyskinetic** | **24 (12)** |
| **Mood stabilizer** | **26 (13)** |
| **Sedative hypnotic** | **31 (15)** |

* Based on chart review

## 3.2 Component A: Cardiovascular Risk Factors

### *3.2.1 Modifiable cardiovascular risk factors: Blood pressure, lipids, smoking*

Results for blood pressure, lipids, and smoking are shown in Table 3-4, stratified by sex. Data were complete for blood pressure and self reported smoking. However, LDL cholesterol could not be determined for eight participants. The LDL is calculated by Calgary Laboratory Services, and for a valid calculation the triglyceride level must be within a certain range; for these eight participants the triglyceride level was above the range.

Results regarding previous knowledge/detection, treatment, and control of these and other CVD risk factors are presented in Table 3-11.

As may be seen in Table 3-4, 15.4% (95% CI 10.7-21.1) of the sample either had a measured blood pressure over 140/90 mmHg in the study assessment, or were currently taking

**Table 3-4: Measures of blood pressure, lipids, and smoking**

| | MEN (N=134) | WOMEN (N=68) | TOTAL (N=202) |
|---|---|---|---|
| **BLOOD PRESSURE (mgHg)** | | | |
| **Systolic, *Mean/SD*** | ***116/11.7*** | ***118/16.4*** | ***117/13.4*** |
| **Diastolic, *Mean/SD*** | ***76/8.9*** | ***75/7.9*** | ***76/8.9*** |
| **Percent BP≥ 140/90, N(%)** | **10 (7.5)** | **9 (13.2)** | **19 (9.4)** |
| **Newly detected** | **7 (70.0)** | **5 (55.6)** | **12 (63.2)** |
| **Percent BP≥ 160/90, N(%)** | **9 (6.7)** | **5 (7.4)** | **14 (6.9)** |
| **Newly detected** | **6 (66.7)** | **3 (60.0)** | **9 (64.3)** |
| **Hypertension (BP ≥ 140/90 or drug treatment for elevated BP), N(%)** | **17 (12.7)** | **14 (20.6)** | **31 (15.4)** |
| **LIPIDS (mmol/L)** | | | |
| **Total cholesterol (TC)** | | | |
| ***Mean/SD*** | ***4.9/1.0*** | ***5.1/1.2*** | ***4.9/1.1*** |
| **High (≥5.2), N(%)** | **44 (32.8)** | **28 (41.2)** | **72 (35.6)** |
| **LDL cholesterol (N*=126/68/194)** | | | |
| ***Mean/SD*** | ***2.8/0.9*** | ***2.9/1.0*** | ***2.8/1.0*** |
| **High (≥3.4), N(%)** | **28 (22.2)** | **19 (27.9)** | **47 (24.2)** |
| **HDL cholesterol** | | | |
| ***Mean/SD*** | ***1.2/0.4*** | ***1.4/0.4*** | ***1.3/0.4*** |
| **Low (< 1.034 men; <1.293 women), N(%)** | **47 (35.1)** | **34 (50.0)** | **81 (40.1)** |
| **Triglycerides (TG)** | | | |
| ***Mean/SD*** | ***2.0/1.4*** | ***1.8/0.8*** | ***1.9/1.2*** |
| **High (≥1.7), N(%)** | **62 (46.3)** | **34 (50.0)** | **96 (47.5)** |
| **High TC or LDL (N*=67/132/199), N(%)** | **45 (34.4)** | **28 (41.2)** | **73 (36.7)** |
| **Newly detected** | **31 (68.9)** | **17 (60.7)** | **48 (65.8)** |
| **Hypercholesterolemia †, (N*=67/132/199), N(%)** | **51 (38.9)** | **31 (45.6)** | **82 (41.2)** |
| **Dyslipidemia ‡ , N(%)** | **90 (67.2)** | **55 (80.9)** | **145 (71.8)** |
| **SMOKING, N(%)** | | | |
| **Current daily or occasional smoker** | **75 (56.0)** | **19 (27.9)** | **94 (46.5)** |
| **Past smoker** | **41 (30.6)** | **22 (32.4)** | **63 (31.2)** |

* LDL could not be calculated in 8 cases due to elevated triglycerides; in 5 of these cases the participant also had elevated TC
† Elevated TC or LDL, or drug treatment for cholesterol
‡ Elevated TC or LDL or TG, or low HDL, or drug treatment for cholesterol

antihypertensive medication. Almost 7% of individuals had measured blood pressure over 160/90 mmHg, and of these almost two thirds were previously unaware that they had

hypertension. Moreover, Table 3-11 shows that even among those that had been previously diagnosed with hypertension, only 65.4% were treated with an antihypertensive, and 26.9% had inadequately controlled hypertension.

Hypercholesterolemia, defined as ATP III high total cholesterol (TC≥ 5.2 mmol/L) or high LDL cholesterol (LDL≥ 3.4 mmol/L), or currently taking a lipid lowering agent, was present in 41.2% (95% CI 34.3-48.4) (see Table 3-4). Almost three quarters of the sample (71.8%; 95% CI 65.0-77.9) had abnormal lipids, i.e. some combination of measured high triglycerides, high LDL or total cholesterol, low HDL cholesterol, or current lipid lowering agent. Only 34.2 % of those with elevated measured LDL or total cholesterol reported previously being told they had high cholesterol. Moreover, 55.6% of those with previously detected elevated cholesterol were inadequately controlled (high measured LDL or TC) in spite of detection, and only 22.2% were receiving cholesterol lowering agents (Table 3-11).

Almost half the sample were current smokers (46.5%; 95% CI 39.5-53.7), with men being significantly more likely to smoke ($p<.001$). Previous smokers made up almost a third of the sample (Table 3-4). As shown in Table 3-11, only about half reported that they had been encouraged to quit smoking by a health professional in the past year. In spite of that, over half had tried to quit over the same period.

### *3.2.2 Glucose Metabolism*

Glucose results are presented in Table 3-5, while information on diabetes prevention is shown in Table 3-11. Fasting glucose levels were available for the entire sample. Among the 15 (7.4%; 95% CI 4.2-12.0) participants with diabetes (current drug treatment, or ascertained by laboratory results in the study), five new cases were detected by the study protocol, suggesting

that one third of diabetes had not been previously diagnosed or treated (Table 3-5). Impaired glucose metabolism as defined by ATP III was present in 11.9% (95% CI 7.8-17.2).

**Table 3-5: Measures of glucose metabolism stratified by sex**

| | MEN (N=134) | WOMEN (N=68) | TOTAL (N=202) |
|---|---|---|---|
| **Fasting glucose (FPG), *Mean/SD*** | ***5.3/1.2*** | ***5.5/2.0*** | ***5.4/1.5*** |
| **Diabetes (DM)*, N(%)** | **9 (6.7)** | **6 (8.8)** | **15 (7.4)** |
| **Newly detected** | **4 (40.0)** | **1 (16.7)** | **5 (33.3)** |
| **Impaired fasting glucose†, N(%)** | **7 (5.2)** | **2 (2.9)** | **9 (4.5)** |
| **ATP III impaired glucose metabolism‡**, N(%) | **16 (11.9)** | **8 (11.8)** | **24 (11.9)** |

* Fasting glucose ≥7.0 mmol/L on two tests or drug treatment for elevated glucose
† Fasting glucose between 6.1 and 6.9 mmol/L with no history of diabetes
‡ Fasting glucose ≥6.1 mmol/L or drug treatment for elevated glucose

### *3.2.3 Anthropometric measures*

Anthropometric measures are presented in Table 3-6. Three participants had incomplete data: One man could not have height or weight measured because he could not stand; one woman refused all anthropometric measures due to dizziness; and one woman had missing values for waist measurement for unknown reasons.

Just over half the sample had elevated waist circumference (50.5%; 95% CI 43.4-57.6), and the mean BMI was 29.9 (95% CI 28.9-30.9). Over 75% of women had elevated waist circumference compared to 38.1% of men, and the BMI was significantly higher in women (t= -2.4, df=198, p=.016). Multiple regression was used to determine whether this difference in BMI could be explained by age. Because of the right skew of BMI, the BMI variable was transformed to 1/BMI to achieve an adequately normal and symmetric distribution for regression; it was then rescaled to 1000/BMI for ease of reference. Distributional graphs for BMI and 1000/BMI are shown in Figures 3-3 and 3-4 respectively.

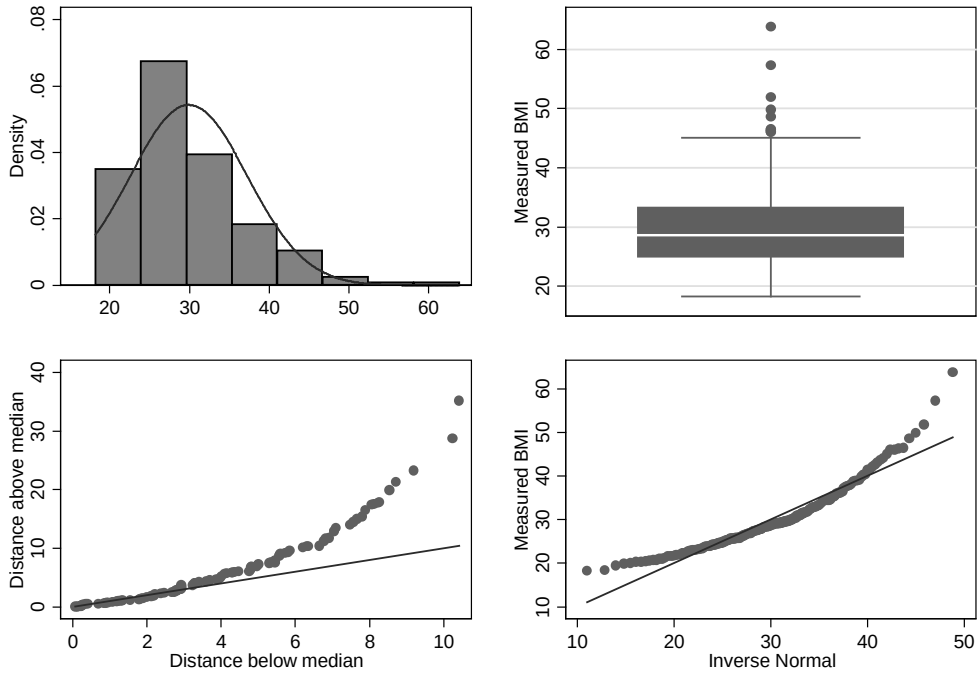
**Table 3-6: Anthropometric measures stratified by sex**

| | MEN (N=134) | WOMEN (=68) | TOTAL (N=202) |
|---|---|---|---|
| **Waist circumference (cm) (N=134, 66*, 200)** | | | |
| ***Mean /SD*** | ***100.3 /16.7*** | ***100.5 /17.8*** | ***100.3 /17.0*** |
| **High†, N(%)** | **51 (38.1)** | **50 (75.8)** | **101 (50.5)** |
| **Body Mass Index (BMI) (N=133, 67, 200) ‡** | | | |
| ***Mean /SD*** | ***29.1 /7.2***** | ***31.7 /7.4***** | ***29.9 /7.3*** |
| **Underweight (<18.5), N(%)** | **2 (1.5)** | **0 (0)** | **2 (1.0)** |
| **Healthy weight (18.5-24.9), N(%)** | **38 (28.6)** | **12 (17.9)** | **50 (25.0)** |
| **Overweight (25-29.0), N(%)** | **51 (38.4)** | **20 (29.9)** | **71 (35.5)** |
| **Obese (≥30), N(%)** | **42 (31.6)** | **35 (52.2)** | **77 (38.5)** |
| **BMI overweight or obese, N(%)** | **93 (69.9)** | **55 (82.1)** | **148 (74.0)** |

* Two women did not have their waist circumference measured, see section 3.3.3
† High waist circumference is defined as >88cm for women and >102cm for men according to NCEP ATP III criteria for abdominal obesity
‡ One woman and one man did not have height and weight measured, see section 3.3.3
** t=-2.4, df=198; p=.016

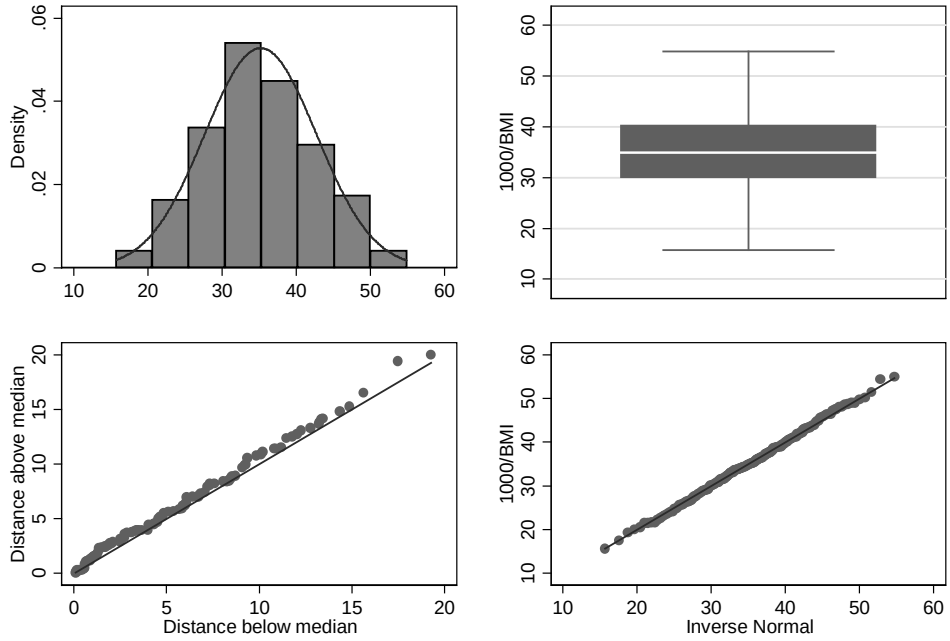
Table 3-7 below shows the multiple regression models for the transformed variable 1000/BMI that were used to assess for potential interaction and confounding of age and sex, together with the regression results. There was no interaction between age and sex (p=.666) in Model 3, so the interaction term was removed. The sex term in Model 2 was significant (p=.021). The age term in this model was not significant, but age was retained in the final model due to a certain amount of confounding of sex, since $\beta_1$ = -2.69 with age in the model, and $\beta_1$ = -3.01 without. All assumptions of linear regression were satisfied as assessed using residual plots. Transforming Model 2 back and plotting the nonlinear predicted BMI against age demonstrates a BMI for women at each age in the range that is approximately two units higher than for men (Figure 3-5).

**Figure 3-3: Distributional graphs of body mass index (BMI)**




Clockwise from top left: Histogram, Box plot, Quantile normal plot, Symmetry plot

**Figure 3-4: Distributional graphs of the scaled inverse of body mass index (1000/BMI)**



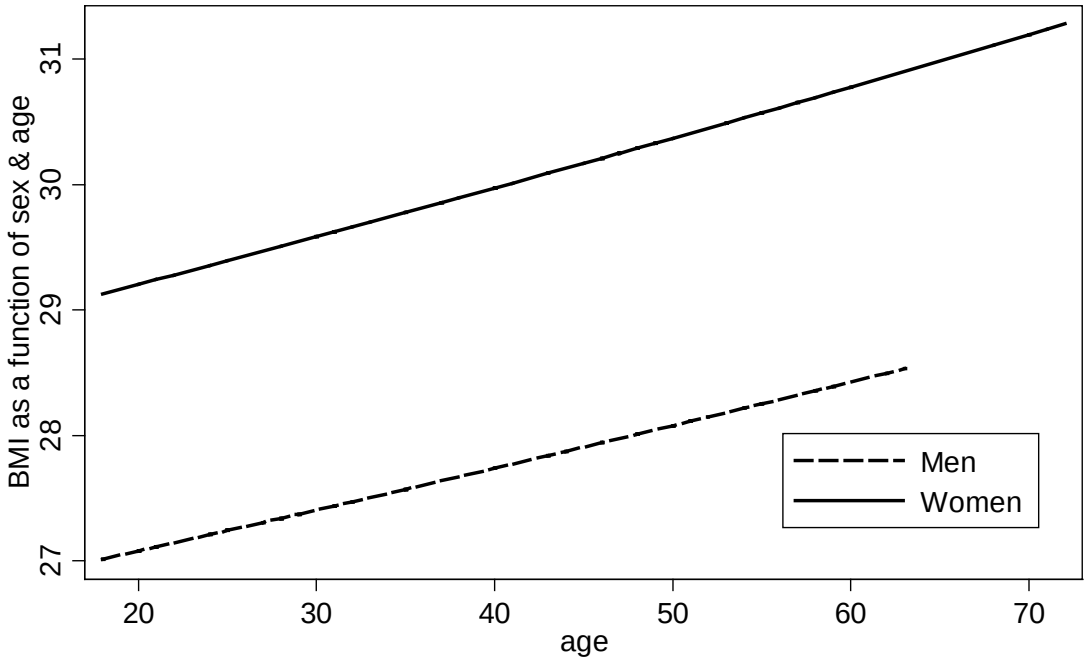

Clockwise from top left: Histogram, Box plot, Quantile normal plot, Symmetry plot

**Table 3-7: Regression models for 1000/BMI as a function of sex† and age**

| Regression models | | Estimate of β ( p ) | | | |
|---|---|---|---|---|---|
| **Model Number** | **Model for 1000/BMI** | **βo** | **$\beta_1$** | **$\beta_2$** | **$\beta_3$** |
| **3** | **$\beta o + \beta_1 sex + \beta_2 age + \beta_3 age*sex$** | 37.34 (p<.001) | -1.18 (p=.770) | -.0313 (p=.531) | -.0375 (p=.666) |
| **2** | **$\beta o + \beta_1 sex + \beta_2 age$** | 37.80 (p<.001) | -2.69 (p=.021) | -.0438 (p=.284) | - |
| **1** | **$\beta o + \beta_1 sex$** | 36.18 (p<.001) | -3.01 (p=.008) | - | - |

† sex=1 for women; sex=0 for men;

**Figure 3-5 Predicted BMI as a function of sex and age (Model 2)**



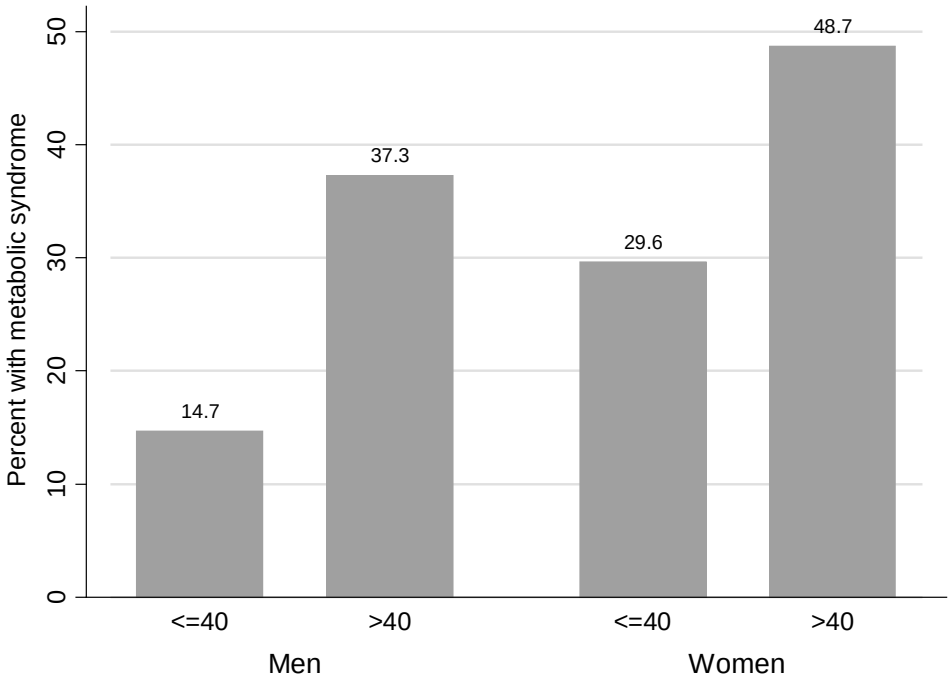
Moreover, logistic regression examining obesity (BMI in the obese range, Table 3-6) as a function of sex revealed that the crude OR for women versus men was 2.37 (95%CI: 1.30-4.33, p=.005), whereas the OR adjusted for age was 2.27 (95%CI: 1.22-4.24, p=.01). Again there had been no interaction between age and sex (p=.499). This can be interpreted as meaning that the log odds of obesity increased at the (assumed) same rate with age in both men and women, allowing calculation of a single age-adjusted OR for obesity (for women compared to men).

### *3.2.4 Metabolic Syndrome*

Metabolic syndrome was calculated as defined by the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), or ATP III (Appendix A); results are shown in Table 3-8.

As may be seen in Table 3-8, women were more likely to have MetS (p=.018), as were those over the median age of 40 (p<.001; data not shown). Figure 3-6 presents the proportions with MetS stratified by age for men and women. Logistic regression was used to examine the multivariable relationship, with age as a continuous variable. Results are presented in Table 3-9. There was no interaction between age and sex in Model 4 (p=.453), and although age and sex were each significantly associated with MetS in the crude analysis (Models 1 and 2), the model including both age and sex (Model 3) demonstrated that only age was significantly associated with MetS (p=.007). In spite of this, sex was retained in the final model because sex confounded the association between MetS and age. Figure 3-7 shows the estimated prevalence of MetS in men and women as a function of age using this final model (Model 3).

**Figure 3-6 Metabolic Syndrome stratified by age and sex**



## Table 3-8: Metabolic syndrome (NCEP ATP III definition) [30]

| | MEN (N=134) | WOMEN (N=66*) | TOTAL (N=200) |
|---|---|---|---|
| **METABOLIC SYNDROME (MetS), N(%)** | | | |
| **MetS (ATP III definition; ≥ 3 criteria)** | **33 (24.6)†** | **27 (40.9)†** | **60 (30.0)** |
| **CRITERIA OF MetS , N(%)** | | | |
| **Abdominal obesity‡** | **51 (38.1)** | **50 (75.8)** | **101 (50.5)** |
| **Elevated triglycerides (TG) **** | **62 (46.3)** | **34 (50.0)** | **96 (47.5)** |
| **Reduced HDL cholesterol††** | **47 (35.1)** | **34 (50.0)** | **81 (40.1)** |
| **Elevated blood pressure (BP) ‡‡** | **28 (20.9)** | **23 (33.8)** | **51 (25.3)** |
| **Impaired glucose metabolism***** | **16 (11.9)** | **8 (11.8)** | **24 (11.9)** |
| **NUMBER OF MetS CRITERIA MET (%)** | | | |
| **0** | **27.6%** | **6.1%** | **20.5%** |
| **1** | **24.6%** | **25.8%** | **25.0%** |
| **2** | **23.1%** | **27.3%** | **24.5%** |
| **3** | **18.7%** | **27.3%** | **21.5%** |
| **4** | **4.5%** | **10.6%** | **6.5%** |
| **5** | **1.5%** | **3.0%** | **2.0%** |
| **MEAN NUMBER OF MetS CRITERIA MET, *Mean /SD*** | ***1.5 /1.3*** | ***2.2 /1.2*** | ***1.7 /1.3*** |

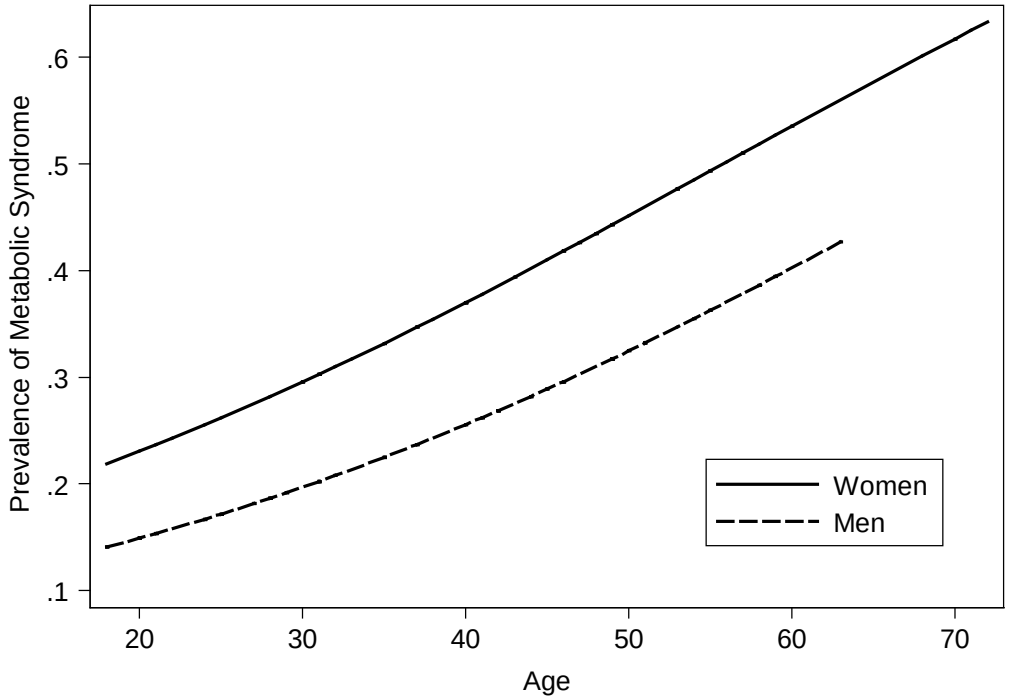
* Two women did not have waist circumference measured; see section 3.3.3
†p (chi-squared)=.018
‡ Abdominal obesity: Waist>88cm for women, >102cm for men
** TG ≥ 1.7 mmol/L
†† HDL < 1.034 mmol/L in men and < 1.292 mmol/L in women
‡‡ BP ≥ 130/85 mmHg or antihypertensive drug treatment
*** Fasting glucose ≥ 6.1 mmol/L or drug treatment for elevated glucose

## Table 3-9: Logistic regression models for Metabolic Syndrome as a function of sex† and age

| Logistic regression models | | Estimate of β ( p ) | | | |
|---|---|---|---|---|---|
| **Model Number** | **Model for logit (MetS)** | **βo** | **$\beta_1$** | **$\beta_2$** | **$\beta_3$** |
| **4** | **$\beta o + \beta_1 sex + \beta_2 age + \beta_3 age*sex$** | -2.64 (p<.001) | 1.16 (p=.315) | .0391 (p=.014) | -.0144 (p=.574) |
| **3** | **$\beta o + \beta_1 sex + \beta_2 age$** | -2.95 (p<.001) | .537 (p=.108) | .0337 (p=.007) | - |
| **2** | **$\beta o + \beta_2 age$** | -2.40 (p<.001) | - | .0380 (p=.002) | - |
| **1** | **$\beta o + \beta_1 sex$** | -1.87 (p<.001) | .751 (p=.019) | - | - |

† sex=1 for women; sex=0 for men

**Figure 3-7 Estimated prevalence of Metabolic Syndrome as a function of sex and age**




### *3.2.5 Ten year risk of coronary heart disease and general cardiovascular disease*

Ten-year risk of hard CHD event was calculated as defined by the NCEP ATP III[30] and categorized as high risk (≥20%), moderate risk (10% to 19%), or low risk (< 10%). Excluded from this calculation were 26 participants who were either under age 20 (N=8), or had diabetes (N=16) and/or self reported history of CHD (N=3). Table 3-10 shows the results of this calculation both with and without the use of coronary heart disease equivalents (diabetes mellitus and known CHD), which can be considered to place an individual in the highest risk group (see section 2.6.2). Without including the individuals with CHD or diabetes as high risk, the mean 10 year hard CHD risk among those over age 20 without baseline diabetes or CHD was 4.0%, and 5.1% of the group fell in the high risk category; adding in the CHD equivalents increased the high risk proportion to 13.9%. Mean risk could not logically be calculated for this second

algorithm that assigns those with diabetes to the high risk category, since they are not assigned any specific risk percentage. For both the algorithms, men were more likely to be in the higher risk categories (Fisher's exact p=.003 when excluding diabetes and CHD, and p=.005 including these as CHD equivalents in the high risk group).

Results for general cardiovascular event risk prediction (CHD, cerebrovascular disease, peripheral vascular arterial disease and heart failure) are also shown in Table 3-10 [31]. This algorithm could not be calculated for 44 individuals under age 30. As expected, the per cent risks are higher for these more general estimates. For general CVD events, the difference between risks for men and women failed to reach significance (Fisher exact p=.063).

**Table 3-10:Ten year risk of coronary heart disease and general cardiovascular disease**

| | MEN | WOMEN | TOTAL |
|---|---|---|---|
| **10 YEAR HARD CORONARY HEART DISEASE (CHD) RISK*** | | | |
| **CHD 10 y risk excluding DM and CHD (%), N=115/61/176†** | | | |
| ***Mean/SD*** | ***5.0/6.2*** | ***1.9/3.6*** | ***4.0/5.6*** |
| **High risk (≥20%)** | **8 (7.0)** | **1 (1.6)** | **9 (5.1)** |
| **Moderate risk (10%-19%)** | **17 (14.8)** | **1 (1.6)** | **18 (10.2)** |
| **Low risk (<10%)** | **90 (78.3)** | **59 (96.7)** | **149 (84.7)** |
| **CHD 10 y risk(%) (with CHD equivalents)‡ (N=127,67,194**)** | | | |
| **High risk (≥20%)** | **20 (15.8)** | **7 (10.5)** | **27 (13.9)** |
| **Moderate risk (10%-19%)** | **17 (13.4)** | **1 (1.5)** | **18 (9.3)** |
| **Low risk (<10%)** | **90 (70.9)** | **59 (88.1)** | **149 (76.8)** |
| **10 YEAR GENERAL CARDIOVASCULAR DISEASE (CVD) RISK ††** | | | |
| **GENERAL CVD 10 y risk (%), N=83/61/141 ‡‡** | | | |
| ***Mean/SD*** | ***10.7/10.0*** | ***6.2/6.2*** | ***8.8/8.9*** |
| **High risk (≥20%)** | **8 (9.6)** | **4 (6.6)** | **12 (8.3)** |
| **Moderate risk (10%-19%)** | **25 (30.1)** | **9 (14.8)** | **34 (23.6)** |
| **Low risk (<10%)** | **50 (60.2)** | **48 (78.7)** | **98 (68.1)** |

* Hard CHD risk calculated using Framingham risk models (2001) 30
† 26 excluded due to age<20 (N=8), DM (N=16), CHD(N=2)
‡ CHD equivalents (diabetes and CHD) are assigned to the highest risk group
** 8 excluded due to age<20
†† General CVD risk calculated using Framingham risk models (2008) [31]
‡‡ 51 excluded due to age<30, CHD, stroke

### *3.2.6 Screening, knowledge/detection, treatment, and control of CVD risk factors*

Table 3-11 presents information on screening, detection, treatment, and control of CVD risk factors and diabetes. One can see that there were variable levels of self reported screening across CVD risk factors, ranging from 98% for hypertension through 60.3% for diabetes and as low as 56.1% for elevated cholesterol. For all of these, the proportion of women who had been tested was higher than for men, although the difference was only significant for cholesterol (p=.013) and diabetes (p=.001). Among those with previously detected CVD risk factors, current drug treatment varied from 90.9% for diabetes to a much lower 22.2% for elevated cholesterol. In terms of control of known CVD risk factors, 26.9% of those with known hypertension had a measured blood pressure over 140/90, while 55.6% of those with known hypercholesterolemia had a measured total or LDL cholesterol in the elevated range, and 45.5 % of those with known diabetes had a blood sugar over 7.0. Hypertension, elevated cholesterol, and diabetes discovered in the study had all gone without previous (self reported) detection in several cases, ranging from 50% for diabetes to 65.8% for high cholesterol.

In terms of body size awareness, almost 20% of those who were overweight or obese (BMI≥25) felt that their weight was “just about right” or “underweight”, although women were significantly more likely to be aware of their being overweight (92.5% versus 75.3%, p=.008).

Current smokers were likely to have tried to quit smoking in the past year (54.3%), and 62.8% reported that professionals had suggested smoking cessation in the past.

## Table 3-11: Screening, knowledge , treatment, and control of CVD risk factors

| | MEN (N=134) | WOMEN (N=68) | TOTAL (N=202) |
|---|---|---|---|
| **BLOOD PRESSURE** | | | |
| Previous blood pressure screen ever*, % | 97.7 % | 98.5 % | 98.0 % |
| Blood pressure screen < 2 years ago* (N=133/67/200), % | 83.5 % | 91.4 % | 86.0 % |
| Self-reported hypertension*, N(%) | 14 (10.5 %) | 12 (17.7 %) | 26 (12.9 %) |
| Taking antihypertensive* (N=14/12/26), % | 57.1 % | 75.0 % | 65.4 % |
| Inadequate control (≥ 140/90), % | 21.4 % | 33.3 % | 26.9 % |
| Measured BP≥ 140/90, N | 10 | 9 | 19 |
| High BP not previously detected*, N=10/9/19, % | 70.0 % | 55.6 % | 63.2 % |
| **LIPIDS** | | | |
| Previous cholesterol screen ever* (N=132/64/196), % | 47.7 % | 73.4 % | 56.1 % |
| Self-reported high cholesterol* (N=134/68/202), N(%) | 26 (19.4 %) | 19 (27.9 %) | 45 (22.3 %) |
| Taking cholesterol lowering drug*, (N=26/19/45), % | 23.1 % | 21.1 % | 22.2 % |
| Inadequate control (TC≥5.2 or LDL≥3.4), (N=26/19/45), % | 53.9 % | 57.9 % | 55.6 % |
| Measured high total or LDL cholesterol, N | 45 | 28 | 73 |
| High cholesterol not previously detected*, N=45/28/73, % | 68.9 % | 60.7 % | 65.8 % |
| **DIABETES** | | | |
| Previous diabetes test ever*, ( N=128/66/194), % | 69 (53.9) | 48 (72.7) | 117 (60.3) |
| Self-reported diabetes* (N=133/68/201), N(%) | 6 (4.5) | 5 (7.4) | 11 (5.5) |
| Taking insulin or oral hypoglycemic*, (N=6/5/11), % | 83.3 % | 100 % | 90.9 % |
| Inadequate control (FPG>7.0), (N=6/5/11), % | 16.7 % | 80 % | 45.5 % |
| Measured high fasting glucose ɨ (N) | 5 | 5 | 10 |
| DM ɨ not previously detected*, (N=5/5/10), % | 80% | 20% | 50% |
| **OBESITY (N=133/67/200)** | | | |
| BMI overweight or obese (≥25), N(%) | 42 (31.6 %) | 35 (52.2 %) | 77 (38.5 %) |
| Proportion aware they are overweight*, % | 75.3 % | 92.7 % | 81.8% |
| **SMOKING** | | | |
| Current daily or occasional smokers* | 75 (56.0 %) | 19 (27.9 %) | 94 (46.5 %) |
| Professional has suggested quitting ever*, (N=75/19/94), % | 61.3 % | 68.4 % | 62.8 % |
| Tried to quit in past year*, (N=75/19/94), N(%) | 39 (52.0 %) | 12 (63.2 %) | 51 (54.3 %) |
| Used smoking cessation aids*, (N=39/12/51), % | 48.7 % | 75.0 % | 54.9 % |

* Based on self report

ɨ FPG>7.0 (on two tests if no previous history of diabetes)

### 3.3 Component B: Preventive health care activities

Table 3-12 presents results on receipt of preventive health care activities stratified by sex. As can be seen, the majority of individuals had access to family physicians in that 87.1% had a regular family physician and 70.2% had seen a family physician in the past year. However, men were significantly less likely to have a regular family physician (p=.002) and to have had a physical examination in the past two years (p=.004). Similarly, there was some variation in receipt of individual preventive activities overall and across age and sex groups. For example, flu shots were uniformly received by all participants over age 65. However, 16.8 % of participants had not seen a dentist in the previous three years and fewer than 75% of women had had a Pap test in the previous 3 years. Again, higher proportions of women than men had accessed several of the services.

The reasons participants gave for not receiving preventive services are shown in Table 3-13. Overall, the two most common reasons for lack of services were the respondent 1) not thinking that the service was necessary, and 2) "not getting around" to obtaining the service. Only for Pap tests did another reason rank in the top two; the physician was reported as not thinking that the test was necessary in four cases.

## Table 3-12: Preventive Health Care Activities* Stratified by Sex

| N (%) | MEN (N=134) | WOMEN (N=68) | TOTAL (N=202) |
|---|---|---|---|
| Regular FP | 110 (82.1) | 66 (97.1) | 176 (87.1) |
| Saw FP in past year (N=133/68/201) | 82 (61.7) | 59 (86.8) | 141 (70.2) |
| Physical examination | | | |
| In past 2 years (N=131/67/198) | 65 (49.6) | 48 (71.6) | 113 (57.1) |
| In past 3 years (N=131/67/198) | 78 (59.6) | 52 (77.6) | 130 (65.7) |
| Never (N=133/68/201) | 24 (18.1) | 8 (11.8) | 32 (15.9) |
| Mammogram (Women) | | | |
| Ever (≥35 y; N=0/52/52) | - | 37 (71.2) | 37 (71.2) |
| Ever (50-69 y; N=0/18/18) | - | 17 (94.4) | 17 (94.4) |
| In past 2 years (50-69 y; N=0/18/18) | - | 10 (55.6) | 10 (55.6) |
| Breast exam (Women) | | | |
| Ever (N=0/67/67) | - | 50 (74.6) | 50 (74.6) |
| In past 2 years (N=0/67/67) | - | 38 (56.7) | 38 (56.7) |
| Pap test (Women) | | | |
| Ever (N=0/68/68) | - | 58 (85.3) | 58 (85.3) |
| In past 3 years (N=0/68/68) | - | 48 (70.6) | 48 (70.6) |
| Dental visit (N=134/68/202) | | | |
| Last visit >=3y ago | 26 (19.4) | 8 (11.7) | 34 (16.8) |
| Eye exam (N=134/68/202) | | | |
| Last visit >=2y ago | 65 (48.5) | 18 (26.5) | 83 (41.1) |
| Influenza immunization | | | |
| Ever (All ages, N=132/68/200) | 77 (58.3) | 43 (63.2) | 120 (60.0) |
| In last year (Age ≥ 65, N=0/5/5) | - | 5 (100) | 5 (100) |

* Based on self report

**Table 3-13: Two most common self reported reasons for not receiving preventive services**

| SERVICE AND TIME ELAPSED (N not receiving service) | | SELF-REPORTED REASON 1 N ( %) | SELF-REPORTED REASON 2 N (%) | REASON 1 OR 2 N (%) |
|---|---|---|---|---|
| **Blood pressure check ≥ 2 years** | **N=28** | Not necessary – R* 17 (61%) | Not gotten around† 14 (50%) | 27 (96%) |
| **Physical examination ≥ 3 years** | **N=68** | Not necessary – R* 39 (57%) | Not gotten around† 22 (32%) | 57 (84%) |
| **Dentist visit ≥ 3 years** | **N=34** | Not necessary – R* 14 (41%) | Not gotten around† 7 (21%) | 20 (59%) |
| **Pap test (Women 18-69) ≥ 3 years** | **N=18** | Not necessary – R* 8 (44%) | Not necessary-MD‡ 4 (22%) | 11 (61%) |
| **Mammogram (Women 50-69) ≥ 2 years** | **N=8** | Not gotten around† 6 (75%) | Not necessary – R* 2 (25%) | 7 (88%) |
| **Breast examination (Women) ≥ 2 years** | **N=29** | Not necessary – R* 16 (55%) | Not gotten around† 6 (21%) | 22 (76%) |
| **Eye examination ≥ 2 years** | **N=83** | Not necessary – R* 63 (76%) | Not gotten around† 17 (20%) | 77 (93%) |

* Interview item: "Respondent – Did not think it was necessary"
† Interview item: "Have not gotten around to it"
‡ Interview item: "Doctor – Did not think it was necessary"

# Chapter Four: **Discussion**

In this chapter, the main results are reviewed (Section 4.1) and placed in context with the existing literature (Section 4.2). Strengths and limitations are presented in Section 4.3. Section 4.4 presents a discussion of implications and future directions.

## 4.1 Overview

This cross-sectional study of outpatients with schizophrenia and related disorders had two broad objectives: first, to examine cardiovascular risk, metabolic syndrome, and 10 year risk of cardiovascular event, and second, to describe the receipt of preventive health services.

In a randomly selected sample of 202 outpatients (mean age 39.6 years, 66.3% men) it was found that hypertension or treatment was present in 15.4%, elevated total or LDL cholesterol or treatment in 41.2%, any high lipids or low HDL cholesterol in 69.8%, diabetes in 7.4%, and current smoking in 46.5%. Almost three quarters (74.4%) of the sample had BMI in the overweight or obese range, with the mean BMI being 31.7 in women and 29.1 in men. Many cases of hypertension, elevated cholesterol, and diabetes had not previously been detected. Moreover, many previously detected cases of these three conditions were found not to be adequately treated. The overall prevalence of metabolic syndrome according to the NCEP ATP III definition was 30.0%. The predicted 10 year risk of myocardial infarct or coronary death among those over age 20 was in the high risk range (over 20% risk) for 5.1% of those without diabetes or CHD. When those with diabetes and CHD were included as “high risk equivalents”, 13.9% fell into the high risk group. A large proportion (87.1%) reported having a regular family physician, yet there was variable receipt of other preventive services. Women were generally

more likely than men to receive services, but women also had lacunae in access, in that only 70.6% reported receiving a Pap test in the past 3 years, while only 55.6% of those in the age range 50 to 69 stated they had had a mammogram in the past 2 years. The commonest reasons given for not receiving specific services were that the individual "did not think it was necessary" or they "had not gotten around to it".

### 4.2 Discussion of the study findings

A number of observations can be made regarding the randomly selected study sample. First, with a mean age of 39.6 years (men 37.1 years, women 44.5 years), a sex breakdown of 66.3% men, and a mean time since first antipsychotic treatment of 11.8 years it was similar in many ways to that of a number of other relevant studies that have considered CVD risk factors and preventive care in those with schizophrenia. For example, the CATIE sample had a mean age of 40.4 years, a higher proportion of men (73.9%), women older than men, and a mean of 14.5 years since starting antipsychotic treatment [38;51]. There was a difference in race/ethnicity breakdown, with 60% being white and 35% black in the CATIE study, whereas in the current study 75% had self identified themselves as white and (data not shown) 1% as black. The Cohn study (Toronto, Canada) also had a similar age and sex breakdown, though a longer duration of illness (19.4 years since first hospitalization); moreover, 66.7% of the Cohn study were currently inpatients and it is unclear whether they were hospitalized chronically or acutely [43]. Almost the entire sample in the current study reported taking at least one antipsychotic medication, as would be predicted in a treatment setting. As expected, a number of individuals had a probable depressive (9.9%) or alcohol use (16.8%) disorder, and since 32% were taking an antidepressant, one would expect that others had a currently resolved past episode of depression [101-103].

The ratio of men to women in the study sample might seem high, given that evidence suggests that the prevalence of schizophrenia does not differ significantly between men and women (in spite of incidence being higher in men) [2;104;105]. However, the current study's proportion of men is similar to the 66% found by Longenecker and colleagues in their systematic review of 220 non-epidemiological studies that had been published in seven high impact journals in 2006 [106]. In fact, the incongruity between incidence and prevalence mentioned above is a focus of some interest in the epidemiology of schizophrenia, and has been postulated to be partly related to increased mortality in men in the initial years after diagnosis (which would affect point and period prevalence estimates though not lifetime prevalence) [2;107].

In terms of age of onset of illness, Larsen and colleagues found a mean age of onset of 26.3 years for psychotic symptoms and a mean duration of untreated psychosis (DUP) of 114.2 weeks in their Norwegian sample of 43 early psychosis patients [108]. Cascio and colleagues (Early Int in Psychiatry 2012) performed a systematic review of duration of untreated psychosis and found a mean age of first treatment of 25.4 years in men and 27.5 years in women, with a mean DUP of 64.1 weeks [109]. These results are consistent with the current study's mean age of onset of 26.1 years.

Interestingly, only 13.4% of the sample had a score of 13 or higher on the K6 nonspecific distress scale, although 13 has been validated as a cut point for probably serious mental illness (SMI) in the general population [94]. In fact, consideration of the validation sample may explain this discrepancy. The validation study was done with a convenience sample of only 155 individuals, enriched for mental illness by telephone screening using the Composite International Diagnostic Interview-Short Form (CIDI-SF) stem questions (including a screening question for non-affective psychosis). SMI was defined in a second assessment stage as a DSM-IV non-

substance use diagnosis according to the Structured Clinical Interview for DSM-IV, in addition to a Global Assessment of Functioning score below 60 [110-113]. The authors note that there was only a "small number" that screened positive for non-affective psychosis in the telephone screen, and these were found to be false positives in the second stage. Thus, psychosis was not explicitly represented among those with SMI in the validation sample. It should be noted that since the publication of this validation, Kessler and colleagues have gone on to validate the K6 in the WHO World Mental Health survey for use in epidemiological data, and concluded that the scale items "might not span the full conceptual space that defines SMI in the population, leading to less sensitivity in detecting some types of SMI" [114;115]. Moreover, other researchers have determined different cut points for use with other specific populations (e.g. those receiving disability payments) [116].

#### *4.2.1 Cardiovascular disease risk factors, metabolic syndrome, and predicted risk*

With respect to CVD risk factors, there are a number of previous studies of samples with schizophrenia and related disorders that permit the current results to be placed in context; no attempt is made at statistical comparison. Comparison is made below to the baseline results from the CATIE study, which were used to produce one article on metabolic syndrome and one on 10% risk of CHD event [38;51]. These baseline CATIE data were collected between 2001 and 2003. The Cohn study of CVD risk factors is also of interest, as it took place in Toronto, although the sample is over 60% inpatients and its data collection took place in 1999 and 2000, somewhat earlier than the current study [43]. Mitchell and colleagues examined the prevalence of metabolic syndrome, smoking, and the CVD risk factors that are components of the definition for metabolic syndrome in a large systematic review of 77 studies published between 2003 and 2011

[48]. Finally, where appropriate and possible, some comment is made on general population prevalence estimates. Table 4-1 summarizes these comparisons.

**Table 4-1: Comparison of Cardiovascular Disease Risk Factor Results with Other Studies**

| Risk Factor Concept | Current study % | CATIE [38;51] | Cohn [43] | Mitchell [48] | Canadian General Population |
|---|---|---|---|---|---|
| **Hypertension** | 15.4 | ↓ | ↓ | ↔ | ↓ Atwood [117] |
| **Smoking** | 46.5 | ↓ | ↓ | ↓ | ↑ Tanuseputro [118] |
| **Total cholesterol elevated** | 35.6 | ↓ | ↔ | N/A | |
| **HDL* decreased** | 40.1 | ↓ | ↓ | ↔ | ↑ Riediger [50] |
| **Triglycerides elevated** | 47.5 | ↔ | ↔ | ↑ | ↑ Riediger [50] |
| **Obesity ǂ (Waist size/BMI)** | 50.5/38.5 | ↔ | ↔men/ ↑women | ↔ | ↑ Riediger [50] |
| **Glucose (IGM‡/DM**)** | 12.4/7.4 | ↓ | N/A | ↔ | ↓ Riediger [50] |
| **Metabolic syndrome** | 30.0 | ↓ | ↓ | ↔ | ↑ Riediger [50] |
| **10 year CHD ǂǂ risk ≥ 20 %** | 13.9 | ↓ | ↓ | N/A | ↓ Setayeshgar [119] |

↑ Current study prevalence higher than comparator
↓ Current study prevalence lower than comparator
↔ Current study prevalence similar to comparator
* HDL: High density lipoprotein (cholesterol)
ǂ Obesity calculated using waist circumference/ Obesity calculated using BMI (body mass index)
‡ IGM: Impaired glucose metabolism [30]
** DM: Diabetes [30]
ǂǂ CHD: Coronary heart disease

For hypertension, the current study found a crude prevalence of hypertension of 15.4% (95% CI 10.7-21.1). This point prevalence is lower than the Canadian general population rates reported by Atwood and colleagues for ages 20 to 79 years [120]. They estimated hypertension prevalence using population based Canadian data from three sources: administrative data from the Canadian Chronic Disease Surveillance System 2007/2008 (20.3%; 95% CI, 20.3-20.3); self report data in the Canadian Community Health Survey 2007/2008 (18.2%; 95% CI, 17.8-18.5); and measured blood pressures in the Canadian Health Measures Survey (CHMS) 2007-2009 (19.5%; 95% CI, 18.1-20.9). One simple explanation for this counter-intuitive lower result in

schizophrenia is the younger age of the current sample compared to the general population (for example less than 5% of the sample are aged over 60 years, whereas in the Canadian general population, about 14% of the 20 to 79 age group was over age 65 in 2008) [121]. Since hypertension prevalence increases with age, this might explain the lower prevalence in the study sample [122]. Of note, the results in the current report are not age and sex standardized to the general population; this issue of age standardization is mentioned under the limitations below. Another potential contributor to a relatively higher general population frequency of hypertension could be the year of the study (2004/2005) compared to the Atwood paper (2007 to 2009). Robitaille and colleagues have reported that the prevalence of hypertension is increasing over time in Canada [123].

The 15.4% prevalence of hypertension found in the current study is also considerably lower than the 27% found in the CATIE study, which used a similar definition of hypertension (blood pressure over 140/90 or antihypertensive treatment) [38]. As noted above, the age and sex distribution of the CATIE participants resembled that of this study's sample. However, hypertension is both more common and more severe in African Americans, and also in those with alcohol use, both of which were more prevalent in the CATIE study and might partially explain the difference in hypertension frequency [124-127]. The Cohn report presents hypertension prevalence only in a graph [43]. The prevalences for men and women appear to be about 25% and 20% respectively, again considerably higher than in the current study in spite of the age and sex distribution being similar. Whether inpatient status or the fact that the Cohn study measured blood pressure only once might have impacted this is unclear; regional variation is also known to exist for hypertension in the general population so one might also expect it to occur in schizophrenia [123].

Mitchell and colleagues examined hypertension as defined for the computation of NCEP ATP III metabolic syndrome, i.e. over 130/85 mmHg or antihypertensive treatment [48]. The prevalence of hypertension in the current study by this definition was 40.1%, consistent with Mitchell's systematic review findings of 38.7% (95% CI: 35.6%–41.9%).

The current smoking prevalence of 46.5% (95% CI 39.5-53.7) in this study (men 56.0%, women 27.9%) was relatively low compared to most reports for schizophrenia, yet (as would be expected) higher than in the general population (Table 4.1). In the CATIE study, current smokers made up 68% of the sample, while Cohn and colleagues found that 74% of men and 66% of women smoked [38;43]. The Mitchell review found a pooled proportion of 54.3% (95%CI: 50.9-57.5%) [48]. It is important to note that smoking definitions vary by study, and none of these three research groups report how they assessed smoking. The general population rate of smoking for Albertans over age 12 was found by Tanuseputro and colleagues to be much lower at 27.7%, using self report data from the 2000-2001 Canadian Community Health Survey [118].

Smoking is not only known to be associated with CVD risk and mortality, but it is also a risk factor for incident diabetes and for dyslipidemia [25;128]. The Canadian Cardiovascular Society Dyslipidemia guidelines state that smoking cessation is probably the single most important behavioral modification for decreasing CVD risk [25]. In the current study, 54.3% of current smokers had tried to quit in the past year. It is also notable that 31.2% (men 30.6%, women 32.4%) were past smokers, presumably indicating that smoking cessation occurs quite regularly in this population. Data on past smoking is not available in the other studies discussed here, but the individuals in the current study who had succeeded in smoking cessation would have thereby decreased the overall predicted CVD risk of the sample as a whole.

Given the recommendations for smoking cessation to address CVD risk reduction, and

particularly in view of the high rate of smoking among those with schizophrenia, smoking would be a natural target for intervention in this population. There is evidence in the schizophrenia literature that some smoking cessation interventions can be successful [129]. Unfortunately, a recent review suggests that the gains tend to be short lived, so strategies must be developed to overcome barriers to long term abstinence that are most relevant to individuals with schizophrenia [129;130].

In terms of lipids, the results of this study did not have a consistent pattern with respect to the existing literature that was examined (Table 4.1). For mean values of total and HDL cholesterol, the CATIE sample had a more compromised profile: CATIE mean total cholesterol was 204.9 mg/dl or 5.3 mmol/L, which was higher than the current study's mean of 4.9 mmol/L, while their HDL levels were slightly lower with a mean of 1.1 mmol/L compared with this study's 1.3 mmol/L[38]. One possible contributor to this discrepancy might be the higher frequency of smoking (as noted above, a risk factor for dyslipidemia) [25]. On the other hand, CATIE's prevalence of elevated triglycerides (48.5%) was similar to this study's results (47.5%); both studies used the same cut point [51]. A potential explanation for these apparently contradictory patterns (ie. a better profile in the current sample except for triglycerides) relates again to the higher prevalence of African Americans in the CATIE sample. African Americans with insulin resistance are known to have a "paradoxically" low prevalence of hypertriglyceridemia [131;132].

For lipid outcomes, Cohn and colleagues again only graphed their results; however, from their graphs one can determine that the sample probably had similar mean triglyceride and total/ LDL cholesterol levels in both men and women to those found in the current study, with perhaps slightly lower mean HDL cholesterol. Compared to international results, the current study had a

prevalence of elevated triglycerides (47.5%) somewhat higher than that found by Mitchell and colleagues in their systematic review (39.3%; 95% CI 35.0%–43.6%) and similar prevalence of low HDL cholesterol (40.1%) compared with Mitchell's 42.6% (95% CI: 39.3%–46.0%). In the Canadian general population aged 18 and older, Riediger and colleagues reported lower weighted prevalence estimates of elevated triglycerides (24.5%) and of low HDL cholesterol (33.6%) using data from the Canadian Health Measures Survey (2007-2009) [50].

The mean BMI of 29.9 (95% CI 28.9-30.9) in the current study (men 29.1, women 31.7) was similar to CATIE (29.7 overall; see Table 4.1) and the same relationship between BMI and sex held in both; ie. BMI was significantly higher in women. The proportions obese in the Calgary sample using the definition BMI ≥ 30 (men 31.6%, women 52.2%) was similar to Cohn (31%) for men, though higher than Cohn (43%) for women. Waist circumference was high (indicating abdominal obesity) in 50.5% of the current sample, consistent with the Mitchell review's pooled prevalence of 49.4% (95%CI: 44.8%-53.3%) [48]. Regardless of comparisons, however, these prevalences of obesity were disturbingly high, given the associated risks for diabetes and CVD [133;134]. As a comparator, the prevalence of obesity in the Canadian general population aged 18 and older as assessed by measured waist circumference with the same cut point in the Canadian Health Measures Survey (2007-2009) was 35.0% [50].

Given the elevated rates of obesity in those with schizophrenia and/or serious mental illness, interest has arisen in weight-loss interventions for these groups. Until very recently, most interventions were of short duration and had only modest results, and Cabassa and colleagues' systematic review noted methodological variability that was related to outcomes [135;136]. Challenges have been noted to include a lack of enrolment in programs by individuals who are overweight, and lack of attendance by those who do enrol [137]. Recently, however, there

have been more positive results in longer term trials with multi-pronged interventions. Most notably, Daumit and colleagues published results of their 18 month behavioural weight loss intervention for individuals with severe mental illness (of whom 58.1% had schizophrenia or schizoaffective disorder), in which 37.8% of the participants in the intervention group lost 5% or more of their initial weight, as compared with 22.7% of those in the control group (P = 0.009) [138]. The intervention was quite intense, involving group (weekly) and individual (monthly) weight management meetings as well as 50 minute group exercise sessions three times weekly. Zhang and colleagues also used a multimodal intervention over 12 months, and found that 42.1% of those with psychotic spectrum disorders lost over 5% of their baseline weight in last observation carried forward analysis, significantly more compared with the other psychiatric disorders (18.4%) and no psychiatric disorder (23.0%) groups ($p<.01$) [139]. However, the group with psychotic disorders had a longer treatment duration (median 11.5 months versus 4.2 and 3.0 months, log rank $p<.001$), which was the strongest predictor of weight loss ($p<.001$). Seemingly, this population is able to lose weight and make lifestyle changes in relatively long multimodal programs.

It is interesting to note that both the Daumit and Zhang interventions involved an exercise component [138;139]. Physical activity is suggested in Canadian clinical practice guidelines for the general population regarding diabetes, lipids, and hypertension [25;26;140]. Moreover, this is a domain of lifestyle modification that is receiving growing attention in the schizophrenia literature as evidence begins to emerge for correlates and benefits of exercise that might extend beyond the realm of weight loss and cardiovascular health. For example Knochel and colleagues published a 2012 narrative review of cognitive and behavioral effects of physical activity in psychiatric patients, and concluded that exercise “can enhance neuronal plasticity and cognitive

performance" in schizophrenia [141]. Vancampfort and colleagues' systematic review of exercise interventions for schizophrenia in multidisciplinary settings found that some exercise modalities reduced psychiatric symptoms, state anxiety, and/or psychological distress or improved health-related quality of life or short-term memory [142]. The authors did comment that overall conclusions were limited due to heterogeneity and small sample sizes.

Impaired glucose metabolism as defined in ATP III was present in 12.4% (95% CI 7.8-17.2) of the current sample. This point prevalence compares favorably with the 16.1% in the CATIE study; similarly diabetes prevalence was lower in the current sample (7.4%; 95% CI 4.2-12.0) compared to CATIE (13%) [38;51]. To be remembered is that about one third of the CATIE sample was African American, and as demonstrated by Brancati and colleagues, this group has a much higher risk of diabetes [143]. The Cohn study did not examine diabetes, but Bresee and colleagues found an Alberta period prevalence of treated diabetes of 10.3% in treated schizophrenia between 1995 and 2006 in their administrative data study, and a Canadian self reported prevalence of diabetes of 11.3% for those with self reported schizophrenia in the 2005 Canadian Community Health Survey [19;20]. Both of these had diabetes point prevalences that were higher than the 7.4% in the current study (though within the confidence interval); any differences could potentially be due to measurement bias in administrative data and survey data, or to other systematic differences between patients diagnosed with schizophrenia and related disorders by a psychiatrist in a mental health clinic, and patients so diagnosed by other health professionals. Finally, diabetes prevalence in the current study was in the range of that found by Mitchell and colleagues in their systematic review (10.9%; 95% CI:7.0-15.5%) [48]. Riediger and colleagues found a Canadian general population prevalence of ATP III impaired glucose metabolism of 16.2% in their Canadian Health Measures Survey analysis of those 18 years and

older [50]. This point prevalence was unexpectedly higher than that in the current study; however it must be remembered that their national sample was older, and impaired glucose metabolism increases with age. To illustrate this, 4.4% of those between 18 and 39 years in the Riediger sample had impaired glucose metabolism, compared to 42.9% between ages 70 and 79 years [50]. As noted above, age standardization was not done in the current study, and is mentioned in the limitations below.

Metabolic syndrome is an indicator of risk of insulin resistance and CVD [45;47]. Thirty per cent of the current study sample (30.0; 95% CI 23.7-36.9) satisfied the ATP III criteria for metabolic syndrome (men 24.6%, women 40.9%); this was considerably lower than the CATIE study at 40.9% (Table 4.1). This difference was not unexpected, since the current sample had lower criterion prevalences than CATIE for all criteria except waist circumference (see Appendix A for definition of metabolic syndrome). Moreover, age was a significant predictor of metabolic syndrome in multivariable analysis for both men and women in CATIE, as it was in the current study. The Cohn study found rates of metabolic syndrome in men (42.6%) and women (48.6%) that were also noticeably higher than point prevalences in the current study ; again this was somewhat anticipated given the higher prevalences of many of the component criteria. However, in the Cohn study, age dichotomized at the median was not associated with metabolic syndrome, which was different from both the Calgary and CATIE studies. The Mitchell review calculated a pooled proportion of 32.8% (95%CI: 30.0%-35.7%) with metabolic syndrome as defined by ATP III, so the current study's estimate falls at Mitchell's lower confidence bound [48]. The Canadian general population prevalence of ATP III metabolic syndrome computed using data from the Canadian Health Measures Survey (2007-2009) in those aged over 18 was considerably lower, at 17.7% (men 15.9%, women 19.5%) [50] .

As such, the local prevalence of metabolic syndrome was found to be at the low end of what would be expected for those with schizophrenia. However, it is still about one and a half times as high as in the general Canadian population, suggesting that the recent proliferation of guidelines and calls for action are justified [61;144;145].

The CATIE study computed 10 year CHD risk using Framingham criteria, and obtained mean risk percents of 9.4% in men and and 6.3% in women, compared with this study's 5.0% (95% CI 3.9-6.2) and 1.9% (95% CI 1.0-2.9) respectively (Table 4.1) [38]. The lower frequency in Calgary can be explained by generally lower criterion frequencies as noted above, as well as a different method of calculation, since the CATIE study seems to have used an earlier Framingham algorithm that included diabetes in the formula [29]. Ten year CHD event risk estimates were also calculated by Cohn and colleagues using the NCEP ATP III algorithm, providing mean predictions of 8.9% in men and 2.6% in women [43]. The authors note that they were unable to factor diabetes into the equation since they did not collect diabetes data; therefore their results represent a mixed sample with and without diabetes. On the other hand, the Calgary mean risk results include only those without diabetes (as explained in the Results section, a mean 10 year CHD risk could not be calculated for the entire sample), who had lower risk than the entire local sample. This, together with the lower Calgary proportions noted above for many CVD risk factors, could explain the relatively lower mean risk in the current study. In the Canadian general population, Setayeshgar and colleagues computed the mean 10 year risk of CHD for those aged 30 to 74 using CHMS data from 2007 to 2009, obtaining a result of 7.70% (95% CI 7.07–8.32), which is interestingly higher than the current study mean of 4.0% (95% CI 3.1-4.8). This difference could again be related to the age distribution of their sample, and/or to the fact that they also used an earlier Framingham calculation that included diabetes and

excluded those under 30, both of which would be likely lead to higher risk estimates [29;119].

### *4.2.2 Screening, knowledge, treatment, and control of CVD risk factors*

Regarding preventive health services, the results suggest that individuals with schizophrenia have variable and often inadequate receipt of a number of preventive health services related to CVD risk factors [60]. This issue has been the focus of a number of studies worldwide; Table 4.2 presents a summary of the current study's results in comparison to other published data [3;56;65;77].

**Table 4-2: Comparison of Screening and Treatment Results with Other Studies**

| Preventive Health Service | Current study % | CATIE [65] | Mitchell [60] | Voruganti [146] | Jennex [64] |
|---|---|---|---|---|---|
| **Screening** | | | | | |
| **Hypertension:** | 98.0 | | ↑ | ↑ | ↑ |
| **Diabetes:** | 60.3 | | ↑ | ↓ | ↔ |
| **Lipids:** | 56.1 | | ↑ | ↑ | ↔ |
| **Drug Treatment** | | | | | |
| **Hypertension** | 65.4 | ↑ | | | |
| **Diabetes:** | 46.5 | ↑ | | | |
| **Lipids:** | 35.6 | ↑ | | | |

* CVD: Cardiovascular disease
↑ Current study preventive health service prevalence higher than comparator
↓ Current study preventive health service prevalence lower than comparator
↔ Current study preventive health service prevalence similar to comparator

Nasrallah and colleagues examined the individuals in the baseline CATIE study, and found that 37.6% of those with hypertension were treated with antihypertensive medication, 69.9% of those with diabetes were receiving hypoglycemic agents, and 12.0% of those with elevated lipids were taking lipid lowering medication [65] . The Calgary study found notably higher treatment rates (see Table 4.2). Reasons for this discrepancy are not clear, although one

might wonder about the contribution of better access to treatment in Canada versus the United States for this group, for example through universal health insurance.

As noted in Chapter 1, Mitchell and colleagues performed a meta-analysis of screening of metabolic risk that included studies between 2000 and 2011 of persons on antipsychotic medications [60]. They found that in the 25 studies of schizophrenia (N=169,289), blood pressure was monitored in 57.9% (95% CI 34.9–79.3), glucose in (40.0%, 95% CI 30.1–50.3), and cholesterol in 33.3% (95% CI 6.4–68.5). Of note, Mitchell's study specifically excluded self report of screening, and included studies that used medical record review or administrative data; by contrast the current study used self report to determine screening. In the current study, point prevalences of screening were higher as shown in Table 4.2. Differences might have been due to the time interval over which the monitoring occurred; the current study examined "ever" having received screening. The Mitchell report does not specify the required monitoring interval for screening in their inclusion/exclusion criteria, but at other points in the article the authors speak of the screening prevalences being of "routine monitoring". If "routine monitoring" required two or more readings whereas the current study considered screening to have occurred after only one reading, this could explain Mitchell's study finding a lower prevalence of screening.

In Canada, the availability of comparison studies assessing similar preventive health services is limited. Chapter 1 notes that Voruganti and colleagues examined screening in an Ontario chart audit/study of individuals with schizophrenia or schizoaffective disorder aged 16 and above [146]. They found that fasting glucose levels were recorded for 78%, LDL and total cholesterol for 48.2% and 42.7% respectively, and blood pressure for 64.2% (see Table 4.2). Again, comparison with the current study is difficult given the different modalities of data collection (chart review versus interview and self report), and the fact that the Voruganti study

assessed a six month period whereas the Calgary study asked about "ever" having had the screening.

Jennex and colleagues reported frequencies in a mental health clinic of documented screening of diabetes (61%), dyslipidemia (40%), and hypertension (70%), all of which were lower than the control HIV group [64]. In this case, blood pressure and lipids screening frequencies in the Toronto mental health clinic were rather lower than the Calgary study (see Table 4.2), but again the comparison is compromised by different data collection methods.

The current study also demonstrated some gaps in body size awareness, which could potentially make it difficult to engage patients in programs aimed at weight loss. Almost 20% of individuals who were overweight or obese were unaware of their overweight status. On a more positive note, there were indications that smoking cessation was common in schizophrenia, if one considers the 31.2% of the sample made up by former smokers to have succeeded at smoking cessation.

### *4.2.3 Preventive health care activities not related to cardiovascular disease*

The results suggest that outpatients with schizophrenia have relatively good availability of a regular family physician (87.1%) as would be expected for those with at least one chronic disease. This is also consistent with the results of Bresee and colleagues in both provincial administrative data and national-level general population survey concerning good access to general practitioner (see Introduction for further details) [19;39]. Unfortunately, in spite of family physician availability, the results of the current study suggested variable utilization of preventive health services. Most notably, men reported significantly less access to all services examined, including a regular family physician. General population studies have also suggested that

women use preventive health services more than men, and this was true in the current sample as well [147;148]. Yet the results demonstrate that women also reported variable receipt of Pap tests, mammograms, and breast examinations by a health professional.

This variability in utilization of preventive health services concurs with a review by Lord and colleagues which examined 26 reports of studies comparing receipt of preventive services by those with and without mental illness, of which seven reports were about schizophrenia or bipolar disorder [56]. Among those with schizophrenia, inferior preventive care was found in some but not all of the reviewed reports. One issue that makes interpretation of these reports more difficult is that utilization of preventive services can be increased by having more contact with physicians (surveillance bias), which could explain some of the variability in results observed by Lord. In Canada, Chochinov and Martens used administrative data to examine women aged 50 to 69 in Manitoba and found that 44.8% of women diagnosed with schizophrenia and 58.3% without had had a mammogram in the past two years ($p<.001$); the Calgary study sample had a two year mammography rate of 55.6% in the same age group, which was more like the Manitoba general population rate. Of note, there was significant regional variation in the Manitoba data [67]. The same team examined cervical screening using similar methodology, and found that a lower proportion of women with schizophrenia had had a Pap test (58.8% vs. 67.8%) in the past three years ($p<.001$) compared to those without schizophrenia [68]. The Calgary sample had a higher Pap screening prevalence of 70.6%.

The most common self reported reasons for not receiving preventive health services were that the participant did not think the service was necessary, or did not “get around to it”. These reasons are consistent with poor health literacy in the first case, and could be thought to be related to negative symptoms of schizophrenia, in the latter.

There has been some recent interest in the concept of health literacy related to those with schizophrenia. For instance, Brosnan and colleagues assessed a group of patients taking clozapine using the REALM tool that assesses health literacy through understanding and pronunciation of medical terms, and concluded that over a quarter had marginal to low levels of health literacy [149]. Moreover, a recent Australian study by Maguire and colleagues suggested that individuals with schizophrenia are less likely to obtain medical information from a physician, less likely to trust this information, and less likely to use the internet [150]. Taken together, these reports suggest that there are probably multifactorial reasons for patients not recognizing the importance of preventive health care services, and that this could be impacting their seeking out of these services. The common reason "didn't think it was necessary" given for not obtaining services in the current study would be consistent with the findings of Brosnan and Maguire.

### 4.3 Strengths and limitations of the study

One strength of this study is that it included a randomly selected sample of participants, rather than a sample of convenience (e.g. Cohn's Canadian study) or a sample chosen for a switch of medication (e.g. the CATIE study) [43;51]. This would be expected to present a more representative portrait of the risks and treatment profiles of an outpatient population that is not necessarily in transition between medications. Moreover, the sample size was larger than that of many such studies, being at the mean of sample sizes in the systematic review by Mitchell and colleagues [48].

This study also had the advantages that it used primary data, and collected several modalities of data (measured, chart review, and self reported) that could be integrated to shed

light on the interplay between the measured CVD risk factors and health service variables; for example, it was possible to examine whether those with measured hypertension pressure had been previously diagnosed or were currently treated for high blood pressure.

Another strength of the study is its Canadian context of universal health insurance, since this allows examination of access to health services for those with schizophrenia without the known potential confounder of inequity in insurance coverage. For example, access to mammography has been shown to be related to insurance status in the United States, and preventive health activities were decreased among individuals with severe mental illness who were uninsured compared to those with insurance [151;152]. Interestingly, a group from the Harvard School of Public Health examined colorectal screening in a low income, racial-ethnic minority group who nevertheless predominantly had health insurance (97.2%), and found that screening rates were higher than among similar populations lacking insurance [153]. Thus, variable access to insurance coverage can complicate the interpretation of utilization of health services.

Regarding generalizability of these results, the sample was drawn from two clinics at a tertiary care centre in Calgary. One of these clinics, the Early Psychosis Treatment Service, might plausibly be considered to be population based, as it is the only early psychosis program in the area. The other clinic, the Outpatient Schizophrenia Service, is one of several multidisciplinary mental health clinics in Calgary serving individuals with schizophrenia and related disorders. It is likely that the majority of outpatients with these diagnoses attend one of these mental health services, since local family physicians usually refer patients with psychosis to psychiatrists, and most psychiatrists in private practice refer these patients on to programs with multidisciplinary teams. As such, it is likely that the study population was reasonably representative of the Calgary outpatients with schizophrenia and related disorders.

One potential limitation of this research is that self report was used to assess both previous diagnoses of CVD risk factors and receipt of preventive health service, and the validity of these results might be questioned. A number of studies have employed administrative data or medical charts to investigate the accuracy of self-report of health variables, and although results have differed, in fact, many studies have concluded that self report data remain useful [117;154-160].

One further concern regarding self report data might be that the validity of reporting could be lower among those with schizophrenia and/or those who are socially disadvantaged compared to the general population. In fact, some studies argue against this. For example, Lofters and colleagues performed a recent systematic review examining the relationship between level of disadvantage (race, education, or/income) and accuracy of self reported cervical cancer screening [155]. They found no difference between disadvantage subgroups, although interestingly, there was pervasive over-reporting of screening across subgroups. If anything, such over-reporting, if it were present in the current study, would present a conservative picture of the need for services. In another study, Goldberg and colleagues demonstrated the reliability of self-report of health service use by individuals with schizophrenia in a small sample (N=29) [156].

Another potential limitation of the data is the year of data collection, as this occurred several years ago. A recent meta-analysis of prevalence of metabolic abnormalities and metabolic syndrome in schizophrenia and related disorders by Mitchell and colleagues found that year of publication was not associated with prevalence of metabolic syndrome [48]. However, other important variables examined in this study (e.g. smoking, obesity, hypertension) are known to display time trends in their prevalence, at least in the general population [123;161]. Yet to our knowledge this is the most recent Canadian study characterizing CVD risk factors in combination in individuals with schizophrenia, with data collection taking place about five years

after that of Cohn and colleagues' [43].

The data from this study have not been standardized to the Canadian population, although this was considered. This decision was made because the main goal of the study was to quantify CVD risk factors and preventive health services in individuals with schizophrenia, and not to make comparison to the general population. Moreover, since the populations against which comparison is made here (in the Discussion) varied from result to result, even for comparisons against the general population, it was felt that standardization would not improve the interpretability of results.

The sample was randomly selected, yet 35% declined to take part in the study when it was suggested to them by their psychiatrist, and another 5% declined at the full informed consent. It is possible that those declining to take part differed from those that signed consent. However, those declining at the preliminary consent stage made up the large majority of those choosing not to participate. This group had very little information on the study, and as such would potentially be less likely to have characteristics that were directly related to study outcomes (e.g. less likely to avoid the study because they did not wish to be asked about their heavy smoking or not getting a Pap test). Nonetheless, it is possible that those declining at either the preliminary or full consent stages would be more likely to have higher levels of negative symptoms, depression, substance use, or other comorbidity. If this were the case, such an excluded group could potentially have higher levels of CVD risk and lower levels of service use, suggesting that the study's results might be conservative due to selection bias.

### 4.4 Implications and future directions

These results suggest that individuals in outpatient treatment for schizophrenia and

related disorders in a Canadian urban centre have a substantial burden of CVD risk factors, and that they also have variable access to preventive services. This is consistent with results of other studies in the field, but adds information beyond other Canadian results in that this study collected primary data from a randomly selected outpatient sample, and was able to integrate information on measured CVD risk factors with information on receipt of health services.

The degree of medical illness among those with schizophrenia and related disorders has received more interest in the past decade, as psychiatrists and other health care professionals and researchers became aware of the weight gain associated with the use of atypical antipsychotic medications and began to investigate the added cardiometabolic burden potentially introduced by antipsychotic treatment . Out of this has come a proliferation of research studies, reviews, and guidelines suggesting the optimal monitoring and treatment of these patients [61;144;145].

Yet it appears from the results of this study that the issue is complex and challenging and the "solution" does not lie simply in guidelines directed at health care professionals. Not only are there gaps in both detection and management of medical illnesses on the part of health care providers, but the results of this study suggest that sometimes preventive services might be available but are not received because some individuals with schizophrenia do not recognize that the service is necessary or they delay in obtaining it . Programs will need to be comprehensive and innovative to address all of these issues. They will need to take into account not only the required services, but the characteristics associated with these psychotic illnesses, such as the negative and cognitive symptoms, the lack of health literacy, and the lack of trust in information received from physicians. Based on results to date on behavioral interventions for weight loss, such programs will likely need to be multimodal and of longer duration than those designed for the general population, which in turn will increase costs. Advocacy will be required to promote

policy that allows for such targeted programming. There is almost certainly no simple way to address this multifaceted issue: there is a need for better prevention of medical illness, for better detection, for better management once detected, and probably for strategies to increase health literacy and address other barriers to care as well. Substantial change will be needed at a systemic level in order to make a difference in the health of people with schizophrenia.

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## APPENDIX A: METABOLIC SYNDROME

Criteria for diagnosis of the metabolic syndrome: National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) (2001) [1], Modified NCEP ATP III (2005) [2], and Canadian Diabetes Association (2013) [3].

| Risk factor criterion | NCEP ATPIII Criteria | NCEP ATPIII Revised | Canadian Diabetes Association |
|---|---|---|---|
| | 3 or more of: | 3 or more of: | 3 or more of: |
| Elevated waist circumference (WC) | WC >102 cm in men and > 88 cm in women | WC ≥102 cm in men and ≥ 88 cm in women | WC ≥102 cm in men and ≥ 88 cm in women (Canada/US only) |
| Elevated fasting triglycerides (TG) | TG ≥ 1.7 mmol/L | TG ≥ 1.7 mmol/L OR On drug treatment for elevated triglycerides | TGs ≥ 1.7 mmol/L OR On drug treatment for elevated triglycerides |
| Reduced High Density Lipoprotein (HDL) | HDL < 1.034 mmol/L in men and < 1.292 mmol/L in women | HDL < 1.03 mmol/L in men and < 1.3 mmol/L in women OR On drug treatment for reduced HDL-C | HDL < 1.0 mmol/L in men and < 1.3 mmol/L in women OR On drug treatment for reduced HDL-C |
| Elevated blood pressure (BP) | BP ≥ 130/85 mmHg* | BP ≥ 130/85 mmHg OR On antihypertensive drug treatment for elevated BP | BP ≥ 130/85 mmHg OR On antihypertensive drug treatment for elevated BP |
| Elevated fasting glucose (FPG) | FPG ≥ 6.1 mmol/L† | FPG ≥ 5.6 mmol/L OR On drug treatment for elevated glucose | FPG ≥ 5.6 mmol/L OR On drug treatment for elevated glucose |

* For the current study antihypertensive drug treatment for elevated blood pressure was considered to be an alternative criterion for elevated blood pressure for ATP III (2001).

† For the current study drug treatment for elevated glucose was considered to be an alternative criterion for elevated fasting glucose for ATP III (2001).

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## APPENDIX B: OPERATIONAL DEFINITIONS

**Alcohol use disorder:** Alcohol use disorder is defined as a score of at least 8 on the AUDIT scale [1].

**Body Mass Index (BMI):** BMI is defined as (weight in kg) divided by (height squared in meters squared).

**Current smoking:** Current smoking is defined as any smoking in the past month. This definition was chosen for consistency with NCEP ATPIII , for computation of 10 year CVD risk. Research has shown that any current smoking is associated with increased ischaemic heart disease mortality [2].

**Depression:** Depression is defined as over the validated cut point of 6 on the Calgary Depression Scale for Schizophrenia [3].

**Diabetes (mellitus):** Diabetes is defined as a fasting (no caloric intake for ≥ 8 hours) plasma glucose greater than 7.0 mmol/L on two days, using the 2013 Canadian Diabetes Association definition, OR current drug treatment for elevated glucose [4].

**HDL Cholesterol (low) :** HDL is considered low if it is ≤ 1.034 in men and ≤ 1.293 in women as defined by the Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on ATP III [5].

**Hypercholesterolemia:** Hypercholesterolemia is defined as total cholesterol ≥5.2 mmol/L or LDL-C ≥ 3.4 mmol/L as defined by the Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) OR current drug treatment for elevated cholesterol [5].

**Hypertension:** Hypertension is defined as a mean diastolic blood pressure on at least two readings of at least 90 mmHg or a mean systolic blood pressure of at least 140 mmHg, or current drug treatment for elevated blood pressure.

**Impaired fasting glucose**: Impaired fasting glucose is defined as a fasting plasma glucose level between 6.1 and 6.9 mmol/L, using the 2013 Canadian Diabetes Association guideline [4].

**LDL Cholesterol (high) :** LDL is considered high if it is ≥ 3.4 mmol/L as defined by the Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) [5]

**Metabolic syndrome:** Individuals are classified as having the metabolic syndrome if they satisfy the ATP III criteria as in Appendix 1 [5].

**Obesity:** Obesity is defined as a BMI of at least 30 kg/m$^2$.

**Schizophrenia and related disorders:** Participants are considered to have schizophrenia or a related disorder if there is clear documentation in their chart of a psychiatrist making a diagnosis of schizophrenia or schizoaffective disorder, or, in the EPTS, of psychosis NOS, schizophreniform disorder, or another psychotic disorder not felt to be secondary to a mood, medical, or substance use disorder. In this report, these diagnoses are referred to as "schizophrenia" at times for brevity.

**Ten-year CHD risk (high):** The 10-year CHD risk is classified as >20% if the individual has diabetes or a history of myocardial infarct or coronary heart disease (CHD), and as the 10-year risk calculated using the ATP-III risk algorithm otherwise [5].

**Ten-year general CVD risk:** The 10-year general CVD (CHD, stroke, heart failure, peripheral vascular disease) risk is calculated using the 2008 Framingham algorithm [6]

**Total Cholesterol (high) :** Total cholesterol is considered high if it is ≥ 5.2 mmol/L as defined by the Executive Summary of the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) OR if there is drug treatment for hypercholesterolemia [5].

**Triglycerides (high)**: Serum triglycerides are defined as high if they are ≥ 1.7 mmol/L as defined by the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) [5]

**Waist Circumference (high):** Waist circumference is defined as high if it is over 88 cm in women and over 102 cm in men [5].

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