METABOLIC SYNDROME IN CANADIAN ADULTS

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By

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Abstract

Background: There is limited information available about the prevalence of Metabolic Syndrome (MetS), its trend over time and its predisposing risk factors according to different definitions in Canadian adults. No studies have compared the ability of the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) and the International Diabetes Federation (IDF) definitions to predict Cardiovascular Disease (CVD) mortality among Canadian adults.

Objectives:

a) To examine the age and sex specific prevalence of the Metabolic Syndrome in Canadian adults by using the ATP III and the IDF definitions.

b) To examine the risk factors for Metabolic Syndrome in Canadian adults by using the ATP III and the IDF definitions.

c) To examine the association between Metabolic Syndrome and cardiovascular disease mortality in Canadian adults by using the ATP III and the IDF definitions.

Methods: The Canadian Heart Health Survey was a cross-sectional probability sample survey conducted in all 10 Canadian provinces between 1986 and 1992. The first two studies in this thesis were based on individuals for whom full anthropometric measurements were obtained and for whom data on all components of MetS were available (provinces of Alberta, Manitoba, Ontario, Quebec and Saskatchewan). Statistics Canada linked the CHHS data set to Canadian Mortality Database. The third study was based on three provinces (Alberta, Manitoba, and Saskatchewan) for whom full anthropometric measurements, mortality data, and data on all components of MetS were available. MetS was defined according to ATP III and IDF

definitions. A weighted analysis using SPSS PASW Complex Samples (version18) was used to conduct stepwise logistic regression analysis to identify risk factors significantly associated with MetS ($p < 0.05$). Cox-regression analyses using the STATA (version11) was conducted to predict CVD mortality.

Results: According to ATP III, 17.9% and 15.3% of men and women have MetS, while according to IDF, 23.8% and 17.3% of men and women have MetS, respectively. Kappa agreement between the definitions is 72 % for men and 80% for women ($p \leq 0.05$). Older age and low level of physical activity are significant risk factors for the MetS regardless of gender and definition. Higher level of education and alcohol consumption are additional significant protective factors for women, whereas retirement and being unemployed are additional significant risk factors for men. The hazards of death due to CVD events in women with the syndrome according to the ATP III and the IDF definitions are 3.96(1.30-12.09) and 2.56 (1.32-4.97), respectively. The comparable numbers for men are 2.21(1.16-4.02) and 2.50(1.50-4.17).

Conclusion: In Canadian adults the prevalence of MetS is higher when the IDF definition is applied but the metabolic derangement of individuals identified is less severe. Demographic, socio economic factors, and lifestyle habits are significantly associated with MetS among the Canadian adults. The ATP III definition predicts CVD mortality better in women, while the IDF definition predicts CVD mortality better in men.

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This dissertation is dedicated to the loving memory of my dear father, *Khashayar*. I will never forget how difficult it was for him to leave him to further my education even though he was sick. Unfortunately, he is not here with us today. However, I am sure he is watching me closely and is happy to see the whole thing finished.

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List of Abbreviations

4S	Scandinavian Simvastatin Survival Study
AACE	American College of Endocrinology
ACE	Angiotension Converting Enzyme
ACS	Acute Coronary Syndrome
AFCAPS/TexCAPS	Air Force/Texas Coronary Atherosclerosis Prevention Study
ATP III	Adult Treatment Panel III
BMI	Body Max Index
CHD	Coronary Heart Disease
CHHS	Canadian Heart Health Survey
CI	Confidence Interval
CRP	C-Reactive Protein
CTEP	Cholesteryl Ester Transfer Protein
CVD	Cardiovascular Disease
DECOD	Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe
dL	Deciliter
DXA	Dual-energy X-ray Absorptiometry
EGIR	European Group of the study Insulin Resistance
FFA	Free Fatty acid
FRS	Framingham Risk Score
G	Gram
HDL	High Density Lipoprotein

HR	Hazard Ratio
ICD	International Statistical Classification of Diseases
IDF	International Diabetes Federation
IL	Interleukin
KHAS	Keewatin Health Assessment Study
LDL	Low Density Lipoproteins
MET	Metabolic Equivalent of Task
MetS	Metabolic Syndrome
Mg	Milligram
MHHS	Manitoba Heart Health Survey
Min	Minutes
MI	Myocardial Infarction
mm/mL	millimole/milliliter
MmHg	Millimeters of mercury
mmol/L	millimol per liter
NCEP	National Cholesterol Education Program
NICDS	Northern Indians Chronic Disease Study
OR	Odds Ratio
PIR	Poverty Income Ratio
ROC	Receiver Operating Characteristics
RR	Relative Risk
SAPHIR	Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk

SES	Socioeconomic Status
SLHDP	Sandy Lake Health and Diabetes Project
TG	Triglycerides
TIA	Transit Ischemic Attack
VLDL	Very Low Density Lipoproteins
WC	Waist Circumference
WHO	World Health Organization

1.Introduction

1.1. Background

In 1920, Kylin, a Swedish physician, described, for the first time, the concept of Metabolic Syndrome as a clustering of hypertension, hyperglycemia, and gout (1). An association between upper body adiposity (android or male obesity) and some metabolic abnormalities present in patients with type 2 diabetes and cardiovascular disease was observed by Vague in 1947 (2).Reaven outlined the clinical importance of the Metabolic Syndrome for the first time approximately 40 years ago. He did not consider obesity as a risk factor for the development of the Metabolic Syndrome but described the syndrome as a cluster of metabolic abnormalities in which insulin resistance had a "causative role" and called it Syndrome X (2-4).

The Metabolic Syndrome has been identified by different names, such as" syndrome X", the "insulin resistance syndrome" and the "deadly quartet" over the past few decades (1,2). As researchers begun to accept the concept of Metabolic Syndrome, there was a need to define it. As number of organizations developed different definitions over the past decades. Although several definitions have been proposed and they include different details, the essential components of the Metabolic Syndrome are the same: glucose intolerance, obesity, hypertension and dyslipidemia (1,2,5,6).

1.2. Definitions of Metabolic Syndrome

The World Health Organization (WHO) published the first definition in 1999, as shown in table-1 (2,5,7). In this definition, attention was drawn to the biological and physiological description of insulin resistance (3). This definition had several limitations. Measuring insulin sensitivity with the highly complex euglycemic clamp was one of the most important limitations. Indeed, using a euglycemic clamp to measure insulin sensitivity was not easily applicable to clinical practice or epidemiological studies (2). Another limitation of the WHO definition was inclusion of individuals with diabetes which lead to limits its value in identifying individuals who are at risk of developing diabetes (2).

Table 1. World Health Organization definition of the Metabolic Syndrome

Insulin resistance, identified by 1 of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions

Plus any 2 of the following:

- Antihypertensive medication and/or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic)
- Plasma triglycerides (TG) ≥150 mg/dL (≥1.7 mmol/L)
- High Density Lipoprotein(HDL) cholesterol <35 mg/dL (<0.9 mmol/L) in men or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m^2 and/or waist: hip ratio >0.9 in men, >0.85 in women
- Urinary albumin excretion rate ≥20 µg/min or albumin:creatinine ratio ≥30 mg/g

Subsequently, since applying the WHO definition was difficult, the European Group of the study Insulin Resistance (EGIR) modified the WHO definition in 1999 (8). They

called it insulin resistance syndrome and similar to the WHO definition considered insulin resistance as a key component of the disease. They restricted their definition to the subjects without diabetes because they believed that measuring insulin resistance in diabetic patients was neither reliable nor practical. They also explained that measuring fasting insulin is more practical than measuring insulin resistance, so they included measuring fasting insulin as a component in the definition. Indeed, they excluded "impaired glucose tolerance" or "impaired fasting glycemia" as a requirement for diagnosing the syndrome. They included waist circumference as the measurement for adiposity because they believed waist circumference was a better indicator for abdominal obesity than BMI and waist-to-hip ratio. They modified the cut-off points for hypertension, triglycerides, and high-density lipoprotein based on the recommendation of European Task Force (Table 2). They also argued that because there was not sufficient evidence to show a strong relationship between Metabolic Syndrome and microalbuminuria, so this component should not be included in the definition (1-3,5,8,9).

Table 2. European Group of the study Insulin Resistance definition of the Metabolic Syndrome

Insulin resistance* or hyperinsulinemia (only non-diabetic subjects)
Plus two of the following:
Central obesity: waist circumference ≥94 cm (M), ≥80 cm (F)
Raised TG (≥2.0 mmol/L) and/or low HDL-cholesterol (<1.0 mmol/L) or treatment
Fasting/2 h plasma glucose ≥6.1/7.8 mmol/L but <7.0/11.1 mmol/L
Raised arterial blood pressure (≥140/90 mmHg) or treatment
*defined as the top quartile of fasting insulin in the non-diabetic population

In 2001, the National Cholesterol Education Program of the USA developed the ATP III definition. In this definition all the components had equal importance and they excluded

In 2001, the National Cholesterol Education Program of the USA developed the ATP III definition. In this definition all the components had equal importance and they excluded any measurement of insulin resistance and focused more on cardiovascular disease risk factors. Each of the diagnostic criteria was justified based on its prevalence among American people. In the definition, they applied the new cut-off points for waist circumference as the measurement of abdominal adiposity. They explained that men and women develop several metabolic abnormalities when their WC is greater that 102 and 88 cm, respectively (3,10). In fact, there was a shift from pathophysiological to clinical features in the definition their definition was easy to apply in clinical practice and epidemiological studies, and so became popular over the last few years (Table 3) (2,3,5,6). One of the most important criticisms of their definition was applying the higher cut-off value for waist circumference compared to two previous definitions.

Table 3. Adult Treatment Panel III definition of the Metabolic Syndrome

3 or more of the following:

1. Abdominal obesity: waist circumference ≥102 cm in men and ≥88 cm in women;
2. Hypertriglyceridemia: ≥150 mg/dL (1.7 mmol/L);
3. Low HDL cholesterol: <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.30 mmol/L) in women;
4. High blood pressure: ≥130/85 mm Hg;
5. High fasting glucose: ≥110 mg/dL (≥6.1 mmol/L)

In 2004, the American College of Endocrinology (AACE) modified the ATP III definition because it believed insulin resistance was a key component in developing Metabolic Syndrome. Their definition focused on the pathophysiological cause of insulin resistance. It described two categories of risk factors. The first group was those risk

factors which help researchers and clinicians to identify individuals who are more likely to have insulin resistance. They explained these factors as "identifying abnormalities": including elevated triglyceride, reduced HDL, elevated blood pressure, and elevated fasting and post load glucose. The second group consisted of those risk factors which increase the chance of developing of Metabolic Syndrome , such as obesity, family history of diabetes, hypertension, or CVD, non –European ancestry, age greater than 40 years, sedentary lifestyle, personal history of gestational diabetes or glucose intolerance, coronary heart disease, hypertension, polycystic ovarian syndrome, or non-alcoholic fatty liver disease. One of the most important criticisms of their definition was not including obesity as an ""identifying abnormality". In fact, their justification was that obesity is not a consequence of insulin resistance, but it is a contributing factor to the development of insulin resistance. Compared to the WHO and the EGIR definitions, the AACE definition did not include hyperinsulinemia as a component in their definition (1-3,5).

Table 4. American College of Endocrinology criteria for diagnosis of the Insulin Resistance Syndrome*

Identifying abnormalities:

Elevated triglycerides ≥ 150 mg/dL (1.69 mmol/L)
Low HDL cholesterol

- Men <40 mg/dL (1.04 mmol/L)
- Women <50 mg/dL (1.29 mmol/L)

Elevated blood pressure ≥130/85 mm Hg
Glucose:

- 2-Hour post glucose challenge >140 mg/dL
- Fasting glucose Between 110 and 126 mg/dL

Other risk factors: obesity, family history of type 2 diabetes, hypertension, or CVD, Sedentary lifestyle, Advancing age, Ethnic groups, Personal history of gestational diabetes or glucose intolerance, coronary heart disease, hypertension, polycystic ovarian syndrome, non-alcoholic fatty liver disease

*Diagnosis when individual has risk factors and at least two of the identifying abnormalities

In 2005, the International Diabetes Federation (IDF) developed a new definition of the Metabolic Syndrome of which central obesity, as measured by waist circumference, was an essential component (Table 5a, b). Their aim was to identify individuals at the higher risk of developing diabetes and vascular events, and to develop a practical definition which can be used in both clinical practice and research (3). The essential components of the ATP III definition were included because they were easy to apply in clinical practice (9). It also adopted the same threshold for triglycerides, HDL cholesterol, blood pressure, and plasma glucose as the ATP III definition. The major difference between the IDF and the ATP III definition was the inclusion of waist circumference as a key component. The IDF definition proposed different cut-off values for waist circumferences according to ethnic background of individual in contrast with single, high cut-off point under the ATP

III definition. The IDF argued that there is a strong association between waist circumference, cardiovascular disease, and other components of Metabolic Syndrome, and they also believed that abdominal obesity was the earliest step in developing of Metabolic Syndrome. As a result, waist circumference should be considered a principal risk factor. It recommended the ethnic-specific waist circumference. Indeed, they believed that the cut-off value for abdominal obesity should be different between Asians and other populations because several studies confirmed that the Asian population developed diabetes and CVD with at the lower level of abdominal adiposity than the European population. It defined different cut-off values for different ethnicity based on the studies which investigated the relationship between waist circumference and other components of the Metabolic Syndrome among different populations (2). However, one of the most important criticisms of their definition was the exclusion of individual who are metabolically abnormal but do not have abdominal obesity. The IDF also argued explained that abdominal obesity and high triglycerides are highly correlated with insulin resistance and that there are some difficulties in measuring insulin sensitivity in clinical practice. Thus, insulin sensitivity should be excluded from the definition of the Metabolic Syndrome (2,3,6). They also suggested that further studies are needed to investigate the other criteria which should be included in the definition of the Metabolic Syndrome. They listed those criteria in their reports which included: tomographic assessment of visceral adiposity and liver fat, biomarkers of adipose tissue, apolipoprotein B, LDL particle size, formal measurement of insulin resistance and an oral glucose-tolerance test, endothelial dysfunction, urinary albumin, inflammatory markers, and thrombotic markers (3).

Table 5a. International Diabetes Federation definition of the Metabolic Syndrome

According to the new IDF definition, for a person to be defined as having the Metabolic Syndrome they must have:

Central obesity (defined as waist circumference* with ethnicity specific values)
Plus any two of the following four factors:
Raised triglycerides: ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose: (FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes. If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

Table 5b. Ethnic group specific values for waist circumference

Country/Ethnic group		**Waist circumference**
Europids In the USA, the ATP III values (102 cm male; 88 cm female) are likely to continue to be used for clinical purposes	Male	≥94 cm
	Female	≥ 80
South Asians Based on a Chinese, Malay and Asian-Indian population	Male	≥90
	Female	≥80
Chinese	Male	≥90
	Female	≥80
Japanese	Male	≥90
	Female	≥80
Ethnic South and Central Americans	Male	Use South Asian recommendations until more specific data are available
	Female	
Sub-Saharan Africans	Male	Use European data until more specific data are available
	Female	
Eastern Mediterranean and Middle East (Arab) populations	Male	Use European data until more specific data are available
	Female	

In 2005 the National Cholesterol Education Program of the USA modified the ATP III definition, which was developed in 2001. As in the original definition all the components had an equal importance, but now included individuals receiving treatment for elevated triglycerides, elevated blood glucose, hypertension, and reduced HDL cholesterol. In the modified definition, the threshold for fasting plasma glucose was reduced from 6.1mmol/L (110 mg/dL) to 5.6 mmol/L (100 mg/dL). This modification was based on the updated definition of impaired fasting glucose by the American Diabetes Association. (9,11). In the updated version, although the committee explained that different cut-off points might be used bases on the ethnicity, they did not apply these cut-off points. In the present thesis when we refer to the ATP III definition, we mean the updated version of the definition.

Table 6. Updated Adult Treatment Panel III definition of the Metabolic Syndrome

3 or more of the following:

1. Abdominal obesity: waist circumference ≥102 cm in men and ≥88 cm in women; *

2. Hypertriglyceridemia: ≥150 mg/dL (1.7 mmol/L); or drug treatment for elevated TG**

3. Low high-density lipoprotein (HDL) cholesterol: <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.30 mmol/L) in women; or drug treatment for reduced HDL *
4. High blood pressure: ≥130/85 mm Hg; or drug treatment for hypertension
5. High fasting glucose: ≥100 mg/dL (≥6.1 mmol/L); or drug treatment for elevated glucose

* Some US adults of non-Asian origin (e.g., white, black, Hispanic) with marginally increased waist circumference (e.g., 94–101 cm [37–39 inches] in men and 80–87 cm [31–34 inches] in women) may have strong genetic contribution to insulin resistance and should benefit from changes in lifestyle habits, similar to men with categorical increases in waist circumference. Lower waist circumference cut point (e.g., _90 cm [35 inches] in men and _80 cm [31 inches] in women) appears to be appropriate for Asian Americans.

** Fibrates and nicotinic acid are the most commonly used drugs for elevated TG and reduced HDL cholesterol. Patients taking 1 of these drugs presumed to have high TG and low HDL.

In 2009, the IDF and the National Cholesterol Education Program groups attempted to provide unified criteria for diagnosis of MetS. They agreed that WC should not be a prerequisite to diagnose the Metabolic Syndrome, and that its threshold should be defined based on the population ethnicity. In fact, they applied the ATP III definition with the IDF cutoff points for WC (table7a, b) (12).

Table 7a. Unified definition of the Metabolic Syndrome

3 or more of the following: **Central obesity*** (defined as waist circumference* with ethnicity specific values) **Raised triglycerides:** ≥150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality **Reduced HDL cholesterol**:** < 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality **Raised blood pressure:** systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension **Elevated fasting glucose***:** ≥ 100 mg/dL (5.6 mmol/L), or treatment of elevated glucose

*It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.
**The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose _-3 fatty acids presume high triglycerides.
** *Most patients with type 2 diabetes mellitus will have the Metabolic Syndrome by the proposed criteria.

Table 7b. Ethnic group specific values for waist circumference by organization

Population	Organization (Reference)	Recommended Waist Circumference threshold for abdominal obesity	
		Men	Women
Europid	IDF	≥94	≥80
Caucasian	WHO	≥94	≥80
United States	AHA/NHLBI (ATP III) *	≥102	≥88
Canada	Health Canada	≥102	≥88
European	European Cardiovascular Societies	≥102	≥88
Asian (including Japanese)	IDF	≥90	≥80
Asian	WHO	≥90	≥80
Japanese	Japanese Obesity Society	≥85	≥90
China	Cooperative Task Force	≥85	≥80
Middle East, Mediterranean	IDF	≥94	≥80
Sub-Saharan African	IDF	≥94	≥80
Ethnic Central and South American	IDF	≥90	≥80

*Recent AHA/NHLBI guidelines for Metabolic Syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of _94 cm in men and _80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

1.3. Pathophysiology of the Metabolic Syndrome

Two hypotheses regarding the underlying pathophysiological processes which lead to the development of the Metabolic Syndrome have been developed (insulin resistance and/or hyperinsulinemia versus abdominal obesity).

The most accepted hypothesis among the researchers regarding the pathophysiology of the Metabolic Syndrome identifies central role plays by insulin resistance**.** It has been defined as a defect in insulin action whereby normal levels of insulin cannot trigger the signal for absorption of glucose which subsequently leads to hyperinsulinemia. Free Fatty acid (FFA) which is released from adipose tissue mass is a major contributor in development of insulin resistance. FFA in the liver triggers the production of glucose, triglycerides and also increases the secretion of very low density lipoproteins (VLDL). Associated lipid abnormalities consist of increasing in the level of low density lipoproteins (LDL) and decreasing in the level of high density lipoprotein (HDL). FFA also inhibit insulin-mediated glucose uptake which lead to a reduction in insulin sensitivity in muscle. Associated defects include reduction in transformation of glucose to glycogen and an increase in lipid accumulation in form of triglyceride (TG) in the liver. Increases in amount of circulating glucose and FFA will lead to an increase in secretion of insulin from pancreas which subsequently leads to hyperinsulinemia. Hyperinsulinemia stimulates the lipolysis phase and produce more fatty acids which also inhibit the antilipolytic effect of insulin which subsequently create additional lipolysis (1).

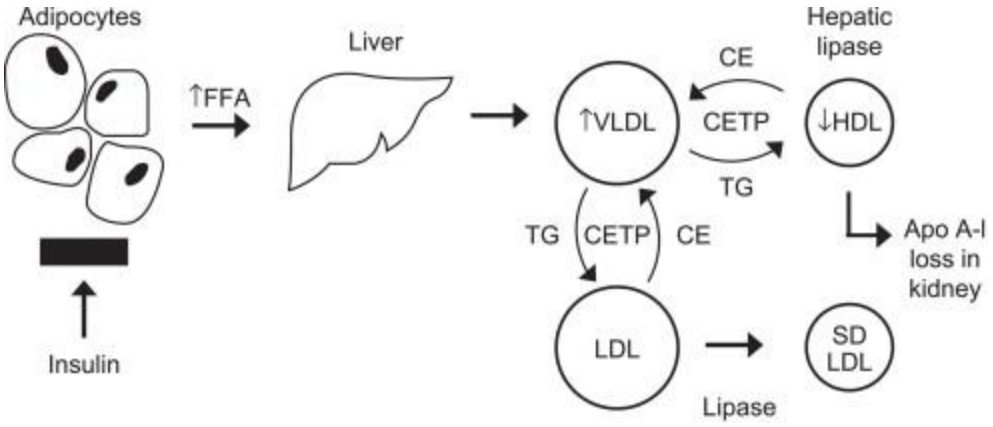

Figure 1. Pathophysiology of the Metabolic Syndrome (13)

I. Dyslipidemia

Insulin resistance at the adipocytes leads to the increase in release of FFA into circulation by blocking the inhibitory effect of insulin on adipocyte lipolysis. Subsequently, FFA will be delivered to the liver and muscle. Increased FFA flux to the liver stimulates production of very low-density lipoproteins (VLDL) which lead to hypertriglyceridemia. In addition, VLDL stimulates the action of cholesteryl ester transfer protein (CTEP) which leads to exchange of TG for cholesteryl ester from low-density and high density lipoproteins. Lipoprotein or hepatic lipase act on TG-enriched LDL and create smaller and denser LDL. Apolipoprotein A-I dissociates from TG-enriched HDL and is exerted in the kidney which reduce the available HDL for reverse pathway. This series of actions will lead to high TG, low HDL, and high small dense LDL (13,14).

II. Glucose intolerance

Defects of glucose metabolism in insulin-resistant individuals include two deficiencies: a) inability to suppress gluconeogensis in liver and muscle which lead to failure of suppression of glucose production b) inability to mediate glucose uptake in insulin sensitive tissues such as muscle and adipose tissue. To compensate for these defects, pancreatic beta cells secrete more insulin to maintain euglycemia. On the other hand, prolonged hyper function of pancreatic beta cells can lead to "beta cell exhaustion' which subsequently leads to hyperglycemia. As discussed previously, FFA can stimulate insulin secretion but is has been documented that prolonged exposure to high level of FFA can lead to fall in secretion of insulin which leads to hyperglycemia and subsequently leads to insulin resistance (1,13).

III. Hypertension

Insulin resistance may produce hypertension through a variety of mechanisms. FFA can cause vasoconstriction in the circulatory system by increasing the production of angiotensinogen. Insulin reduces nitric oxide which causes vasodilatation in vessels in normal weight people and also promotes the reabsorption of sodium from the kidney. In individuals with insulin resistance, the sodium reabsorption effects are preserved but the vasodilatory function will be lost. This can lead to hypertension. In addition, insulin stimulates the activity of the sympathetic nervous system. Through these mechanisms, insulin resistance promotes the development of hypertension (1,13).

IV. Insulin resistance and obesity

It has been well documented that variations of fat distribution have differing effects on insulin action. Independent of total adiposity, that there is a strong association between visceral adiposity and insulin resistance (15). In fact, an increase in visceral adipose tissue leads to a higher rate of flux of adipose tissue-derived FFA to the liver, which leads to insulin resistance (1).Yet, whether this relation is a causal relationship is still controversial (15). Abdominal subcutaneous fat release lipolysis products, which avoid glucose production lipid synthesis, and secretion of prothrombotic proteins. Although type of fat distribution is important, differentiation of visceral vs subcutaneous abdominal adiposity is not part of the clinical diagnosis of the Metabolic Syndrome (1).

V. Abdominal Obesity and Metabolic Syndrome

It has been reported that visceral adiposity leads to insulin resistance. In fact, accumulation of visceral adipose tissue will lead to impaired FFA metabolism because visceral adipocytes are resistant to antilipolytic effect of insulin and they also can cause impaired FFA etherification. Thus, there will be high flux of FFA into the liver which leads to increase secretion of TG, enhanced hepatic production of glucose, and decreased hepatic degradation of insulin, which subsequently causes insulin resistance. Moreover, viscerally obese patients have a high level of TG-rich lipoproteins which leads to transformation of TG from the TG enrichment of LDL and HDL in exchange for choelsteryl esteras. Also, hepatic lipase activity is elevated in people with visceral obesity which leads to formation of small LDL and HDL particles, which subsequently leads to low amount of HDL cholesterol and high amount of small LDL particles. Thus,

abdominal obesity leads to insulin resistance, hyperinsulinema, high TG, glucose intolerance, low HDL cholesterol, small LDL dyslipidemia (16,17).

1.4. Issues with having different definitions for Metabolic Syndrome

Several studies showed that risk of developing diabetes and cardiovascular disease were higher in individuals with the Metabolic Syndrome (18-22). A detailed literature review was done by Cameron et al. The results showed that the prevalence of Metabolic Syndrome differed widely between studies because of study design, study population, and definitions of the Metabolic Syndrome (Figure 1) (1,5). However, most studies agree that the prevalence of Metabolic Syndrome is increasing and Metabolic Syndrome is becoming a global problem (3). Several studies compared the prevalence of Metabolic Syndrome according to different definitions, and the degree of concordance between definitions. Most these studies agreed that the prevalence of Metabolic Syndrome was higher when the IDF definition was applied (3,11,23-27). The use of different definitions may lead to confusion in the interpretation the results of epidemiological studies. Thus, there is a need for a standard definition that eliminates the confusion for both researchers and clinicians (3,11). The IDF and ATP III groups attempted to harmonize the definition of the Metabolic Syndrome in 2009. They agreed that abdominal obesity should not be an obligatory component in the definition, and that different cut-off points should be applied for WC based on the ethnicity (12). There is considerable debate about which criteria should be used, which definition identifies individuals with more adverse metabolic profiles, which is more suitable for clinical practice, which better predicts future CVD events, and whether all components of the Metabolic Syndrome should have an equal

weight in the definitions (3,24-32). Most previous studies applied the WHO and EGIR definitions while more recent studies applied the ATP III and IDF definitions (11).

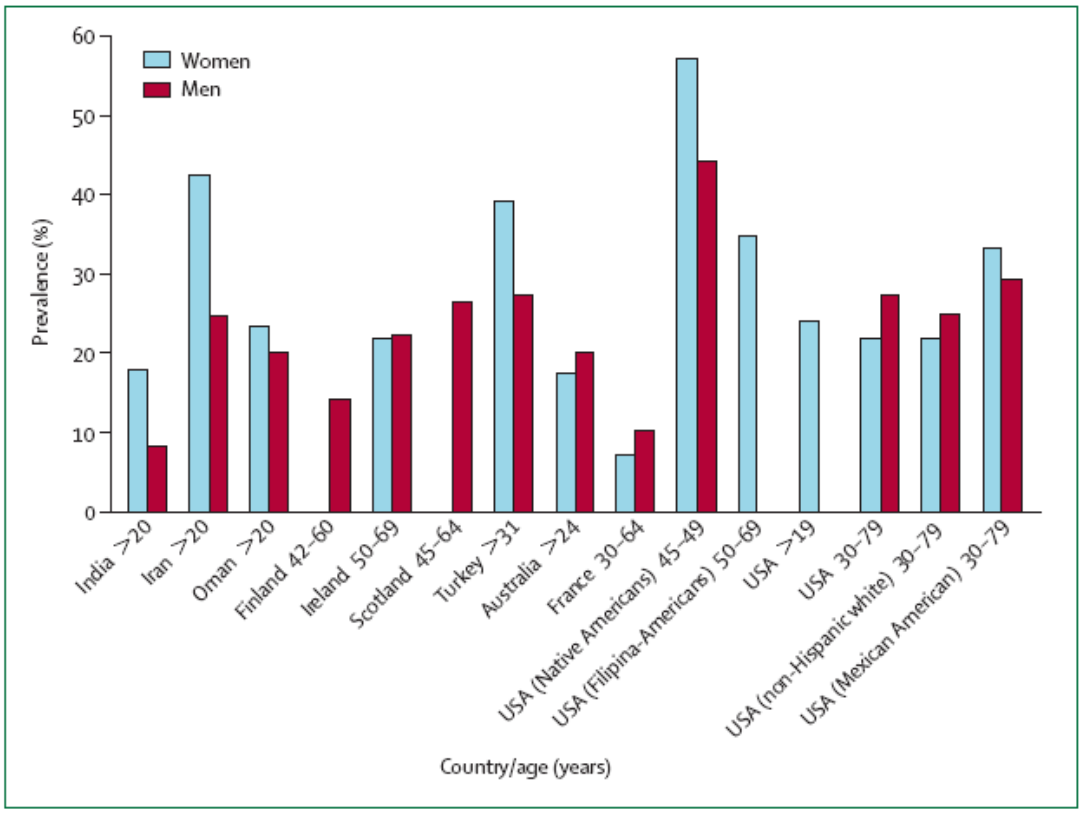

Figure 2. Prevalence of the Metabolic Syndrome according to Adult Treatment Panel III definition (1,5)

1.5. How to best define the Metabolic Syndrome

Several definitions have been developed to define the Metabolic Syndrome. As discussed earlier, all these definitions attempted to cluster the key components. In fact, two conceptual frameworks have been applied in developing of the definitions. In one paradigm, there was a focus on etiology of the Metabolic Syndrome which has been discussed earlier (abdominal obesity or insulin resistance) (Figure 3a), however, in another paradigm, the components were selected based on their statistical strength of their association with other components, which subsequently might identify underlying feature (Figure 3b) (33).

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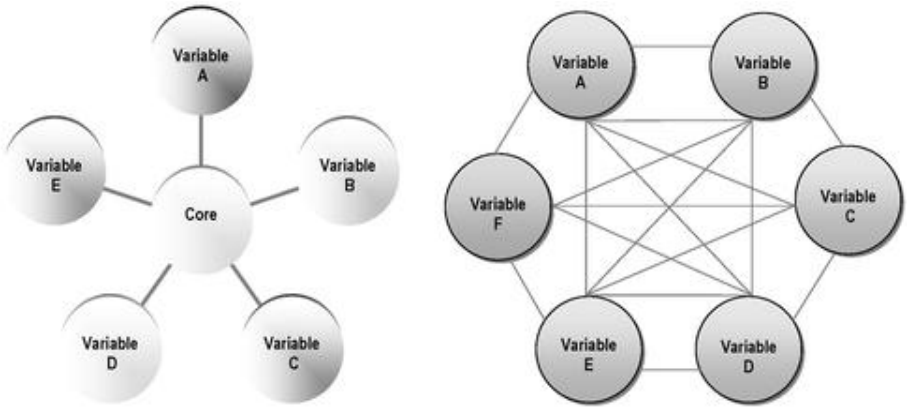

Figure 3. Conceptual frameworks for the Metabolic Syndrome definition (33)

Several factors should be considered in developing the definition for the Metabolic Syndrome. These include considering the components which capture individuals with the condition, defining the thresholds which identifies abnormalities, defining different thresholds in different ethnic groups, and defining the definition which can easily be applicable in both clinical practice and research. As it was discussed earlier, several

definitions have been developed during the past years. Applying each of them has some benefits and disadvantages. In summary, the WHO definition considers insulin resistance as a main cause of the syndrome and a mandatory component. Thus, the WHO definition does not include those people who have other criteria but do not have insulin resistance. In addition, using the euglycemic clamp to measure insulin resistance is not easily applicable in clinical practice and large epidemiologic studies (34). It has been shown that there are no absolute criteria which can classify individuals as being insulin resistant (34,35). Waist-hip ratio or BMI, which has been considered in the WHO definition, has been shown to accurately measure the visceral obesity. Similar to the WHO definition, the EGIR definition considers insulin resistance as a mandatory component which also leads to the exclusion of individuals who have other criteria but not insulin resistance. One of the strengths of EGIR definition is the application of the WC as an indicator for visceral adiposity.

The ATP III definition uses measurements which are readily available in clinical practice and epidemiological research. This definition does not give any specific notion to underlying cause of Metabolic Syndrome (insulin resistance or obesity).However, it has been discussed that WC threshold should be different in different ethnic groups. In the IDF definition, obesity, not insulin resistance, has been considered as a key factor. Thus, the IDF definition does not cover those individuals who are insulin resistant and have other metabolic abnormalities but are not abdominally obese.

As discussed earlier, having different definitions for the Metabolic Syndrome reflect on different conceptual frame works. For researchers and clinicians who consider the Metabolic Syndrome as a clinical manifestation of insulin resistance, the WHO and EGIR definitions are the more relevant definitions. However, for those who believe that the main etiological factor in the development the Metabolic Syndrome is abdominal obesity, clustering of those factors associated with abdominal obesity predict development of CVD, the ATP III or the IDF definition are felt to be most appropriate. Thus, choosing the most appropriate definition can be based on the purpose of defining the Metabolic Syndrome. However, among different definitions the highest priority should be given to the definitions which can identify people who are at the risk of developing of CVD or diabetes because the primary purpose of defining the syndrome was to identify these high risk groups (33).

1.6. Prevalence of Metabolic Syndrome

Several studies compared the prevalence of Metabolic Syndrome based on different definitions, and also the degree of concordance between definitions (3,11,23,25-27,31,36-41). Most studies agreed that the prevalence of Metabolic Syndrome was higher when the IDF definition was applied.

Sandhofer et al recruited 943 Austrian men aged between 40 and 60 years and 575 Austrian women aged between 50 and 70 years from "Salzburg Atherosclerosis Prevention Program in Subjects at High Individual Risk" (SAPHIR) data base. Individuals with diabetes or cardiovascular disease were excluded in the study. The results showed that the prevalence of Metabolic Syndrome in men was 18.7%, 18.9%, and 25.8% when the WHO, the ATP III, and the IDF definitions were applied, respectively. The comparable numbers in women were 16.2%, 17.0%, and 19.5%, respectively. They explained that concordance between the definitions of WHO and IDF was 50% and was 67% between the ATP III and IDF definitions (25).

Moebus et al conducted a cross sectional study among 35869 German patients (38.9% men, 61.1% women) between the ages of 18 and 99 from general practices in 2005. They compared the prevalence of Metabolic Syndrome according to the ATP III (2001), ATP III (2005), and the IDF definitions. Prevalence of Metabolic Syndrome was 22.7% in men and 18% in women when the ATP III (2001) definition applied, and 40.3% in men and 28.0% in women when the IDF definition applied. Prevalence of the syndrome was 34.8% in men and 24.8% according to the ATP III (2005) definition. The kappa

agreement between the ATP III (2001) and the IDF definitions was 61% in men and 74% in women. Agreement of the ATP (2005) and the IDF definitions was 79 % in men and 89% in women (11).

In another cross-sectional study among the 10206 Norwegians men and women (Nord-Trøndelag Health Study) between age of 20 and 89 years by Hildrum et al the prevalence of the Metabolic Syndrome was reported (1995-97). The prevalence of Metabolic Syndrome was 26.8% in men and 25% in women according to the ATP III definition, and 29% in men and 30.3% in women according to the IDF definition. Kappa agreement between these definitions was 57% in men and 76% in women (23).

In another cross-sectional study by Olijhoek on 2373 Dutch patients who had vascular disease (coronary heart disease, TIA or ischemic stroke, peripheral arterial disease or abdominal aortic aneurysm), they reported that the prevalence of the Metabolic Syndrome was higher according to the IDF (52%) than the ATP III definition (41%). Their results showed that out of 974 individuals who had Metabolic Syndrome according to the ATP definition, only 838 had Metabolic Syndrome by the IDF definition. There were 402 individuals who had Metabolic Syndrome according the IDF definition but not the ATP III definition. They did not report the kappa agreement between the definitions (27).

The DECOD study group (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe) examined 14222 people (6577 men and 7645 women) non-diabetics

and 1516 diabetic individuals with Asian origin (Native Asian Indians and Mauritian Indians, native Chinese, and native Japanese). The results showed that the prevalence of Metabolic Syndrome was higher by applying the IDF definition than the ATP III definition. Overall, 1082 men and 1299 women had Metabolic Syndrome by either of the definitions in this study. 49% of individuals who had Metabolic Syndrome by the IDF definition had Metabolic Syndrome by the ATP III (2001). 68% of individuals who had Metabolic Syndrome by the ATP III had Metabolic Syndrome by the IDF. The agreement between the definitions was poor in men (Kappa= 36%) and moderate in women (Kappa= 58%) (26).

Hadeagh et al in the Tehran Lipid and Glucose study, among 720 Iranian men and women older than 65 years, reported that the prevalence of Metabolic Syndrome was 50.8%, 41.8% and 41.9% based on the ATP III (2001), the WHO, and the IDF definitions. They reported that there was a good agreement between the IDF and the ATP III definition (Kappa statistics= 63.4%), and there was low agreement between the IDF and the modified WHO definitions (Kappa statistics= 38.3%) (41).

Ford et al obtained the data from the National Health Nutrition Examination Survey (1988-1994), a cross sectional study among 8708 Americans , 4167 men and 4441 women, aged older than 20 years, reported the age-adjusted prevalence of Metabolic Syndrome in men was 25.1 % (applying the ATP III definition,2001) and 27.6% (applying the WHO definition). The comparable numbers in women were 22.7% and

20.3%, respectively. The degree of agreement between two definitions was 86.4% and 86.7% in men and women (37).

Ford et al conducted another study by obtaining the data from the Third National Health Nutrition Examination Survey (1999- 2002). In this study they examined 3601 American men and women older than 20 years of age. Unadjusted prevalence of Metabolic Syndrome for men and women was 33.7% and 35.4%, applying the ATP III definition 2005, and was 35.4% and 38.1 % by applying the IDF definition. The degree of agreement between definitions was not reported in this study (38).

Cheung et al merged data from two cycles of the Nutrition Examination Survey in the USA (1999-2000 and 2001-2002), and estimated the prevalence of Metabolic Syndrome using the IDF, the ATP III, and the WHO definitions. They examined 3584 Americans older than 20 years of age. The prevalence of Metabolic Syndrome in men was 20.1, 33.6, and 39.9, and in women the prevalence of the syndrome was 18.6%, 35.3%, and 38% according to the WHO, ATP III, and IDF definitions, respectively. They concluded that agreement between the IDF and the ATP III definitions in men and women was 89.8 % and 95.9%, respectively. The degree of agreement between the IDF and WHO definitions was reported at 77.1% in men and 79.4% in women (31). The difference in the prevalence might be because of different sample size between these studies.

In 2003, Arden et al, analyzed data from the Canadian Heart Health Survey (1986–1992), a cross sectional study, which include 7981 Canadians aged 18-64. They reported that the

prevalence of Metabolic Syndrome was 17% in men and 13.2 % in women according to the ATP III definition (42). Also, Brien et al obtained data from the Canadian Heart Health Surveys (1986–1992), and studied 12881 Canadians aged between 18-64. The ATP III definition was applied and the reported prevalence of the Metabolic Syndrome was 17.5% in men and 11.2% in women (36).

Katzmarzyk et al, in a study among 20789 white, non-Hispanic American men aged 20–83 years from the Aerobics Center Longitudinal Study, concluded that the prevalence of Metabolic Syndrome was higher by the IDF definition(38.6%) than the ATP III definition (24%) (40).

Liu et al compared the prevalence of Metabolic Syndrome among three ethnic groups (Native Indians, Inuit, and non-aboriginal Canadians) in Canada. They combined four sources of data set: the Northern Indians Chronic Disease Study (NICDS 1986–1987), the Manitoba Heart Health Survey (MHHS 1989–1990), the Keewatin Health Assessment Study (KHAS 1990–1991), and the Sandy Lake Health and Diabetes Project (SLHDP 1993–1995). The prevalence of Metabolic Syndrome by the ATP III (2005) definition was 30.4% in men and 39.7% in women among Oji-Cree Indians. When the WHO definition was applied, the comparable numbers were 32.6% and 34.1%. A moderate agreement between the ATP III and the WHO definition was observed (kappa agreement= 63%) (3,39)

Riediger et al recently published described the prevalence of Metabolic Syndrome in the Canadian adults using data from the first Canadian Health Measures Survey, a cross sectional study which conducted between 2007 and 2009 (12). Both the ATP III and unified criteria have been applied. 1800 individuals was included in their study which represent 24 473 500 Canadians. They reported that the prevalence of Metabolic Syndrome was 15.9 and 19.5 in men and women according to the ATP III definition, respectively. Also, prevalence was 23.4 in men and 22.9 in women based on unified definition when lower WC cutoff points applied (WC≥94 in men, WC≥ in women) (43).

Although there is a strong relationship between the Metabolic Syndrome and development of cardiovascular disease (21) and cardiovascular disease is one of main causes of death in Canada, there is limited information available regarding trends in the prevalence of Metabolic Syndrome in Canada. In addition, to our knowledge, few Canadian studies compared the prevalence of Metabolic Syndrome by applying the IDF and the ATP III definitions (32,40). Several studies compared the degree of concordance between different definitions in the European, American, and Asian populations; however, no study that we found investigated the degree of agreement between the IDF and ATP definitions in Canada.

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1.7. Risk factors for Metabolic Syndrome

Several studies have been conducted to investigate the risk factors for Metabolic Syndrome. It has been shown that the prevalence of the Metabolic Syndrome is age dependent. Also, there is a negative association between physical activity and socioeconomic status and Metabolic Syndrome, and individuals with the marital distress have higher risk of developing the Metabolic Syndrome. It has been shown that the association between smoking, alcohol consumption and Metabolic Syndrome is complex.

I. AGE

Several studies have shown that the prevalence of Metabolic Syndrome was age dependent regardless of the definition (23,44-46). Some studies observed that the prevalence of Metabolic Syndrome reaches its peak in the seventh decade of life, and after that there was a decrease in the prevalence in both sexes or only in men (table 8).

Table 8. Association of Metabolic Syndrome with age

Author	Definition of MetS used	Sample population	Study design	Prevalence association with age
Hildrum, B et al (2007)	IDF ATP III	Norwegians men (n=5101) Norwegians men (n=5105)	Cross-sectional	Increase in both sexes
Azizi, F et al (2003)	ATP III	Iranian men (n=4397) Iranian women (n=5971)	Cross-sectional	Increase in both sexes
Sanisoglu, S. Y et al (2006)	IDF	Caucasian men and women (n=15468)	Healthy Nutrition for Healthy Heart Study /Cross-sectional	Increase in both sexes with peak in seventh decade
Hu, G et al (2004)	WHO	European men (n=6156) European women (n=5356)	11 prospective European cohort studies	Increase in both sexes with peak in seventh decade
Adams, R.J. et al (2005)	IDF ATP III	Australian men (n=1988) Australian women(n=2072)	Cross-sectional study	Men: increase Women: increase with a peak in seventh decade
Li, Z.Y et a l(2006)	ATP III	Chinese men (n=8801) Chinese women (n=7541)	Cross-sectional	Men: increase Women: increases with a peak in seventh decade

In a cross-sectional study among 10206 Norwegians aged 20-89 years, Hildrom et al used the IDF and the ATP III definitions. They found that the prevalence of Metabolic Syndrome increased with age in both sexes according to both definitions (23). Azizi et al recruited 4397 men and 5971 women older than 20 from the Tehran Lipid and Glucose Study. They applied the ATP III definition and found a similar pattern (20,45,47).

Sanisoglu et al obtained the data from the Healthy Nutrition for Healthy Heart Study which was conducted between 2000 and 2002 in Turkey. They recruited 15468 Caucasian men and women aged over 30 and applied the IDF definition for the syndrome. They found that the prevalence of Metabolic Syndrome was age dependent and there was a peak in prevalence in the seventh decade, followed by a decline for both sexes (44). The DECODE Study Group invited 11 prospective European cohort studies (Centers in Europe which conducted population-based studies or large studies in occupational groups) to participate in their study using the WHO definition. They studied 6156 men and 5356 women without diabetes aged between 30 and 89 years, and reported that the prevalence of Metabolic Syndrome was age dependent and peaked at the age 70 and then declined in both sexes, similar to Sanisoglu et al (20).

Adams et al conducted a cross-sectional study in 4060 Australian men and women older than 18 years, and applied the IDF and the ATP III definitions to define the syndrome. They found that prevalence of Metabolic Syndrome reached its peak at the seventh decade and with decline thereafter in men, but not in women (46). Similar pattern also found by Li et al. They conducted a cross-sectional study and applied the ATP III definition among Chinese population (8801 men and 7541 women) aged 20–90 years between 2003 and 2004. In this study participants were those who attended medical examinations, educational faculties and health officers (47).

II. SMOKING

There is a debate regarding the magnitude of association between smoking and the Metabolic Syndrome. Several studies reported that smokers are at a higher risk of developing Metabolic Syndrome than non-smokers (48-50). They interpreted their results as being the result of the association between smoking and some of the components of Metabolic Syndrome. Indeed, smoking can elevate blood pressure and triglyceride level, decrease HDL- cholesterol level, and impair insulin function (49,51-54). However, other studies have shown that smokers had lower prevalence of Metabolic Syndrome (55,56). These authors explained their results as being the result of the inverse relationship between smoking and obesity (56), which could lead to lower prevalence of the Metabolic Syndrome among smokers (table9) (55).

Table 9. Association between Metabolic Syndrome and smoking

Author	Definition of MetS used	Sample population	Study design	Association with smoking
Park, Y.W et al (2003)	ATP III	non-Hispanic blacks (n=3305), Mexican American (n=3477), non-Hispanic whites (n=5581)	Third National Health and Nutrition Examination Survey/ Cross-sectional	Risk factor Men: OR= 1.5(1.1-2.2) Women; OR=1.8(1.2-2.6)
Zhu, S et al (2004)	ATP III	American men(n=5415) American women (n=5824)	Third National Health and Nutrition Examination Survey/ Cross-sectional	Risk factor * Men: OR= 0.63(0.45-0.90) Women: OR=0.58(0.41-0.81)
Park, H.S et al (2004)	ATP III	Korean men (n=3937) Korean women (n=4713)	Korean National Health and Nutrition Examination Survey/ Cross-sectional	Risk factor Men: OR= 1.4(1.1- 1.8) Women: OR=0.58 (1.2-2.1)
Lee, W.Y et al (2005)	ATP III	Korean men (n=2059) Korean women (n=2282)	Cross-sectional	Risk factor OR=1.9 (1.1-3.7)
Santos, A.C et al (2007)	ATP III	Portuguese women (n=1332) Portuguese men (n=832)	Cross-sectional	Protective factor Light smokers: Women: OR=0.32(0.11–0.92) Heavy smokers: Men: OR=0.87(0.32–2.38) Women: OR=0.65(0.34–1.23)
Onat, A et al (2007)	ATP III	Turkish men (n=1674) Turkish women (n=1711)	Cohort	Heavy smokers: Men: OR= 0.84 (NS) Women: RR=0.5(0.26-0.94)

*OR for never smokers

Park et al used the data from the Third National Health and Nutrition Examination Survey (1988-1994), and applied the ATP III definition to diagnose the Metabolic Syndrome. They studied non-Hispanic blacks (n=3305), Mexican American (n=3477), and non-Hispanic whites (n=5581) older than 20 years of age. They excluded 5964 individuals for whom the information about anthropometric measurements and blood studies were not available. They found that the odds of having the syndrome was higher for current smokers compared to those who had never smoked in both sexes (Men: OR= 1.5; CI: 1.1-2.2, women; OR=1.8; CI: 1.2-2.6) (48).

Zhu et al obtained data from the Third National Health and Nutrition Examination Survey a year after Park et al conducted their study. They studies 5415 American men and 5824 American women. The purpose of their study was to investigate the lifestyle risk factors which were related to the Metabolic Syndrome. As expected, their results were similar to the results of the study by Park et al. They found that individuals who had never smoked had a lower odds ratio (OR) for developing Metabolic Syndrome than current smokers in both sexes (Men: OR= 0.63; CI: 0.45-0.90, women: OR=0.58; CI: 0.41-0.81) (50).

Park. H et al obtained data from the Korean National Health and Nutrition Examination Survey (3937 men and 4713 women). They applied the ATP III definition and investigated the lifestyle factors which could put individuals at a higher risk for having the Metabolic Syndrome. They found that current smokers individuals had higher odds of having the Metabolic Syndrome compared to individuals who had never smoked in both sexes (Men: OR= 1.4; CI: 1.1- 1.8, women: OR=0.58; CI: 1.2, 2.1) (49).

Le et al conducted a cross-sectional study among Korean individuals (2059 men, 2282 women) who underwent health check-ups to the Kangbuk Samsung Hospital in Seoul. They excluded subjects who received medication from their study. They defined the Metabolic Syndrome by the ATP III definition, and found that the relative risk of having the syndrome was higher among smokers than non-smokers (OR: 1.9; CI: 1.1-3.7) (51).

Santos et al conducted a study among Portuguese (1332 women and 832 men) aged 18–92 years old, and defined the syndrome by the ATP III definition. They found that smoking was a protective factor against developing the syndrome. They found that women who smoke less than ten cigarettes per day had a lower risk of developing the syndrome than non-smokers (OR: 0.32; CI: 0.11–0.92). Also, a similar pattern was observed for women and men who smoke between ten and twenty cigarettes per day (women; OR: 0.65, CI: 0.34–1.23, men; OR: 0.87; CI: 0.32–2.38), but the association was not statistically significant. However, both men and women who smoke more than twenty cigarettes per day had a higher risk of developing the Metabolic Syndrome but these associations were not significant (55). In a cohort study by Onat et al among Turkish adults(1674 men and 1711 women) found that women who smoke heavily had a lower risk of developing of Metabolic Syndrome presumably due to the inverse association between obesity and smoking (RR=0.5; CI: 0.26-0.94) (56).

III. ALCOHOL COSUMPTION

The relation between alcohol consumption and components of Metabolic Syndrome is complex. Several studies have reported that alcohol consumption was associated with higher HDL-cholesterol in a dose-response manner. A dose-response or J-shaped association also found between alcohol consumption and triglycerides. The association between alcohol consumption and hypertension was also reported as J-shaped, in fact; individuals who drank heavily were at risk of developing high blood pressure. Some contradictory studies showed that alcohol consumption was related to an increased risk of obesity both inversely and directly. It has been reported that individuals who were light or moderate drinkers had a lower risk of developing diabetes than heavy drinkers; their results were explained by the U-shaped relationship between alcohol consumption and insulin resistance. In fact, individuals who drank moderately had minimal insulin resistance; however, heavy-drinkers and never-drinkers had a higher level of insulin resistance (57,58).

There is considerable debate regarding the effect of consuming alcohol on the prevalence of Metabolic Syndrome (57,58). Alcohol consumption has been found to be either a risk factor (57) or a protective factor (58) in developing the Metabolic Syndrome. However, some studies reported that there was no significant association between alcohol consumption and development of the Metabolic Syndrome (table 10) (55,59).

Table 10. Association between Metabolic Syndrome and alcohol consumption

Author	Definition of MetS used	Sample population	Study design	Association with alcohol consumption
Alkerwi, A et al (2009)	ATP III EGIR WHO	7 studies	Meta-analysis	Protective factor Men: OR= 0.84(0.75-0.94) Women: OR=0.75(0.64-0.89)
Fan, A.Z et al (2006)	ATP III	American men (n=1150) American women (n=1668)	Case-control	Risk factor (intensity in quartiles) OR=1.23(0.91-1.67) OR=1.43(1.06-1.91) OR=1.60(1.2-2.30)
Park, H.S et al (2004)	ATP III	Korean men (n=3937) Korean women (n=4713)	Cross-sectional	No significant association Men: 15 g/day OR= 0.8(0.7- 1.1) 15 -day OR=1(0.8-1.5) ≥30 g/day OR=1(0.8-1.3) Women: 15 g/day OR= 0.8(0.7- 1.1) 15 -day OR=0.9(0.5-1.4) ≥30 g/day OR=1.7(0.9-3.0)
Rosell, M et al (2003)		Swedish men (n= 2039) Swedish women (n= 2193)	Cross-sectional	No significant association Men: wine: OR=0.75(0.48 – 1.20) beer: OR=0.88(0.55 – 1.41) spirits: OR=1.67(0.84 – 3.31) mixed OR=0.95(0.65 – 1.39) Women: wine: OR=0.60(0.40 – 0.91) beer: OR= 0.95(0.36 – 2.53) spirits: OR= 2.01(0.82 – 4.92) mixed: OR= 0.84(0.50 – 1.40)
Santos, A.C et al (2007)	ATP III	Portuguese women (n=1332) Portuguese men (n=832)	Cross-sectional	No significant association

Alkerwi et al performed a meta-analysis regarding the relationship between alcohol consumption and Metabolic Syndrome. They searched the MEDLINE and EMBASE data

bases from 1998 to 2007 to find studies which investigated the relationship between alcohol consumption and the prevalence of Metabolic Syndrome. They included only those studies which were cross-sectional, conducted in healthy populations, had a clear definition for Metabolic Syndrome, reported risk estimates, and quantified self-alcohol consumption. Among all 14 studies which met these criteria for eligibility, seven studies which did not report the results for both sexes were excluded from their meta-analysis. They converted alcohol consumption into a same unit (g/day) because different studies used different ways of measuring the alcohol consumption. They concluded moderate levels of that alcohol consumption reduced the prevalence of Metabolic Syndrome in both sexes (Men: less than 40 g/day, women: less than 20 g/day) (58).

Fan et al conducted a study in the healthy American population (men 1150, women 1668) aged 35-79 years and applied the ATP III definition. They investigated the relationship between life time drinking patterns and developing the Metabolic Syndrome. They measured the lifetime drinking pattern by calculating lifetime total drinks, total years of drinking, and intensity of drinking. They categorized each of these variables by quartiles. They reported that drinking intensity was a significant risk factor for the Metabolic Syndrome in the adjusted analysis. Prevalence ratios for Metabolic Syndrome according to the quartiles of intensity, which the first quartile was a reference category, were 1.23 (0.91-1.67), 1.43(1.06-1.91), and 1.60(1.2-2.30) (57).

Park H et al in a cross-sectional study in Korean population, as explained earlier, applied the ATP III definition and found that the consumption of alcohol was not significantly

related to the Metabolic Syndrome in both sexes. They categorized alcohol consumption into four categories based on the amount of alcohol consumed per day. Never-drinkers were considered as a reference category in their analysis. They found following results for men: less than 15 g/day (OR= 0.8; CI: 0.7- 1.1), between 15 and 30 g/day (OR=1; CI: 0.8-1.5), and greater than 30 g/day (OR=1; CI: 0.8-1.3). They reported the following results for women: none, less than 15 g/day (OR= 0.8; CI: 0.7- 1.1), between 15 and 30 g/day (OR=0.9; CI: 0.5-1.4), and greater than 30 g/day (OR=1.7; CI: 0.9-3.0) (49).

Rosell et al conducted a cross-sectional study among 60 year old Swedish men and women who lived in Stockholm County to investigate the association between intake of wine, beer, and spirits and Metabolic Syndrome. No significant association was found between alcohol consumption and Metabolic Syndrome. The odds of developing the Metabolic Syndrome in men who drinks wine, beer, spirits, and mixed were 0.75 (CI: 0.48 – 1.20), 0.88 (CI: 0.55 – 1.41), 1.67 (CI: 0.84 – 3.31), and 0.95 (CI: 0.65 – 1.39), respectively. The comparable numbers in women were 0.60 (CI: 0.40 – 0.91), 0.95 (CI: 0.36 – 2.53), 2.01 (CI: 0.82 – 4.92), and 0.84 (CI: 0.50 – 1.40), respectively (60).

In another study, Santos et al studied Portuguese adults, as previously discussed. They defined the Metabolic Syndrome by the ATP III definition and gathered information about the consumption of different types of alcoholic beverages (ethanol, wine, beer, and spirits). They gathered information about the frequency, quantity, duration of consumption, and total ethanol intake. They divided each of the alcoholic beverage variables into four categories based on the amount of alcohol consumed per day: 0.0 g,

0.1–9 g, 10–29 g, and ≥30 g. They reported there was no association between alcohol consumption (ethanol, wine, beer, and spirits) and Metabolic Syndrome (55).

IV. PHYSICAL ACTIVITY

It has been well documented that physical activity can reduce blood pressure, triglyceride levels, and abdominal obesity, while it can increase HDL cholesterol level (61-64). Many studies have shown that being physically active can reduce the prevalence of the Metabolic Syndrome (table 11) (36,49,64-66).

Table 11. Association between Metabolic Syndrome and physical activity

Author	Definition of MetS used	Sample population	Study design	Association with physical activity
Rennie, KL et al (2003)	ATP III	White European (n= 5153)	Cross-sectional	Protective factor OR=0.52(0.40-0.67) OR= 0.78(0.63-0.96)
Brien, S.E et al (2006)	ATP III	Canadian men (n=6406) Canadian women (n= 6475)	Cross-sectional	Protective factor men: OR=0.45(0.29-0.69) women: 0R=0.67(0.44-1.02)
Wamala, SP et al (1999)	WHO	Swedish women (n= 300)	Case-control	Protective factor* OR =2.82(1.46-5.44)
Ford, E.S. et al (2004)	ATP III	American men (n=812) American women (n=814)	National Health and Nutrition Examination Survey/Cross-sectional	Protective factor OR=1.90(1.22-2.97)
Park, H.S. et al (2005)	ATP III	Korean men (n=3937) Korean women (n=4713)	Cross-sectional	Protective factor Men: OR= 0.6(0.5-0.9) Women: OR= 0.9(0.6-1.5)

*OR for individuals who are not active

Rennie et al in a Whitehall II study of civil servants, a cross-sectional study of non-industrial civil servants aged 45–68 years who worked in London, investigated the association between self-reported physical activity and the Metabolic Syndrome. They applied the ATP III definition to measure Metabolic Syndrome. They used the Metabolic Equivalent of Task (MET) value to define the intensity of the activities. Leisure-time physical activity was categorized into moderate and vigorous activity classes. They divided the moderate activity into two categories (MET<24 and ≥24 MET hours per week), and vigorous activity into four categories (no vigorous activity MET <5, 5 ≤MET <12.5, and 12.5≤ MET hours per week). They reported that moderate and vigorous

physical leisure-time activity reduced the risk of having the Metabolic Syndrome. OR and CI for top categories of vigorous and moderate activity were 0.52 (CI: 0.40, 0.67) and 0.78 (CI: 0.63, 0.96) (64).

Brien et al obtained the data from the Canadian Heart Health Survey (1986–1992) to investigate the relation ship between physical activity and Metabolic Syndrome. They studied 6406 men and 6475 women aged 18–64 and applied the ATP III definition to define the Metabolic Syndrome. Participants were considered physically active if they were engaged in strenuous activity at least once per week for at least 30 minutes during the past 30 days. They found that active individuals had lower odds of developing the Metabolic Syndrome than non-active individuals. The odds ratios for Metabolic Syndrome for active versus non-active individuals in men and women were 0.45 (CI: 0.29–0.69) and 0.67 (CI: 0.44–1.02), respectively (36).

Wamala et al conducted a study among healthy Swedish healthy women between the ages 30 and 65 years, and defined the Metabolic Syndrome. They applied the WHO criteria to assess physical exercise which has four categories: individuals who are involved in sedentary leisure activities (Grade I), individuals who do some form of activity such as walking or cycling (Grade II), individuals who engage in physical activity at least four hours per week (Grade III), and individuals who do vigorous training several times a week (Grade IV). They reported that a lack of physical exercise increased the odds of developing Metabolic Syndrome (OR= 2.82; CI: 1.46–5.44) (65).

Ford et al obtained the data from the National Health and Nutrition Examination Survey (1999-2000) including 812 men and 814 women. The ATP III definition was used. They asked participants to report the frequency and the duration of moderate or vigorous physical activity. They calculated the total minutes that participants were engaged in moderate or vigorous physical activity per week and divided it into three categories: 0, <150, and ≥150 min/wk. They reported that individuals who did not participate in any moderate or vigorous physical activity had higher odds of developing the Metabolic Syndrome than those who engaged in more than 150 min/wk activities in unadjusted analysis (OR=1.90; CI: 1.22 to 2.97). However, although the odds were higher after adjustment for age, sex, ethnicity, educational status, smoking status, and alcohol consumption, the association between physical activity and the Metabolic Syndrome was not significant (OR=1.46; CI: 0.87-2.45) (66).

Park et al used the ATP III definition to define the Metabolic Syndrome and conducted a cross-sectional study among 3937 Korean men and 4713 Korean women to investigate lifestyle risk factors for Metabolic Syndrome. They obtained information from participants about the frequency and extent of physical exercise per week during the past month. They split the variable into four groups: not at all, once per week, 2–3 times per week, or ≥4 times per week. They adjusted their model for age, residential area, marital status, educational status, occupation, smoking status, BMI, alcohol consumption, and carbohydrate intake. They reported that although physical activity decreased the odds of developing the Metabolic Syndrome , their association was statistically significant only in men who engaged moderate exercise (OR= 0.6; CI=0.5- 0.9) (49).

V. MARITAL STATUS

Some studies suggested that marital distress is associated with cardiovascular mortality and morbidity in both women and men (67,68). There is limited information available about the association between Metabolic Syndrome and marital status (table 12).

Table 12. Association between Metabolic Syndrome and marital status

Author	Definition of MetS used	Sample population	Study design	Association with marital status
Troxel, W.M. et al (2005)	ATP III	American women (n=413)	Longitudinal	Marital dissatisfaction: OR=3.02(1.46-6.24) Divorced: OR=2.47(1.02-5.97) Widowed: OR= 5.82(1.88-18.03)
Park, H.S. et al (2004)	ATP III	Korean men (n=3937) Korean women (n=4713)	Cross-sectional	Men: OR= 0.9 (0.6-1.4) Women: OR=2 (1.2-3.3)

Troxel et al conducted a prospective study in 413 American women aged 42- 50 years and followed up them for 11 years to investigate the presence or absence of Metabolic Syndrome at the last contact. Participants visited five times: baseline, one year postmenopausal, and every three years postmenopausal. Participants were asked about their marital status and completed a questionnaire to assess satisfaction with marital status. They applied the ATP III definition to diagnose the Metabolic Syndrome, which was assessed at the baseline and latest follow up visit. They found that maritally dissatisfied (OR=3.02; CI: 1.46-6.24), divorced (OR=2.47; CI: 1.02-5.97), and widowed women (OR= 5.82; CI: 1.88-18.03) had higher risk of developing the Metabolic Syndrome than maritally satisfied women. They justified their results by explaining that

not having a relationship or marital distress can act as a psychosocial stressor which can increase the risk of developing Metabolic Syndrome. Also, marital distress had a negative effect on immune-inflammatory response which can lead to CVD events (69).

Park et al conducted cross-sectional study among 3937 Korean men and 4713 Korean women, found that unmarried women had a higher risk of developing Metabolic Syndrome than married women (OR=2; CI: 1.2-3.3), but no significant association between marital status and Metabolic Syndrome was found in men (49).

VI. SOCIEOECONOMIC STATUS

Several studies have shown that low socioeconomic status (SES), are determined by income or educational level, is a risk factor for the development of cardiovascular disease (70). The association between the individual components of the Metabolic Syndrome and cardiovascular disease risk factors has been demonstrated by many researchers. A low SES was associated with hypertension, impaired glucose tolerance, diabetes, physical inactivity, and obesity (48,70-76). Lee et al also explained that low socioeconomic status can cause mental and social stress which can subsequently activate hypothalamus-pituitary-adrenal axis and causing obesity (51).

Most studies agree that there is an inverse relationship between Metabolic Syndrome and the development of socioeconomic status(43,48,65,73,77-80).However, a few studies observed that there was no association (table 13) (49,81).

Table 13. Association between Metabolic Syndrome and socioeconomic status

Author	Definition of MetS used	Sample population	Study design	Socioeconomic status	
				level of education	income
Ana, S et al (2008)	ATP III	Portuguese men (n=1207) Portuguese women (n=755)	Nutrition survey/ Cross-sectional	Inverse	-
Loucks, E.B et al (2007)	ATP III	American men (n= 7895) American women (n= 8821)	Third National Health and Nutrition Examination Survey/ Cross-sectional	Inverse	-
Dallongeville, J et al (2005)	ATP III	French men (n= 1695) French women (n=1644	Population survey/ Cross-sectional	Inverse	Inverse
Brunner, EJ et al (1997)	ATP III	British men (n=4978) British women (n=2035)	Cross-sectional	-	Inverse
Wamala, SP et al (1999)	ATP III	Swedish women (n= 300)	Case-control	Inverse	-
Silventoinen, K et al (2005)	ATPIII WHO	Finnish men (n=864) Finish women (n=1045)	Longitudinal	Inverse	-
Park, M.J et al (2007)		Korean men (n=3657) Korean women (n=4884)	Korean National Health and Nutrition Examination Survey/ Cross-sectional	Inverse	Inverse
Park, Y.W et al (2003)		American men (n=6145) American women (n=6680)	Third National Health and Nutrition Examination Survey/ Cross-sectional	No association	Inverse
Park, H.S. et al (2004)	ATP III	Korean men (n=3937) Korean women (n=4713)	Cross-sectional	No association	No association

Santos et al recruited 1207 men and 755 women from a health and nutrition survey, of a representative sample of the non-institutionalized Portuguese, to investigate the association between socioeconomic status and the Metabolic Syndrome. They applied the ATP III definition to define the syndrome, and considered total years of education (<5, 5-12, ≥12) and social class (five classes) as indicators of socioeconomic status. Social class was defined based on people occupation and registrar five social classes which people in the highest social class will be considered as class I. They found that there was inverse relationship between level of education of women and risk of developing Metabolic Syndrome. (0-4 years of education: OR= 2.28; CI: 1.48-3.51, 5–11 years of education: OR=1.49; CI: 0.93-2.36). Also, there was an inverse relationship between social class (social class I has been considered as a reference category) and risk of development of the Metabolic Syndrome (social class III (OR=1.85; CI: 0.89-3.85), IV (OR=2.56; CI: 1.45-5.72), and V (OR=2.13; CI: 0.97-4.70). In men, the magnitude of association was similar to women, but the association was not significant. They also concluded that social and economic situation had more effect on women than on men in developing Metabolic Syndrome (77).

Loucks et al obtained data from the Third National Health and Nutrition Examination Survey to investigate the association between socioeconomic status and Metabolic Syndrome in American adults. Socioeconomic status was determined by total years of education and poverty income ratio (PIR which is calculating by dividing the midpoint of family income category to the official poverty threshold which is published by USA census). Odds of developing the Metabolic Syndrome were higher for individuals with

less than 12 years of education than for individuals with more than 12 years education (men: OR= 1.27; CI: 0.97-1.66, women: OR=1.77; CI: 1.39-2.24). They also reported that women in the low PIR group (≤1) had a higher risk of developing the syndrome than women in the high PIR group (>3) (OR: 1.98; CI: 1.50-2.62), but this association was not significant in men (OR= 0.98; CI: 0.74-1.29). As explained by the researchers, socioeconomic status had a greater influence in women than men with respect to development of the Metabolic Syndrome (78).

Dallongeville et al conducted a study among (1695 French men, 1644 French women) to investigate the association between household income and the Metabolic Syndrome, as defined by the ATP III criteria. They reported that education level was inversely associated with developing the Metabolic Syndrome in both men and women. Household income and Metabolic Syndrome were inversely associated in women, but not in men. They also believed that the association between socioeconomic status and the Metabolic Syndrome had a sex-pattern (80).

Brunner et al recruited data from the Whitehall II study phase three. Their study included 4978 British men and 2035 British women aged 39-63 years, and applied the ATP III criteria to define the syndrome. Six employment grades, as indicators of socioeconomic status, were defined based on annual salary. Grade 1 (£ 28904-87620), grade 2 (£ s 25 330-36 019), grade 3 is Senior Executive Officer (£ 18 082-25 554), grade 4 is Higher Executive Officer (£ 14 456-20 850), grade 5 Executive Officer (£ 8517- 16,668) and

grade 6 Clerical and Office Support staff (£ 6483- 11 917). There was an inverse association between the employment grade and the Metabolic Syndrome (73).

In another study among healthy Swedish women aged 30-65 years, Wamala et al examined the association between level of education and the Metabolic Syndrome. The ATP III definition was used. Education level was divided into three categories; low education (≤ 9 years), middle level of education (10-13 years), and high level of education (≥14 years). Their results showed that women in the lowest education category had greater odds of having the syndrome than women in the highest group (OR=2.34; CI: 0.98-5.84). Also, results showed that women with middle education level had lower risk of development of Metabolic Syndrome than women in the highest group , but the association was not significant (OR=1.27; CI: 0.39-4.14) (65).

Silventoinen et al conducted a longitudinal study among middle aged (45-65) Finnish men (864) and women (1045) without a history of coronary heart disease. The study used the ATPIII and the WHO definitions to define the Metabolic Syndrome. They followed up participants to investigate whether they develop CHD events over ten years, and considered death or hospitalization due to CHD as outcome variables. They observed that there was an inverse association between education level and Metabolic Syndrome. Their results also showed that there was an educational gradient in development of CHD events after the adjustment for the Metabolic Syndrome in their analysis (HR=0.73; CI: 0.52-1.04) (79).

Park et al obtained the data (men=3657, women=4884) from the Korean National Health and Nutrition Examination Survey (2001) to examine the association between education or income level and the Metabolic Syndrome. The inverse relationship found between education (7-9 years, 10-12 years, and >12 years), income level (low, middle, high), and Metabolic Syndrome was only significant in women, not in men (59).

Park et al in a study of American adults, as discussed earlier, considered education level and income level as measure of socioeconomic status. They found that women with household incomes of less than $15000(low income) had higher odds of developing Metabolic Syndrome (OR=1.5; CI: 1.0-2.3) than women with household income greater than $25000(high income). They did not find any significant association between level of education and the Metabolic Syndrome in either sexes (48).

Park et al in a cross-sectional study among Korean adults, as explained previously, found that there was no association between income or education level and Metabolic Syndrome in both sexes (49).

VII. EMPLOYMENT

A few studies evaluated the association between Metabolic Syndrome and employment status. There is a debate regarding the association of these two variables. Most studies agree that employment is a protective factor (49,77), but a few studies reported that it was a risk factor (table 14) (82).

Table 14. Association between Metabolic Syndrome and employment status

Author	Definition of MetS used	Sample population	Study design	Association with employment status
Park, H.S. et al (2004)	ATP III	Korean men (n=3937) Korean women (n=4713)	Cross-sectional	Unemployment: Men OR= 2.0(1.4-2.8) Women OR=1.7(1.0-2.7)
Ana, S et al (2008)	ATP III	Portuguese women (n=1332) Portuguese men (n=832)	Nutrition survey /Cross-sectional	Women: Retirement OR=1.48(0.96-2.27) Housewife: OR=1.77(1.16-.7)
Lucove, J.C et al (2007)	ATP III	African Americans (n= 1006)	Longitudinal	Employment Men: OR= 0.48(0.12-1.87) Women: OR= 1.52(1.04-2.21)

Park et al in a cross-sectional study among Korean adults found that unemployed individuals had a higher risk of developing Metabolic Syndrome than employed individuals; men (OR= 2.0; CI: 1.4-2.8) and women (OR=1.7; CI: 1.0-2.7) (49). Santos et al also found that being retired (OR=1.48; CI: 0.96-2.27) or a housewife (OR=1.77; CI: 1.16-.7) were risk factors for developing the Metabolic Syndrome in women. In men, although the odds of developing Metabolic Syndrome for retirees or homemakers were higher, their association was not significant (77).

Lucove et al obtained data from the Pitt County Study, a prospective study, started in 1988 with two follow up visits (1993 and 2001), to investigate the risk factors for the development hypertension . They obtained information about the components of Metabolic Syndrome and employment status of participants in their first visit.

Participants with normal blood pressure were invited for the first follow up visit. Their results showed that being employed was a risk factor for developing the Metabolic Syndrome (OR= 1.52; CI: 1.04-2.21) in women, and a protective factor in men (OR= 0.48; CI: 0.12-1.87) (82).

1.8. Metabolic Syndrome and cardiovascular disease

The association between the components of Metabolic Syndrome and cardiovascular disease incidence and mortality has been shown in several studies (83-86).
Also, several studies showed that the risk of developing cardiovascular events was higher in people with the Metabolic Syndrome than those without the syndrome (21,22,87,88). As explained earlier, the prevalence of the syndrome varies based on the definitions of the Metabolic Syndrome used, and there is dilemma regarding which definitions should be used in clinical practice and research (12). The main purpose of the definitions is to identify individuals who have a higher risk for developing CVD and diabetes. Thus, one of the best ways to answer these questions would be comparing the definitions regarding their predictive accuracy of CVD events and mortality. Several studies compared CVD mortality and all cause mortality by applying different definitions. Yet these studies varied as to the baseline population, the number of deaths, modification of the definitions and adjustment for different potential confounders in the analyses. Thus, these issues make the comparison of studies difficult (89).

Ford et al in a meta-analysis searched the PubMed database from 1998 to 2005 to find studies which examined the association between Metabolic Syndrome and cardiovascular disease. To be included, studies needed to be prospective, and used the WHO, the ATPIII, or modified definitions. Twenty one studies were included; follow up years ranged from 3 to 13.5 years. Covariates considered as potential confounders were varied in different studies. The population-attributable fraction for cardiovascular events for subjects with Metabolic Syndrome was calculated by Ford et al. In the formula the

prevalence of the syndrome was considered 21.8% and relative risk was obtained from the meta-analysis. Risk of developing of cardiovascular events was higher for individuals with the syndrome than those without the syndrome when the precise definitions of Metabolic Syndrome were applied. (ATP III RR=1.65; CI: 1.38-1.99, WHO RR=1.93; CI: 1.39-2.67). Also, similar results were found when the studies which used the exact or modified definition were pooled together (ATP III RR=1.74; CI: 1.43-2.12, WHO RR=2.06; CI: 1.72-2.47). RR was higher in those studies which included individuals with diabetes (2.2) than those studies which did not include individuals with diabetes (1.58). The population-attributable fraction was 12% and 17% when the ATP and the WHO definition were applied, respectively (87).

Galassi et al, in another a meta-analysis, searched the MEDLINE data base from 1966 to 2005 to find studies which investigated the association between the Metabolic Syndrome and risk of cardiovascular disease. They included those studies which had prospective design and applied the WHO, the ATP, or modified definitions. Among eligible studies, only those studies were included in which the end points were non-fatal cardiovascular events, cardiovascular mortality, or all cause mortality, and those which calculated relative risk (RR), hazard ratio, or odds ratio. Twenty one studies, 11 in the US and 10 in Europe, met the inclusion criteria. Sixteen, five, and two studies used the ATP, the WHO, and both definitions, respectively. The range of follow- up period was between 2.8 years and 13.5 years. Cardiovascular disease mortality was reported to be higher in individuals with the Metabolic Syndrome than those without the syndrome (men RR=1.5; CI: 1.41-1.75, women RR=2.1; CI: 1.79-2.45). The pooled RR was higher for studies applying the

WHO as opposed the ATP definition (WHO RR=1.82; CI: 1.27-2.61, ATP III RR=1.61; CI: 1.42-1.83) (21).

One year later, Gami et al conducted another meta-analysis with a more comprehensive search. They searched MEDLINE (from 1966 till 2005), Ovid EMBASE (from 1988 till 2005), Web of Science (from 1993 till 2005), abstracts were presented in scientific sessions in 2003 and 2004, and studies were that referenced Reaven's article. The following studies were included: cohort studies or randomized trials, studies that reported risk estimates or its synonym, and studies that reported non-fatal cardiovascular events or CVD mortality. Follow-up times ranged from 2.2 to 18.8 years. Thirty seven studies met the inclusion criteria. Six studies used the WHO, twelve the ATP III, four modified WHO, and ten modified ATP definitions. 5 studies used factor analysis, which means to create a variable which was nearly similar to the components of the Metabolic Syndrome in the WHO or ATP definitions. The results showed that individuals with Metabolic Syndrome had a higher risk of non-fatal cardiovascular events or CVD death than those without the syndrome (RR=1.78; CI; 1.58-2.00). Seven studies estimated the RR for both sexes; the risk of cardiovascular events was higher in women than men in those studies (RR 2.63 VS 1.89; p=0.09). Their results also showed that the WHO definition predicts cardiovascular events better than the ATP III definition (RR 2.68 vs 1.35; p=0.005) (22).

Qiao et al analyzed data from the DECODE study. The DECODE study included nine European population based cohort studies which primarily examined the prevalence of diabetes in European adults. Studies were started around 1990, and the follow-up was

between 6.6 to 16 years. Qiao et al studied 4715 men and 5554 women, aged 30-89 years. They used the ATP, IDF, and the WHO definitions of Metabolic Syndrome. They found that CVD mortality was higher for individuals with Metabolic Syndrome than without the syndrome for both sexes regardless of the definition. Hazard Ratio for CVD mortality in men were 2.09 (CI: 1.59-2.76), 1.74 (CI: 1.31-2.30), and 1.51(CI: 1.15-1.99) according to the WHO, the ATP, and the IDF definitions, respectively. The comparable numbers in women were 1.60(CI: 1.01-2.51), 1.39(CI: 0.89-2.18), and 1.53 (CI: 0.99-2.36). They conclude that all definitions can predict the CVD mortality, but the association was weaker in women regardless of definition (90).

Katzmarzyk et al studied 20789 men aged 20-83 years from Aerobics Center Longitudinal Study in the USA. They examined the association between the Metabolic Syndrome and CVD mortality and all cause mortality by using ATP III (2001 and 2005) and the IDF definitions. The results showed that RR for CVD mortality was 1.79(1.35-2.37), 1.67(1.27-2.19), and 1.67(1.27-2.20) according to the ATP III 2001, ATP III 2005, and IDF definitions, respectively. As shown in the results, the ability of the IDF and ATP III to predict mortality was almost the same (40).

Nilsson et al used that data from the Malmo Diet and Cancer study. The study was started in 1992, and participants were followed until 2003. The primary purpose of the study was to examine which definition of Metabolic Syndrome will best predict cardiovascular events, which has been defined as fatal or non-fatal myocardial infarction (MI; ICD-9 code 410), fatal or non-fatal stroke (ICD-9 codes 430, 431, 434, 436), or death due to

ischemic heart disease (ICD 410–414). They recruited 3382 non-diabetic women and 1665 non-diabetic men. They defined the syndrome by the ATP III, the IDF, and the EGIR definitions. The prevalence of the syndrome was higher by the IDF definition than the ATP III definition in both men and women after adjusting for age, sex, LDL, smoking, alcohol intake, level of education and physical activity. Adjusted Hazard ratios for CVD events in men according to the ATP, the EGIR, and the IDF definitions were 1.71(CI: 1.26-2.31), 1.33(CI: 0.97-1.82), and 1.17 (CI: 0.85-1.60), respectively. The corresponding numbers in women were 1.45(CI: 0.97-2.17), 1.42 (CI: 0.92-2.18), and 1.05(0.68-1.62). As a result, they concluded the IDF definition was not better than other definitions at predicting CVD events (91).

Wang et al conducted a cohort study between 1988 and 2001 to examine the relationship between the Metabolic Syndrome and CVD (ICD-9 codes 390 to 459), CHD (ICD-9 codes 410 to 414), and all-cause mortality among non-diabetic Finnish people (377 men, 648 women) aged 65-74. The syndrome was defined by the WHO, the APT III (2001 AND 2005), the IDF, and the ACCE definitions. In men, the syndrome predicts the CVD mortality by WHO, the ACCE definitions, both versions of ATP III definitions (borderline significant). However, in women, none of the definitions predicted CVD mortality. Hazard ratios for CVD mortality in men were 1.43(CI:1.00-2.03), 1.32 (CI:0.93-1.98),and 1.34(CI:0.94-1.92), and 1.27(CI:0.89-1.82), 1.29(CI:0.89-1.87),and 1.32(CI:0.90-1.94) in women, according to the ATP III (2001), ATP III (2005), and the IDF definitions, respectively (89).

Benetos et al studied French men (55794) and women (28963). Participants had no CVD at the baseline of study and were followed for five years. At the end of the study period cause of death were obtained from death certificates. The syndrome was defined by the ATP III (2001 and 2005) and the IDF definitions. Hazards of CVD mortality were 2.05(1.28-3.28), 1.64(1.08-2.05), and 1.77(1.18-2.64) according to the ATP III (2001), ATP III (2005), and the IDF definitions, respectively (92).

Choi et al used the data from the 2001 Korean Nation Health and Nutrition Survey, which was nationally representative of the Korean population, to compare the association between the Metabolic Syndrome and cardiovascular disease. Men (2583) and women (3381), 20 years and older were included in this study and the Metabolic Syndrome was defined by the ATP III and the IDF definitions. The results showed that the prevalence of the Metabolic Syndrome was higher according to the IDF definition (23.9 %) than the ATP III definition (20.5%), while it was reversed in men (IDF:15%, ATP III 17.8%). Also, the odd of developing coronary artery disease were 2.3 (CI: 1.2-4.3) and 1.5 (0.8-2.7) by the ATP III and the IDF definitions, respectively (93).

Koutsovasilis et al conducted a cross-sectional study among 211 patients who were admitted to hospital for the first time for acute coronary syndrome (ACS) between 2006 an 2007. A control group of 210 individuals who had chest paint with no cardiac origin was included in this study. They used the ATP (2001 and 2005) and the IDF definitions to define the syndrome. The corresponding prevalence of the Metabolic Syndrome among patients with ACS were 72.5%, 81.2%, and 79.1%. The significant association between

the Metabolic Syndrome and developing the ACS was only observed when the IDF definition applied (IDF OR=2.23; CI: 1.30-3.82, ATP III- 2001 OR=1.13; CI: 0.63-2.00, ATP III-2005 OR=1.42; CI: 0.79-2.56) (94).

1.9. Metabolic Syndrome versus other assessment tools

There is a debate regarding the ability of Metabolic Syndrome to predict CVD events in comparison with other assessment tools such as Framingham Risk Score (FRS) (32). Some studies suggested that the Metabolic Syndrome was inferior to the Framingham Risk Score (FRS) in the prediction of CVD events (95-97). However, other studies agreed that the syndrome was a superior predictor of CVD than the FRS (98,99).

McNeil et al conducted a longitudinal study, between 1987 and 1989, to examine the association between the Metabolic Syndrome and cardiovascular events. The ATP III definition was used. 12089 black and white Americans men and women aged 45-64 who lived in North Carolina, Mississippi, Minnesota, and Maryland were included in the study. They calculated the Framingham Risk Scores for the participants and divided the scores into two categories (<10% and ≥10%). They also generated the receiver operating characteristics (ROC) curves to examine whether Metabolic Syndrome can predict the CHD better than the FRS. The results showed that hazard ratios for developing CHD were higher in subjects with Metabolic Syndrome than those without the syndrome (men HR=1.46; CI: 1.23-1.74, women HR=2.05; CI: 1.59-2.64). Also the results showed that individuals with the Metabolic Syndrome within lower strata (FRSs<10%) had a higher incidence of CHD than those without the syndrome within the same strata.

(men 90.3 vs 65.4, women 52.2 vs 21.8). The similar results were also found for individuals at higher strata, FRSs≥10%. (men 164.6 vs 133.8, women not estimable in women). According to the ROC curves, they explained the Metabolic Syndrome did not predict CHD events better than the FRS (men 0.631 vs 0.634, women 0.729 vs 0.731). However, they explained that individuals who had Metabolic Syndrome had higher risk of developing CHD than those without the syndrome within the same the FRSs category. They explained that, by using the FRS clinicians can identify individuals who are at the later stage of development of CVD events, while by identifying individuals with the syndrome clinicians can identify individuals who are at the earlier stage (95).

Another prospective study was conducted between 1979 and 2000 by Wannamethee et al to compare the Metabolic Syndrome and the FRS regarding their ability in prediction of CHD, stroke, and diabetes. 5128 British men without history of CHD, stroke and diabetes from 24 towns in England, Wales, and Scotland were included in the study. They used the ATP III definition. The results showed that individuals with the Metabolic Syndrome had a higher risk of developing CHD, stroke and diabetes than those without the syndrome. According to the ROC curves the FRS was a better predictor than the Metabolic Syndrome for CHD (68% vs 59 %), while the syndrome was a better predictor for diabetes than the FRS (70% vs 60%). They also concluded that even though the syndrome was not a better predictor for CHD events, it could be considered as a tool which can identify individuals who were at the risk of development of CHD (96).

Stern et al obtained the data from the San Antonio Heart Study to investigate whether the Metabolic Syndrome had a better predict ability in prediction of diabetes and CVD events than the FRS. The ATP III definition was applied in the study. 1079 individuals without diabetes and CVD were followed for eight years. The results showed that the Metabolic Syndrome could predict the CVD with a sensitivity and false positive rate of 67.3% and 34.2%, respectively. However, they fixed the false-positive rate at 34.2 % to calculate sensitivity for the FRS, and found a higher value (81.4%). They also fixed the sensitivity at the 67.3% and calculated the false positive ratio for the FRS, and found a lower value (20.0).They suggested that the Metabolic Syndrome could not provide any additional information regarding the prediction of CVD events compared to the FRS (97).

Girman et al in obtained data from the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). These studies were double blind clinical trail in patients with hypercholestromia and primarily were designed to investigate the effect of simvastatin on mortality and morbidity. Girman et al recruited data from the placebo groups of both studies (4S: 2223, AFCAPS/TexCAPS: 3301). The ATP III definition was used. They calculate the FRSs, in both studies, for having the cardiovascular events and classified the participants into two groups (FRS≤ 20%, FRS>20%). The cardiovascular events were higher in subjects with the syndrome than subjects without the syndrome in both studies (4S HR=1.46; CI: 1.20-1.79, AFCAPS/TexCAPS HR=1.40; CI: 1.04-1.89). The results demonstrated that individuals who had the Metabolic Syndrome within each categories (FRS≤ 20% or FRS>20%) had higher risk of developing the cardiovascular events than those without

the syndrome within the same category. They also reported that the Metabolic Syndrome could improve the prediction of the CVD events compared to FRS alone (99).

Dekker et al obtained the data from the Hoorn study, which was a Dutch cohort study which started in 1989 and ended in 2000. 615 men and 749 women without diabetes and CVD were included in this study. The ATP III, the WHO, the IDF, and the EGIR definitions were used, and the FRSs were calculated. The hazard ratio for developing nonfatal CVD were significantly higher in men with the syndrome according to the ATP III and the WHO definitions compared with those without syndrome after adjustment for the FRS (ATP HR= 1.64; CI: 1.11–2.44, WHO HR= 1.44; CI: 1.01–2.04, EGIR HR= 1.48; CI: 0.99–2.19, ACE HR= 1.06; CI: 0.74–1.53) . Regardless of definitions, after adjustment for the FRS, the hazard ratios of risk of nonfatal CVD were higher in women with the syndrome than those without the syndrome, but these associations were not significant (ATP HR= 1.17; CI: 0.73–1.87, WHO HR= 1.31; CI: 0.85–2.02, EGIR HR= 1.21; CI: 0.75–1.95, ACE HR= 1.31; CI: 0.81–2.10) (98).

2. Research Objectives

As we discussed, there is limited information available about the prevalence of Metabolic Syndrome, its trend over time and its predisposing risk factors in Canadian adults. No study has compared the prevalence of Metabolic Syndrome and its associated risk factors according to different definitions (NCEP and IDF) in Canada. Most studies examined the association between Metabolic Syndrome and all-causes mortality among non-Canadian population. To our knowledge, no studies have compared the ability of NCEP and IDF to predict CVD mortality among Canadian adults. This thesis will determine the prevalence of Metabolic Syndrome in 1986-1995 by using different definitions to establish the base line for future research, investigate metabolic associated risk factors, and examine the relation between Metabolic Syndrome and CVD mortality in Canadian adults.

Objective 1: To examine the age and sex specific prevalence of the Metabolic Syndrome in Canadian adults by using the National Cholesterol Education Program and International Diabetes Federation definitions.

a) To examine the prevalence of the single components of the Metabolic Syndrome definition and their relationship to defined Metabolic Syndrome.

Objective 2: To examine the risk factors for Metabolic Syndrome in Canadian adults by using the National Cholesterol Education Program and International Diabetes Federation definitions.

Objective 3: To examine the association between Metabolic Syndrome and cardiovascular disease mortality in Canadian adults by using two definitions, National Cholesterol Education Program and International Diabetes Federation.

3. Manuscripts

The Effect of Definition on the Prevalence of Metabolic Syndrome and its Components

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Abstract

Title: The Effect of Definition on the Prevalence of Metabolic Syndrome and its Components.

Background: No studies have compared the prevalence of Metabolic Syndrome (MetS) among Canadian adults using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) and the International Diabetes Federation (IDF) definitions.

Objective: The purpose of this study was to examine the sex specific prevalence of MetS in Canadian adults by using ATP III and IDF definitions, to establish a base line for future research, and to determine the effect of definition on the prevalence of the component factors.

Methods: The Canadian Heart Health Survey was a cross-sectional probability sample survey of 23179 adults ages 18-74, conducted in all 10 Canadian provinces between 1986 and 1992 .The present study was based on 4724 men and 4712 women for whom full anthropometric measurements were obtained (provinces of Alberta, Manitoba, Ontario, Quebec and Saskatchewan) and for whom data on all components of MetS were available. MetS was defined according to ATP III and IDF definitions. A weighted analysis using SPSS PASW Complex Samples (version18) was conducted.

Results: According to ATP III, 17.9% and 15.3% of men and women have MetS, while according to IDF, 23.8% and 17.3% of men and women have MetS, respectively. Kappa agreement between the definitions was 72 % for men and 80% for women ($p \leq 0.05$). In men who have MetS according to IDF 68.3%, 86.8%, 78.3%, and 15.4% have low high-density cholesterol, high triglyceride, hypertension, and diabetes, respectively, versus

79.9%, 93.1%, 87.3%, 17.7% according to ATP III ($p \leq 0.001$). In women, the comparable levels of prevalence are 78.8%, 77.6%, 76.2%, 15.3% according to IDF, and 83.3%, 79.2%, 82.6%, 20.5% according to ATP III ($p \leq 0.001$).

Conclusion: In Canadian adults the prevalence of MetS is higher when the IDF definition is applied but the metabolic derangement of individuals identified is less severe. This may have implications for the prognostic value of the two definitions.

Key words: Metabolic Syndrome, insulin resistance syndrome, insulin resistance, definition.

1. Introduction

The Metabolic Syndrome has been known under different names, such as "syndrome X", "the insulin resistance syndrome", and the "deadly quartet (1-3).

This concept was introduced by Kylin for the first time in 1920 as a clustering of some risk factors which include hypertension, hyperglycemia, and gout. Some years later, Vague explained that there is an association between upper body adiposity and the development of some metabolic abnormalities in people with cardiovascular disease and diabetes. The clinical importance of Metabolic Syndrome was described by Reaven in 1988 which explained Metabolic Syndrome as a cluster of insulin resistance, hyperglycemia, hypertension, low HDL-cholesterol, and raised VLDL-triglycerides (1-6).

After this concept had been accepted by researchers and clinicians, different scientific organizations developed various definitions to standardize investigation of this syndrome. The essential components of their definitions include glucose intolerance, obesity, hypertension, and dyslipidemia (1,2,7,8).

The World Health Organization (WHO) published the first definition in 1999 (2,7,9). After that the European Group for the study Insulin Resistance (EGIR) modified the WHO definition (1,2,7,10). In 2001, the U.S.A National Cholesterol Education Program developed the ATP III definition, which later was modified by the American College of Endocrinology (AACE) (1,2,7). In 2005, the National Cholesterol Education Program modified their first definition and the International Diabetes Federation (IDF) developed a new definition (8). In 2009, IDF and National Cholesterol Education Program groups attempted to unify these criteria (11).

It has been shown by several studies that the risk of developing Cardiovascular disease and diabetes is higher among people with MetS compared to people without MetS (4,12-15). It has been recommended by the American Heart Association and the International Diabetes Federation that individuals with MetS should undergo CVD risk assessment and also receive ongoing follow-up. Thus identifying people with MetS has undeniable impact on both patients and public health care system (3,16,17).

Several studies compared differences in prevalence of depending on definitions, but there is a debate regarding the choice of definition, which definition identifies individuals with more adverse metabolic profiles, which is more suitable for clinical practice, and which better predicts future CVD events (3,17-24). According to Cameron et al noted the prevalence of MetS varied considerably in different studies because of different study designs, study population, and definitions of the Metabolic Syndrome (1,7) . It would therefore be very important to develop a widely accepted, unified definition of this important syndrome (3,11,25).

Although several studies have been done to estimate the prevalence of MetS in Europe and USA, little is known about the prevalence of MetS in the Canadian population. Arden et al (26), in a population study of 7981 Canadians, reported that the prevalence of Metabolic Syndrome according to the ATP III definition was 17 % in men and 13.2 % in women between 1986 and 1992 (26). In another study conducted between 1986 and 1992 among 12881 Canadians aged between 18-64 that was, Brien et al reported that the prevalence of Metabolic Syndrome according to the ATP III definition was 17.5% and 11.2 in men and women, respectively (27). Riediger et al in a cross sectional study which was conducted between 2007 and 2009, first cycle of Canadian Health Measures Survey,

reported that prevalence of Mets was 15.9 in Canadian men and 19.5 in Canadian women according to the ATP III definition (28). Although several studies compared the prevalence of MetS according to different definitions, and degree of concordance between different definitions in the European and American population, to our knowledge no study has compared the prevalence of Metabolic Syndrome by the ATP III and the IDF definition nor investigated the degree of agreement between these two definitions in Canada. Liu et al (29)compared the prevalence of Metabolic Syndrome among three ethnic groups in Canada and found a moderate agreement between the ATP III and the WHO definitions (kappa agreement= 0.63) (3,29).Therefore, the purpose of this study was to examine the sex specific prevalence of MetS in Canadian adults by using the ATP III and the IDF definitions and to determine the effect of definition on the prevalence of the component factors and to assess the concordance between these definitions. Although the prevalence of Mets in Canadian population has been reported recently by Riediger et al, there is lack of base line information in Canada. Thus, the present study will provide the base line base line information which can be used for future research examining trends in this syndrome over time.

2. Methods

The Canadian Heart Heath Survey (CHHS) was conducted between 1986 and 1992 in 10 provinces among non-institutionalized Canadian men and women aged 18 to 74 years. A full description of the method is presented elsewhere (30). The CHHS was conducted in two stages (home interview and clinic visit). In brief, individuals had been invited for interview by using health insurance registration files. In the CHHS, 76% and 69% of

participants completed interview and clinic visit, respectively. During the first stage of data collection, participants were visited in their home by trained study nurses who collected basic demographic data, information about CVD risk factors, and attitudes and opinions about heart health related issues. They took two measurements of blood pressure during the home interview (one at the beginning of the session, another one at the end of session). The second stage of data collection was conducted two weeks later. At this stage, participants visited a clinic where trained study nurses took two measurements of blood pressure again, performed the anthropometric measurements, and took fasting blood samples to determine the plasma lipid levels among the participants. During the data processing stage the mean of the four measurements of blood pressure was calculated.

Weight and height were measured in all provinces, whereas waist circumference (WC) was measured in only five provinces (Alberta, Manitoba, Ontario, Quebec and Saskatchewan). The present study was based on 4724 men and 4712 women for whom full anthropometric measurements were obtained and for whom data on all components of MetS were available out of a total of 5916 (80%) men and 6136 (77%) women in these provinces. Participants were asked to dress in indoor clothing without shoes to perform the anthropometric measurements. Their height was measured to the nearest centimeter while they were standing on a hard surface against a wall. Their weight was measured to the nearest 100g by using a calibrated balance beam scale. During the data processing stage the BMI was calculated by using the standard formula (weight in kg/height in m2). To measure WC, trained study nurses followed the standard protocol by positioning of measuring tape at the level of narrowing waist circumference at the end of normal

expiration, or at the level of the floating rib if measuring the narrowing level of WC was difficult to obtain (30).

Participants had been asked to fast for 12 hours, and subsequently the lipid profile that included low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL), and Triglycerides (TG) was measured. All lipid analyses were performed at the Lipid Research Laboratory at the University of Toronto.

Individuals were considered to be diabetic if they had ever been told by a physician that they had diabetes, although sufficient information was not available to distinguish between Type I and type II diabetes. Metabolic Syndrome was defined using a modification of the criteria from the ATP III (31) and IDF definitions (Tables 1a, 1b) (2). No information was available about the ethnicity of participants, thus the ethnic-specific cutoff point for central obesity was not applied. However, the European cutoff point was applied to define the central obesity because according to Statistic Canada more than 85 % of Canadian populations were Caucasian in 1991. Also, sufficient information was not available about lipid lowering drugs, so individuals with normal lipid profile who were under treatment for dyslipidemia were not were not included in the study.

Table 1a. ATP III definition of Metabolic Syndrome

Metabolic Syndrome :
At least three of the following:

- Central obesity(waist circumference ≥ 102cm for men and ≥ 88 cm for women)
- Triglyceride ≥ 1.7 mmol/L
- HDL< 1.03 mmol/L(men) ; HDL<1.3 mmol/L(women)
- Blood pressure ≥ 130/85mmHg; or Drug treatment for hypertension
- Physician diagnosis of diabetes

* adapted from ATP III definition (Grundy 2005)

Table 1b. IDF Definition of Metabolic Syndrome

Metabolic Syndrome :

Central obesity (defined as waist circumference exceeding specific values)*
Plus any two of the following four factors:
Raised triglycerides: ≥150 mg/dL (1.7 mmol/L)
Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.30mmol/L) in women
Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Physician diagnosis of diabetes

*Ethnicity-specific values were not available; European cutoff point was applied: Men WC≥94; Women WC≥80

* adapted from IDF definition (Zimmet 2005)

3. Statistical analysis

The CHHS was based on a complex survey design, so standard statistical software that assumes the data arises from simple random sampling could not be used. All analyses in this study were conducted by SPSS PASW Complex Samples (version18) that took full account of the complex nature of the study design. A weighted analysis was performed to produce nationally representative and unbiased estimates. Separate models were examined for males and females. Kappa agreement was also calculated to analyze the concordance between the two definitions based on unweighted numbers. The Kappa

index was considered excellent, good, moderate, and weak if values were greater than 0.81, between 0.61and 0.80, between 0.41 and 0.60, and less than 0.40, respectively. SAS Proc Frequency was used to test the difference between proportion for each components involved in the definition of Mets. Specifically "The test of the independence of rows and columns" (chi-square) in SPSS PAWS Complex Survey Software was used to compare the number of components which are present based on the IDF and the ATP III definition.

4. Results

Table 2a, 2b illustrate the characteristics of study subjects according to both definitions. A total of 4724 men and 4712 women aged 18-75 were included in this study. Participants with MetS were older, had higher systolic and diastolic blood pressure, lower HDL level, higher TG level, and higher BMI than individuals without MetS. Women with MetS were older than men with MetS and had higher systolic blood pressure, higher HDL, and higher BMI, while their TG, diastolic blood pressure, and WC levels were lower.

Table 2a. Descriptive statistics (mean± SE) for MetS-components (men)

	MEN (MEAN±SE) ATP III		MEN (MEAN±SE) IDF	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
AGE	39.99±0.39	50±0.64	39.26±0.56	49.83±0.87
Average SBP	123.65±0.38	136.43±1.21	123.05±0.48	135.16±1.21
Average DBP	78.18±.42	85.03±0.52	77.93±0.45	84.15±0.45
HDL	1.24±0.02	0.94±0.01	1.25±0.01	0.99±0.01
TG	1.45±0.3	2.9±0.12	1.41±0.02	2.6±0.11
WC	88.49±0.27	103.21±0.39	87.48±0.30	102.79±0.38
BMI	24.92±0.11	29.31±0.27	24.65±0.11	29.12±0.35

Table 2b. Descriptive statistics (mean± SE) for MetS-components (women)

	WOMEN (MEAN±SE) ATP III		WOMEN (MEAN±SE) IDF	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
AGE	40.93±0.41	53.88±0.66	40.67±0.39	53.62±0.78
Average SBP	116.29±0.79	139.09±1.88	116.09±0.79	137.44±2.00
Average DBP	73.33±0.66	83.12±0.93	73.21±0.68	82.57±0.96
HDL	1.50±0.02	1.13±0.01	1.50±0.02	1.16±0.01
TG	1.19±0.01	2.38±0.05	1.17±0.01	2.34±0.05
WC	75.85±0.54	95.81±0.73	75.47±0.56	95.32±0.76
BMI	23.71±0.35	30.54±0.32	23.58±0.36	30.39±0.18

According to ATP III, 17.9% and 15.3% of men and women have MetS, while according to IDF, 23.8% and 17.3% of men and women have MetS, respectively. The prevalence of MetS is shown in table 3 based on two definitions. Kappa agreement between the definitions is 72 % for men and 80% for women ($p \leq 0.05$).

Table3. Comparison of definitions of MetS according to ATP III and IDF by sex, weighted percentage agreement

Definition		MEN ATP III		WOMEN ATP III	
		Metabolic Syndrome (%)	Normal (%)	Metabolic Syndrome (%)	Normal (%)
IDF	Metabolic Syndrome (%)	16.4	7.1	16.2	4
	Normal (%)	2.7	73.8	1.5	78.2

Table 4 demonstrates the prevalence of the MetS-components according to ATP III and IDF definitions in both sexes. As it is shown, ATP III definition identifies people with a more adverse metabolic profile. In men who have MetS according to IDF definition 68.3%, 86.8%, 78.3%, and 15.4% have low high-density cholesterol, high triglyceride, hypertension, and diabetes, respectively, versus 79.9%, 93.1%, 87.3%, 17.7% according to ATP III ($p \leq 0.001$). In women, the comparable levels of prevalence are 78.8%, 77.6%, 76.2%, 15.3% according to IDF, and 83.3%, 79.2%, 82.6%, 20.5% according to ATP III ($p \leq 0.001$). Furthermore, if one examines the risk profile of individuals in the discordant cells of table 2, one observes that; in men who have been diagnosed only by IDF 50.6%, 76.7% , 62.9%, and 9.9% have low high-density cholesterol, high triglyceride, hypertension, and diabetes, respectively, versus 97.1%,99.6%, 94.1%, 13.8% according to only ATP III. In women, the comparable levels of prevalence are 64.5%, 79%, 53.6%, 2.8% according to only IDF, and 89.1%, 96.1%, 87.1%, 37% according to only ATP III. These data show that 29.9%, 24.4%, 20.1% of men met 0, 1, 2 criteria of IDF definition, respectively, versus 33.6%, 27.4%, 21.1% of men met 0, 1, 2 criteria of ATP III. The data

also show that 42.5%, 33.7%, 4.9% of women met 0, 1, 2 criteria of IDF definition, respectively, versus 39.5%, 30.5%, 14.7% of ATP III (Figs 1 and 2) ($p \leq 0.05$).

Table 4. Prevalence of MetS-components by ATP III and IDF definitions stratified by sex.

	MEN				WOMEN			
	IDF		ATP III		IDF		ATP III	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
Low HDL*	18.5%	68.3%	19.5%	79.9%	27.8%	78.8%	28.2%	83.3%
TG≥1.7	22.4%	86.8%	25.7%	93.1%	11.3%	77.6%	12.6%	79.2%
HTN**	28.8%	78.3%	30.4%	87.3%	17.5%	76.2%	17.7%	82.6%
DM	1.17%	15.4%	2.1%	17.7%	2.1%	15.3%	1.5%	20.5%
Elevated WC***	21.8%	100%	7.1%	59.6%	26.7%	100%	10.9%	78.9%

*Low HDL for men: HDL <1.03, women: HDL<1.3
** Blood pressure ≥ 130/85mmHg or anti hypertensive treatment
***Elevated WC by ATP III for men: WC≥102; for women WC≥88
***Elevated WC by IDF for men: WC≥94; for women: WC≥80
**** The difference of proportions of the two definitions is statistically significant ($p \leq 0.001$) for all components.

In men, the most common combination of three criteria for MetS according to the ATP III definition was low HDL level, hypertriglyceridemia, and hypertension; according to the IDF it was hypertriglyceridemia, hypertension, elevated WC. In women, the most common combination of three criteria for MetS according to the ATP III definition was hypertension, low HDL level, and elevated WC; according to the IDF it was hypertriglyceridemia, low HDL level, and elevated WC.

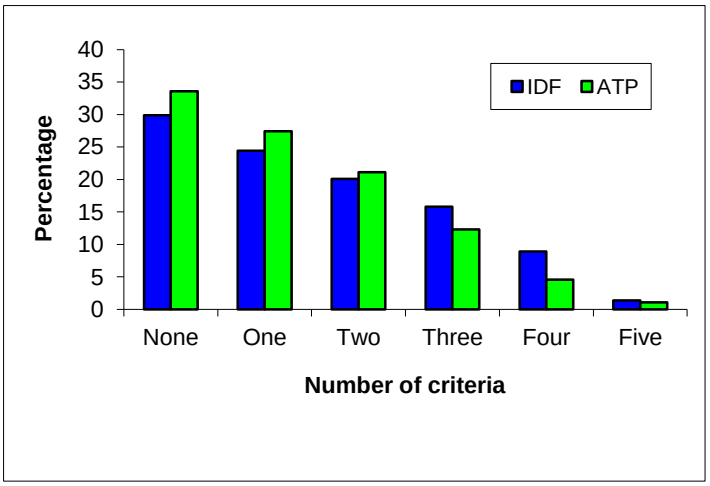

Figure 1. Percentage of men meeting the specified number of criteria from the IDF and ATP III definitions (p≤0.05)

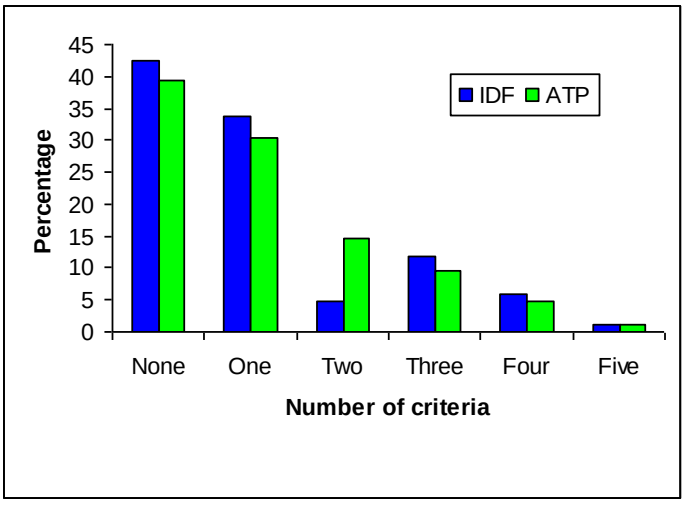

Figure 2. Percentage of women meeting the specified number of criteria from the IDF and ATP III definitions (p≤0.05)

4. Discussion

MetS has become a global epidemic and one the major public health concerns in the world. Having a unified definition which can more reproducibly identify individuals with MetS may improve patient care and help with public health care planning, reducing

overall burden (3,17). To our knowledge this study is the first attempt that compared the prevalence of MetS by the ATP III and the IDF definition and also investigated the degree of concordance between these two definitions in the Canadian population. The present study will establish the base line for prevalence of MetS which can be used in future work.

Over the past twenty years, regardless of the definition used by Riediger et al. (12) to define MetS, the prevalence has increased in Canadian women. However, the trend of the prevalence in Canadian men depends on the definition which is used to define MetS. The prevalence of MetS has decreased in Canadian men according to the ATP III (17.9 vs 15.9). These results should be interpreted with caution. In their study, individuals with WC greater than 102 (for men) and 94 (for women) are considered centrally obese, however, in the present study individuals with WC equal or greater than 102 (for men) and 94 (for women) are considered centrally obese. Also, the threshold for elevated fasting glucose in their study is equal or greater than 6.1, which is not the updated threshold (FBG≥ 5.6) which was included in the 2005 ATP III definition. These two factors may account for the apparent reduced prevalence of MetS in Canadian men over time. It is more appropriate to compare the prevalence of MetS by the ATP III definition in the present study with the prevalence of MetS according to the unified definition with high thresholds in the report by Riediger et al. (WC≥ 102 and WC≥88) as these two definitions of MetS are more alike. In this comparison, the prevalence of the MetS in men has remained essentially the same over the past twenty years (17.9 vs 17.8) (28).

Our results show that the prevalence of MetS is higher in men than women; this finding is consistent with findings in some other countries such as Germany, Finland, Sweden,

France, and Italy. However, it is in contrast with findings in some other countries such as the Netherland, Greenland, Spain (25). The sex difference in Canada appears to have changed in recent decades. Although the present study, reporting on the 1986-95 period, shows a higher prevalence of MetS in men than women, Riediger et al describe a higher prevalence among women than men in the recent 2007-09 period. This finding may reflect differences in the provinces included in the two studies and/or differences in the statistical precision of the two estimates. In the present study, five provinces are considered in the analysis, while in the study by Riediger et al. all ten provinces are included. As well, the larger sample size in the present study provides a narrower confidence interval for prevalence estimate. Overall, these results suggest there is a need for public health initiatives to improve dietary habits and physical activity in Canadian adults, perhaps with more emphasis on women (28).

It is well established that different MetS definitions can either overestimate or underestimate the prevalence of MetS (32).In this study, the results showed that the prevalence of MetS is higher based on the IDF definition, which is consistent with several other studies (16-18,22,23,25,33).

As both definitions are based on the same components, the difference in prevalence could be related to 1.) the importance accorded to central obesity in the IDF definition, and/or 2.) the use of European, not American, WC cutoff points in our use of the IDF definition (16).

This study shows that the concordance between the IDF and the ATP III definition is good (Kappa statistics for men: 72% Kappa statistics for women: 80%) which is similar

with some other studies that found good concordance between these two definitions (20,22,25).

In the present study, the ATP III definition identifies people with a more adverse metabolic profile with respect to blood pressure, LDL, and HDL. The results also show that individuals who have been diagnosed only with the IDF have more favorable metabolic profile than those who have been diagnosed only by the ATP III. These findings are consistent with the study by Olijhoek et al which showed that the IDF definition identifies patients with better cardiovascular risk profile than the ATP III definition (17). Another study which was conducted by Tong et al in Chinese adults, also supported our results and also demonstrated that the IDF definition does not identify individuals who have highest risk of CHD compared to ATP III definition (34). Olijhoek et al (17) presented evidence that the IDF definition identifies individuals who less frequently have metabolic abnormalities due to insulin resistance. They propose that the IDF definition identifies obese individuals who have lower degree of insulin resistance or are have not yet developed insulin resistance. Cameron et al, in the longitudinal study among Australian men and women, explained this finding by stating that central obesity is a crucial component and is the first component that developed before others (35). Also, Sims el al, explained that obese individuals with a metabolically normal profile, at the early stage of MetS may develop symptoms of insulin resistance 10 to 20 years later (36). Therefore, it seems that the prognostic implication of these two definitions is unclear and should be subject of further research; such clarification will assist the assessment of clinical value of these two definitions.

Ardern et al in the study among the Canadian adults found that the most common combination of three criteria for MetS according to the ATP III was low HDL level, hypertriglyceridemia, and hypertension for men, and hypertriglyceridemia, low HDL level and high BMI for women. In the present study, in men, the most common combination of three criteria for MetS according to the ATP III definition was low HDL level, hypertriglyceridemia, and hypertension, which was the same that identified by Arden. When the IDF definition applied, the most combination of three criteria for men was hypertension, hypertriglyceridemia, and elevated WC. In women, the most common combination of three criteria for MetS according to the ATP III definition was hypertension, low HDL level, and elevated WC, which was slightly different from the results that explained by Arden. When the IDF definition applied, the most common combination of three criteria for women was hypertriglyceridemia, low HDL level, and elevated WC. McNeil et al, in a study with 12089 black and white Americans aged 45-64, reported that among the individual components of MetS, hypertension and low HDL level had the strongest effects on developing the CHD risk, which was consistent with findings by Alexander et al among non-institutionalized American adults aged older than 50 (37,38).Thus, as suggested by Arden et al, there should be consideration of whether equal weight should be given to the components of Metabolic Syndrome to define MetS or whether the criteria for MetS should be modified (39,40).

Strengths of this study are the large sample size and a population that is representative of the general Canadian population. However, this study has several limitations. Firstly, the classification of Metabolic Syndrome relied on patient report of a physician diagnosis of diabetes, rather than measured fasting blood glucose. As Arden et al explained, this issue

can lead to underestimation of the prevalence of DM by more than 30% (41), which would have a marked effect on the prevalence of MetS.

Secondly, when the IDF definition was applied, the estimation of prevalence of Metabolic Syndrome was based on the European waist circumference thresholds, which may not have been appropriate in the Canadian sample. Unfortunately, due to the lack of information about the ethnicity of our population, it was not possible to choose a more appropriate cutoff point for central obesity, which could have lead to misclassification of MetS in individuals; Fortunately, according to census data by Statistic Canada, 86% of the population were Caucasian in 1991, so this would likely not have had a major impact.

Thirdly, we had no information about the use of lipid lowering drugs, so individuals being treated for hypertriglyceridemia and who had a normal lipid profile were not consider as having dyslipidemia. This limitation could have lead to underestimation of the true prevalence of dyslipidemia and, subsequently an underestimation of prevalence of MetS.

Finally, in this study we excluded individuals for whom full anthropometric measurements and data on all components of MetS were not available, which might have lead to selection bias, especially if these individuals were not representative of the overall group. For example, these individuals might have been unavailable to testing because they were less compliant or more ill.

5. Conclusion

In Canadian adults the prevalence of MS is higher when the IDF definition is applied but the metabolic derangement of individuals identified is less severe. The interpretation of

epidemiological studies would therefore be much improved by a unified and reproducible definition. Observing that there is an increase in the prevalence of MetS over the past twenty years, confirms that there is a need for public health initiative to decrease the prevalence of MetS in Canadian adults.

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Risk factors for the Metabolic Syndrome in Canadian adults

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Abstract

Introduction: A modest amount is known about the prevalence of the Metabolic Syndrome (MetS) and its associated risk factors in Canadian adults.

Objective: The purpose of this study was to examine the relationship between Metabolic Syndrome and its associated risk factors.

Methods: The Canadian Heart Health Survey was a cross-sectional probability sample survey conducted in all 10 Canadian provinces between 1986 and 1992 .The present study was based on individuals for whom full anthropometric measurements were obtained and for whom data on all components of MetS were available (provinces of Alberta, Manitoba, Ontario, Quebec and Saskatchewan). MetS was defined according to ATP III and IDF definitions. A weighted analysis using SPSS PASW Complex Samples (version18) was used to conduct stepwise logistic regression analysis to identify risk factors significantly associated with MetS ($p < 0.05$).

Results: According to ATP III, 17.9% and 15.3% of men and women have MetS, while according to IDF, 23.8% and 17.3% of men and women have MetS, respectively. Older age and low level of physical activity were significant risk factors for the MetS regardless of gender and definition. Higher level of education and alcohol consumption were additional significant protective factors for women, whereas retirement and being unemployed were additional significant risk factors for men.

Conclusion: Demographic, socio economic factors, and lifestyle habits are significantly associated with MetS among the Canadian adults

Key words: Metabolic Syndrome, insulin resistance syndrome, insulin resistance, risk factor for Metabolic Syndrome.

1. Introduction

The Metabolic Syndrome (MetS) is a clustering of risk factors which poses a risk for diabetes and cardiovascular disease. Several studies have shown that there is an association between the components of MetS and cardiovascular disease mortality (1-4).Other studies have reported that cardiovascular events are higher among people with the MetS (5-7), therefore the identification of the risk factors of MetS is an important issue for both researchers and patients.

It has been well documented that regardless of the definitions that have been used to define MetS, the prevalence of MetS depends on age (8). Some studies have observed that the prevalence of MetS reaches its peak in the seventh decade of life and after that decreases (9-12). However, some studies have found that the prevalence of MetS continues to increase even after the seventh decade of life (8).

The association between the individual components of Metabolic Syndrome and income level or educational level, which are considered as the determinants of socioeconomic status (SES), has been illustrated by many researchers (13). The literature has shown that individuals with low SES have a higher prevalence of cardiovascular risk factors, including smoking, hypertension, impaired glucose tolerance, diabetes, physical inactivity, and obesity (13-20). Most researchers have found an inverse relationship between Metabolic Syndrome and socioeconomic status (14,17,21-26). However, a few studies have found no association between the Metabolic Syndrome and socioeconomic status (27).

The association between employment status and MetS is controversial. Most research has shown that the risk of developing MetS is higher in unemployed than employed

individuals (21,28). However, Lucove et al, in a study in African American population, found that employed individuals had higher risk of developing MetS than unemployed individuals, although this association was not statistically significant (OR= 1.21; 95 %CI= 0.85, 1.73) (29).

Many studies have shown that being physically active can reduce the prevalence of Metabolic Syndrome (12,24,28,30-32) because physical activity can reduce blood pressure, triglyceride level and abdominal obesity but increases HDL cholesterol level (32-35).

There is considerable debate regarding the effect of consumption of alcohol on the prevalence of MetS (36). Some studies have reported that individuals with moderate alcohol consumption have a lower prevalence of MetS (37,38). This protective effect might be explained by the effect of moderate alcohol consumption in increasing HDL cholesterol level, decreasing blood pressure, and improving insulin sensitivity (39-44). However, a few studies have found a negative association (36) or no association between the Metabolic Syndrome and alcohol consumption (31,45).

There is a much controversy about the association between Metabolic Syndrome and smoking. It has been well documented that smoking can increase blood pressure, elevate triglyceride level, decrease HDL- cholesterol level, and impair insulin function (28,46-49). Thus, several studies reported that individuals who are smokers are at an increased risk of developing MetS (14,28,44). However, some studies have reported an inverse relationship between smoking and obesity (31), which could lead to a lower prevalence of MetS among smokers (50).

To our knowledge, there is little reported about the association between Metabolic Syndrome and marital status, although few studies have shown that the risk of developing MetS is higher among divorced, widowed, and unmarried women than married women (28,51).

Although there is some information available about the prevalence of Metabolic Syndrome in the Canadian population, little is known about its predisposing risk factors using the ATP III and the IDF definitions (52,53). The purpose of this study was to examine the relationship between Metabolic Syndrome and its associated risk factors according to both definitions the ATP III and the IDF.

2. Methods

The Canadian Heart Heath Survey (CHHS) is a cross sectional study which was conducted between 1986 and 1992. Non-institutionalized Canadian men and women aged 18-74 years were recruited from ten provinces. A full description of the recruitment method is presented elsewhere (54). The CHHS was conducted in two stages: a home interview and clinic visit. The study population was identified by using provincial health insurance registration files. MacLean et al reported that 76% of participants completed the interview visit. During the home interview, basic demographic data, information about the CVD risk factors, and attitudes and opinions of participants about health-related issues were collected by a by trained study nurses. The nurses measured the blood pressure of participants at the beginning and end of the interview. Participants completed clinic visits within two weeks and were in turn visited by the study nurses. . MacLean et al reported that 69% of participants completed the clinic visit. At this visit, the nurses

measured blood pressure at the beginning and end of the session, performed the anthropometric measurements, and took fasting blood samples to determine the plasma lipid levels. The mean of four blood pressure measurements were calculated by the researchers during the data processing stage. Participants had fasted for 12 hours to measure the lipid profile, which included low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL), and triglycerides (TG). The Lipid Research Laboratory at the University of Toronto conducted all lipid analysis.

Weight and height were measured in all provinces, whereas waist and hip circumference were measured in only five provinces (Alberta, Manitoba, Ontario, Quebec and Saskatchewan). A total of 5916 men and 6136 women from these five provinces participated in the survey. Of these, 4724 men and 4712 women had complete information on anthropometric measurements and all components of Metabolic Syndrome. Participants wore indoor clothes while the nurses measured the anthropometric components. The nurses asked the participants to stand on a hard surface to measure the height and used a calibrated balance beam scale to measure the weight. During the data processing stage the BMI was calculated by using the standard formula (weight in kg/height in m2). The standard protocol was applied by the study nurses to measure waist circumference (WC). Specifically, they placed measuring tape at the narrowest waist circumference at the end of normal expiration, or at the level or at the level of the floating rib if measuring the narrowing level of WC was difficult to obtain (54).

Individuals were considered to be diabetic if they had ever been told by a physician that they had diabetes. However, in the study there was not sufficient information available to

distinguish Type I and type II diabetes. Age was categorized into six categories (18- 24; 25-34; 35-44; 45-54; 55-64; 65-74). Smoking status was categorized as never-smoker (participants who never smoked), current smoker (participants who smoke at least one cigarette every day), and former smoker (participants who had stopped smoking). Drinking status was categorized as never-drinker (participants who never drank), former drinker (participants who had stopped drinking), and current drinker (participants who reported alcohol drinking during the past month).

Participants were considered physically active if they were engaged in physical activity at least once per week during the previous month for a duration of at least half an hour, otherwise they were considered as sedentary individuals.

Income level, educational level, and employment status (which are determinants of socioeconomic status) were considered in the study. Three levels of income were defined in the study based on the ratio of household income to Statistics Canada's income cut-offs for different family sizes (54). One person with an income of $25000 or more, or two or more people with an income of $50 000 or more were considered as high income individuals. One person with an income between $12000 and $24999, two people with an income between $12 000 and $49999, or three or more people with an income between $25 000 and $49 999 were considered as middle income individuals. Finally, one or two people with an income of less than $12 000 or three or more people with an income of less than $25000 were considered as low income individuals (54). The education level of participants was classified into elementary, some secondary, secondary and university degree. To determine employment status, participants were asked "what is your current employment status?" Employment status was categorized into full time, part time,

unemployed, laid off, retired, home maker and other. Marital status was classified as single (which included never married, widowed, and divorced) or married (which included married and common-law marriage).

Metabolic Syndrome was defined using a modification of the criteria from the ATP III (55) and IDF Definitions (Tables 1a, 1b) (56). There was no information available about the ethnicity of participants in this study, thus the ethnic-specific cutoff point for central obesity was not applied. According to Statistic Canada more than 85 % of Canadian populations were Caucasian in 1991, so the European cutoff point was applied to define the central obesity.

There was no information was available about lipid lowering drugs, so individuals who was under treatment for dyslipidemia with normal lipid profile were not considered to be dyslipidemic. Diagnosis of diabetes was based on patient reports of a physician diagnosis because fasting blood glucose was not measured during the data gathering phase.

Table 1a. ATP III definition of Metabolic Syndrome

Metabolic Syndrome :
At least three of the following:

- Central obesity(waist circumference ≥ 102cm for men and ≥ 88 cm for women)
- Triglyceride≥ 1.7 mmol/L
- HDL< 1.03 mmol/L(men) ; HDL<1.3 mmol/L(women)
- Blood pressure ≥ 130/85mmHg; or Drug treatment for hypertension
- Physician diagnosis of diabetes

* adapted from ATP III definition (Grundy 2005)

Table 1b. Definition of Metabolic Syndrome according to IDF

Metabolic Syndrome :
Central obesity (defined as waist circumference exceeding specific values)*
Plus at least two of the following four factors:
Raised triglycerides: ≥150 mg/dL (1.7 mmol/L)
Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.29 mmol/L) in women
Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Physician diagnosis of diabetes

*Ethnicity-specific values were not available; European cutoff point was applied:
Men WC≥94; Women WC≥80

* adapted from IDF definition (Zimmet 2005)

Statistical analysis

The CHHS is a complex survey design, so standard statistical methods that assume the data arise from simple random sampling were not be used. Rather, analysis in our study was conducted by SPSS PASW Complex Samples (version18) that took full account of the complex nature of the study design. A weighted analysis was performed to produce nationally representative and unbiased estimates. Separate univariate and multivariate models were examined for males and females. Crude and adjusted odds ratio and 95 % confidence intervals were computed to estimate the degree of association between

Metabolic Syndrome and different risk factors. Independent variables included in the univariate analysis were: age, the level of education, income adequacy, employment status, alcohol drinking status, smoking status, and marital status. All variables which were significantly associated with the Metabolic Syndrome at the univariate logistic regression analysis ($P \leq 0.25$) were entered into the multivariate logistic regression analysis. After adjusting for relevant variables, the interaction term were examined.

3. Results

According to the ATP III definition, 17.9% of men and 15.3% of women have MetS, while according to the IDF definition, 23.8% of men and 17.3% of women have MetS. Table 2 and table 3 illustrate the characteristics of study subjects in the present study. As it is shown in table 3, the prevalence of MetS is higher according to the IDF definition than the ATP III definition. The magnitude of association between different risk factors and the prevalence of MetS is the same between the two definitions in both sexes. Compared to the ATP definition, prevalence of MetS is higher in different categories of different risk factors according to the IDF definition.

Regardless of definition, in both sexes, there is an inverse relationship between the levels of education and income and prevalence of MetS. Prevalence of MetS is higher among individuals who had stopped drinking alcohol and smoking than those who were current smokers and alcohol drinkers. The prevalence of MetS is higher in married individuals than single individuals. The prevalence of MetS is also higher among sedentary than active individuals.

The age-specific prevalence of MetS according to the two different definitions is shown in figures 1a and 1b. Prevalence of MetS increases with age in both sexes and according to both definitions, the prevalence of MetS in all age groups is higher according to the IDF definition compared to the ATP III definition. Compared to women, men have higher prevalence of MetS according to both definitions in all age groups.

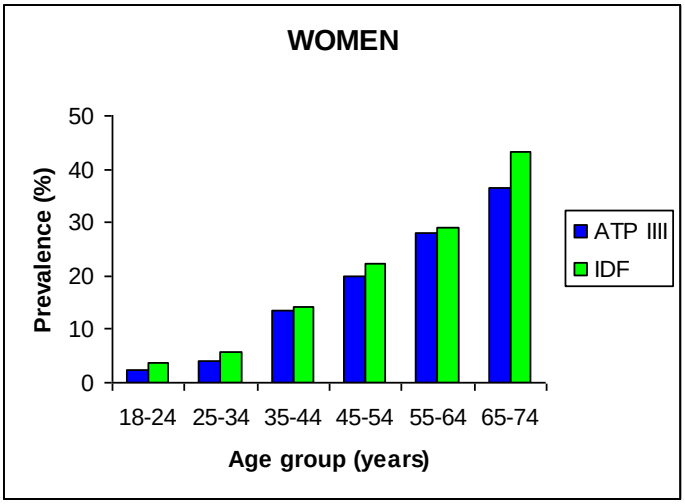

Figure 1a. Age- specific prevalence of MetS by the IDF and ATP III definitions in women

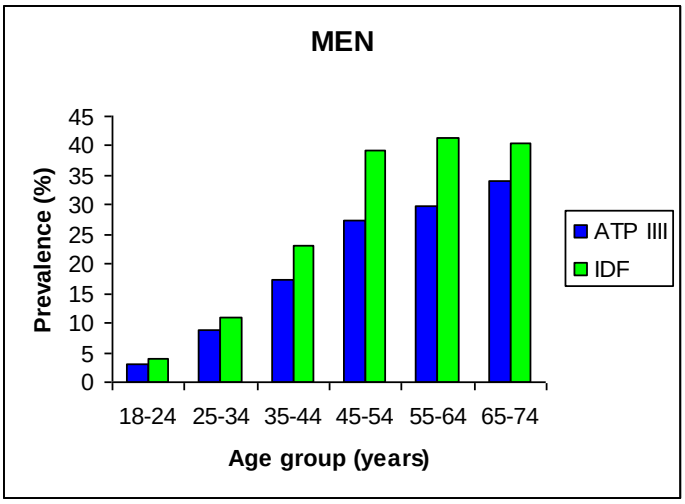

Figure 1b. Age- specific prevalence of MetS by the IDF and ATP III definitions in men

Table 2. Characteristics of study participants stratified by sex.

		Men % (number)	Women %(number)
AGE	18-24	11.4(602)	10.9(608)
	25-34	27.4(1479)	26.1(1545)
	35-44	24.7(700)	23.1(674)
	45-54	15(444)	15.1(492)
	55-64	12.6(432)	13.5(414)
	65-74	8.8(1067)	11.3(979)
Income level	Low	10.8(602)	20(815)
	Middle	44.1(2092)	42.9(2028)
	High	45.1(1585)	37.1(1226)
Educational level	Elementary	5.8(272)	7.2(223)
	Some secondary	21.9(1300)	21.1(1201)
	Secondary	47.9(2183)	52.9(2475)
	University degree	24.3(951)	18.8(795)
Employment status	Full time	66(2822)	38.4(1608)
	Part time	7.7(350)	20.7(824)
	Unemployed	7.7(211)	3.5(131)
	Laid off	1.1(43)	0.6(27)
	Retired	11.4(978)	8.2(543)
	Home maker	0.6(27)	25.1(1334)
	Student	3.9(169)	2.2(153)
	Other	1.6(119)	1.2(90)
Exercise	Yes	60.1(2936)	66.2(3088)
(≥ 1 time/week)	No	39.9(1788)	33.8(1623)
Alcohol	Never Drinker	1.4(72)	7.3(266)
	Former drinker	8.5(482)	10.1(563)
	Current drinker	90.1(4168)	82.6(3882)
Smoking	Never smoker	32.5(1310)	45.9(1963)
	Former smoker	39.7(1908)	29.5(1426)
	Current smoker	27.8(1154)	24.6(1107)
Marital status	Single	32.1(1388)	34.7(1472)
	Married	67.9(331)	65.3(3237)

Table 3. Prevalence of MetsS (in terms of weighted percentages) based on the ATP III and IDF definitions stratified by sex and risk factors.

		Men %		Women %	
		ATP III	IDF	ATP III	IDF
AGE	18-24	3	3.9	2.4	3.7
	25-34	8.7	11	4.1	5.7
	35-44	17.4	23	13.4	14.1
	45-54	27.4	39.3	19.9	22.2
	55-64	29.8	41.2	28	29.1
	65-74	34.1	40.5	36.5	43.4
Income adequacy	Low	17.6	27.3	18.7	19.8
	Middle	19.7	25.5	15.5	17.5
	High	15.5	21.3	10.9	13.6
Educational level	Elementary	32.6	41.6	43	42.6
	Some secondary	24.4	29.2	24.4	25.6
	Secondary	15	22.2	11.3	14.1
	University degree	13	16.5	5.9	7.5
Employment status	Full time	16.2	22	9.6	12.4
	Part time	8.5	11.4	10.4	12.5
	Unemployed	23.1	30.3	7.1	9.2
	Laid off	13	3.6	5.3	5.7
	Retired	36.9	44.4	32.2	36.5
	Other	12.7	44	19.6	20
	Home maker	19.6	20.8	24.9	25
	Student	3.2	4.2	2.9	3.5
Exercise	Yes	13.7	20.1	11.5	13.5
(≥ 1 time/week)	No	24.2	29.4	22.8	24.7
Alcohol	Never Drinker	20	26.2	29.9	30.8
	Former drinker	26.4	35	28.6	30.3
	Current drinker	17.1	22.7	12.4	14.6
Smoking	Never smoker	12.2	15.6	15.8	16.7
	Former smoker	23.1	31.2	17.3	20.3
	Current smoker	19.9	26.7	12.2	15.4
Marital status	Single	11.4	17	15.7	16.4
	Married	21	27	15.1	17.8

As summarized in table 4, age, the level of education, employment status, and physical activity status are significantly associated with MetS in unadjusted analysis in both sexes according to both definitions. Our unadjusted results also show that income adequacy is significantly associated with MetS according to both definitions only in women, marital

status and smoking status are significantly associated with MetS according to both definitions only in men, and alcohol drinking status is significantly associated with MetS only in women when IDF definition applied.

Table 4. Univaraite odds ratios for variables associated with Metabolic Syndrome among men and women

		Men		Women	
		OR(95% CI)		OR(95% CI)	
	Categories	ATP III	IDF	ATP III	IDF
Age	18-24	Ref	Ref	Ref	Ref
	25-34	3.1(1.6-6.2)	3.1(1.7-5.3)	1.8(0.8-3.8)	1.6(0.8-3.2)
	35-44	6.9(2.9-16.4)	7.4(3.8-14.4)	6.4(2.8-14.8)	4.3(2.3-8.1)
	45-54	12.3(5.6-26.8)	16.1(7.4-35.0)	10.3(4.0-26.6)	7.5(3.3-17.0)
	55-64	13.8(7.3-26.1)	17.4(8.7-34.9)	16.1(8.5-30.6)	10.8(6.3-18.4)
	65-74	16.8(9.0-31.5)	16.9(9.4-30.3)	23.8(11.1-51.3)	20.1(10.3-39.4)
Income adequacy	Low	Ref	Ref	Ref	Ref
	Middle	1.2(0.7-1.8)	0.9(0.7-1.3)	0.8(0.5-1.2)	0.9(0.6-1.3)
	High	0.9(0.5-1.6)	0.7(0.5-1.0)	0.5(0.4-0.8)	0.6(0.4-0.9)
Educational level	Elementary	Ref	Ref	Ref	Ref
	Some secondary	0.7(0.4-1.2)	0.6(0.4-0.9)	0.5(0.3-0.7)	0.5(0.3-0.7)
	Secondary	0.4(0.2-0.6)	0.4(0.3-0.6)	0.2(0.1-0.3)	0.2(0.1-0.4)
	University degree	0.3(0.2-0.5)	0.3(0.2-0.4)	0.1(0.0-0.2)	0.1(0.1-0.2)
Employment status	Full time	Ref	Ref	Ref	Ref
	Part time	0.5(0.3-0.9)	0.5(0.3-0.8)	1.1(0.7-1.8)	1.0(0.7-1.5)
	Unemployed	1.6(0.9-2.7)	1.5(0.8-2.8)	0.7(0.3-1.9)	0.7(0.3-1.6)
	Laid off	0.8(0.2-2.6)	0.1(0.0-0.4)	0.5(0.1-3.0)	0.4(0.1-2.1)
	Retired	3.0(2.0-4.6)	2.3(1.7-4.7)	4.5(2.9-6.9)	4.1(3.0-5.5)
	Other	0.8(0.3-2.0)	2.7(0.6-12.1)	2.3(1.1-5.0)	1.8(0.9-3.3)
	Home maker	1.3(0.3-5.1)	0.9(0.2-4.2)	3.1(2.0-4.9)	2.4(1.5-3.7)
	Student	0.2(0.3-1.1)	0.2(0.0-0.7)	0.3(0.1-1.1)	0.2(0.1-0.8)
Exercise	Yes	Ref	Ref	Ref	Ref
(≥ 1 time/week)	NO	2.0(1.6-2.5)	1.6(1.4-1.9)	2.3(1.5-3.6)	2.1(1.3-3.4)
Alcohol	Never Drinker	Ref	Ref	Ref	Ref
	Former drinker	1.4(0.6- 3.8)	1.5(0.8-3.0)	0.9(0.6-1.5)	1(0.6-1.6)
	Current drinker	0.8(0.3-2.1)	0.8(0.3-2.1)	0.3(0.2-0.5)	0.4(0.2-0.6)
Smoking	Never smoker	Ref	Ref	Ref	Ref
	Former smoker	2.2(1.4-3.3)	2.5(1.8-3.2)	1.1(0.9-1.5)	1.3(0.9-1.8)
	Current smoker	1.8(1.2-2.7)	1.9(1.3-3.0)	0.7(0.5-1.2)	0.9(0.5-1.6)
Marital status	Single	Ref	Ref	Ref	Ref
	Married/Common Law	2.1(1.7-2.5)	1.8(1.4-2.3)	0.96(0.7-1.2)	1.1(0.8-1.6)

In both sexes, regardless of definition, no statically significant association was found between MetS and the income adequacy, employment status, smoking status, and marital

status in adjusted analysis. In women, level of education was not statically associated with MetS according to either definition in adjusted analysis.

As summarized in table 5, the results of adjusted analysis showed that older age and low level of physical activity are significant risk factors for the MetS regardless of gender and definition. According to the adjusted analysis, alcohol consumption is an additional significant protective factor, and higher level of education is an additional significant risk factor for women. In men, in adjusted analysis, retirement and being unemployed are additional risk factors.

Table 5. Multivariate odds ratios for variables significantly associated with Metabolic Syndrome among men and women, final model

		MetS OR(95% CI)	
	Categories	ATP III	IDF
Men			
AGE	18-24	Ref	Ref
	25-34	2.9(1.4-6.1)	2.8(1.6-5.1)
	35-44	6.3(2.6-15.0)	6.6(3.4-13.0)
	45-54	11.0(4.6-25.8)	13.9(6.2-31.2)
	55-64	10.1(4.6-21.8)	12.2(6.1-242)
	65-74	8.6(3.3-22.8)	9.2(3.9-22.1)
Exercise	Yes	Ref	Ref
(≥ 1 time/week)	NO	2.0(1.5-2.8)	1.6(1.3-1.9)
Employment status	Full time	Ref	Ref
	Part time	0.8(0.5-1.4)	0.7(0.4-1.3)
	Unemployed	1.9(1.0-3.5)	1.9(1.0-3.4)
	Laid off	1.2(0.4-4.2)	0.2(0.1-0.6)
	Retired	2.1(1.1-3.8)	1.8(0.9-3.9)
	Other	0.5(0.1-2.3)	2.1(0.7-6.6)
	Home maker	1.1(0.2-5.8)	0.8(0.1-4.4)
	Student	0.4(0.1-3.7)	0.4(0.1-2.3)
Women			
AGE	18-24	Ref	Ref
	25-34	1.9(0.8-4.2)	1.7(0.8-3.6)
	35-44	6.2(2.6-14.9)	4.2(2.2-8.4)
	45-54	8.8(3.4-23.3)	6.8(3.0-15.4)
	55-64	9.7(4.7-19.9)	7.6(4.0-14.3)
	65-74	16.7(7.6-37.0)	16.1(7.7-34.0)
Exercise	Yes	Ref	Ref
(≥ 1 time/week)	NO	2.2(1.3-3.8)	2.0(1.2-3.5)
Educational level	Elementary	Ref	Ref
	Some secondary	0.7(0.4-1.1)	0.7(0.4-1.2)
	Secondary	0.5(0.3-0.7)	0.6(0.4-0.9)
	University degree	0.2(0.1-0.5)	0.3(0.1-0.6)
Alcohol	Never Drinker	Ref	Ref
	Former drinker	1.0(0.6-1.6)	1.1(0.6-1.9)
	Current drinker	0.5(0.4-0.7)	0.6(0.4-0.9)

4. Discussion

There is no doubt that the risk of developing cardiovascular disease is higher in individuals with MetS than individuals without MetS (6,7,9,57,58), and MetS is one the major public health concerns in our societies today (59,60). Thus, identification of its associated risk factors could enable researchers and clinicians to implement interventional programs to reduce these risk factors, which should subsequently reduce the prevalence and incidence of MetS and result in benefits for patients and the public health care system (61).

Our results showed that the final model was the same based on the both definitions, but the magnitude of the association between risk factors and MetS was slightly different. Our results showed that the prevalence of MetS increases with age in both sexes, regardless of definition, as has been seen elsewhere (8,10,11,62,63). Park et al proposed that aging can lead to increase in the visceral adipose tissue and development of insulin resistance (14). Compared to the ATP III definition, when the IDF definition was applied, prevalence of MetS was higher in all sex stratified age group. This finding was also observed by Hildrum et al in Norwegian population. As both definitions are based on the same components, the possible explanation for the difference in prevalence could be 1.) the importance accorded to central obesity in the IDF definition, and/or 2.) the use of European, not American, WC cutoff points in our use of the IDF definition, which could have lead to the identification of more individuals as being obese (8).

Our results showed that risk of having MetS significantly linearly increased by age in unadjusted analysis, however, after adjusting for other risk factors, it reached its peak level between the age of 45 and 55.

Several studies found that the risk of developing MetS is lower among individuals who are physically active (12,28,31,32). In the present study, low level of physical activity was also a significant risk factor for the MetS regardless of gender in both adjusted and unadjusted analysis. This protective effect of physical activity is probably mediated through decreasing blood pressure level, triglyceride level, abdominal obesity and increasing HDL cholesterol level (30-35,44).

Our results showed that alcohol consumption was a significant protective factor for women in both unadjusted and adjusted analysis. The protective effect of moderate alcohol consumption also has been observed in several other studies (36). This protective effect could be due to the effect of moderate alcohol consumption on increasing HDL cholesterol level, decreasing blood pressure and insulin level, and improving insulin sensitivity (data is not shown) (44). However, there was no statistically significant association between alcohol consumption and MetS in men. No association between alcohol consumption and MetS for both sexes has been reported in studies among Mediterranean, Irish, and Portuguese populations (31,45). Different sex-patterns regarding the effect of alcohol consumption have also found by Zhu et al in a study among the American Population (44). This gender difference regarding the effect of alcohol consumption can support the idea, suggested by Fan et al, that men are less susceptible to long-term health effect of alcohol than women (41). Indeed, higher dose of alcohol consumption in men appears to lead to adverse metabolic profiles.

In women, we found that the level of education was inversely and significantly associated with MetS in both adjusted and unadjusted analysis. However, in men, this inverse association was statistically significant only in unadjusted analysis. This inverse

significant association that is observed only in women (not in men) is consistent with the results of several other studies in other populations (22,31,64). There are other studies that observed this inverse association in both men and women (25,26). However, Hye Park et al and Yong Park et al, in the studies among Korean and American adults, reported that there was no association between educational level and MetS in either sex (14,28). The explanation for the inverse association between educational level and MetS could be that the individuals with low educational levels are at the higher risk of developing of MetS- components that include hypertension, impaired glucose, diabetes, and overweight (14).

Some researchers believe that the health impact of SES is affected by gender, as we found in this study. The potential reasons for this might be explained by Dallongeville et al 1) women are more health-oriented than men that help them to have better understanding about the health life style and 2).being educated can have more influence on food choices and health behaviors in women than men (25) 3) the association between SES and abdominal obesity is different between men and women, which might lead to different pattern of MetS as well.

In the studies in the USA and France, level of income instead of educational level was reported as a significant risk factor for MetS (14,24), but in the present study this association was significant only in unadjusted analysis and only for women. The literature shows that individuals with low income level tend to have more undesirable health behaviors including unhealthier food choices, lack of physical activity, and lack of enough attention to their physical condition which would prone them to insulin resistance, dyslipidemia, and obesity (25,64). Thus we expect that the risk of developing

of MetS would be higher in both men and women with low level of income. However, some researchers argue that low income women are more likely vulnerable to the limited source of income than men (25). This could partially explain gender differences in the relationship between income level and MetS that was shown in the present and some other studies (25).

Our results show that retirement and being unemployed (borderline significance by both definitions) are additional risk factors for men, as has been seen elsewhere (28). Our results also showed that, in women, being retired and self-defining themselves to be housewives were risk factors in developing of MetS in only unadjusted analysis, but not significant in the adjusted analysis. Possibly unemployment may lead to psychosocial stress that can induce the elevation of components of Metabolic Syndrome (24).

We observed that the determinants of socioeconomic status, which can be considered as risk factors for developing MetS, are not same in men and women. This observation can support the hypothesis of Silventionen et al that education level and employment status "*can lead to different results regarding the socioeconomic disparities in MetS*" (23).

Regardless of definition, smoking was a significant risk factor for MetS in men in unadjusted analysis, but not in adjusted analysis. Earlier studies have shown that smoking can cause dyslipidemia by inducing lipolysis, hypertension by stimulating sympathetic nerve activity, and insulin resistance by impairing insulin action, (28,31,46,50) thus clustering of these abnormalities or one might expect to observe a higher prevalence of MetS among smokers. In the present study, men who smoked had higher systolic and diastolic blood pressure, lower HDL level, higher TG level, and higher WC than non-

smoking man, which may explain why smoking-men had a higher risk of having MetS than never-smoker men (data is not shown).

In women, regardless of definition, the risk of having MetS was lower in smoking women than non-smoking women, but this association was not statistically significant.

Onat et al in a study among 3385 Turkish people and Santos et al in a study among 2164 Portuguese people reported that smokers had a lower risk of having MetS.

They explained this protective effect could be due to the inverse relationship between smoking and obesity. In this study, the waist circumference of female smokers was smaller than waist circumference of female non-smokers (data is not shown).

It has been shown that marriage can bring health benefits that lead to lower cardiovascular mortality and morbidity, however our results show that marriage or common-law marriage in men was a significant risk factor in only unadjusted analysis.

A similar finding has been also reported by Hye Park et al, who found that unmarried men had lower risk of developing MetS than married men, although their association was not significant (28). Troxel et al explained that satisfaction of marriage can play an important role on the association between cardiovascular risk factors and marital status, thus being on unhappy relationship can lead to psychosocial stressor that can increase the risk of developing disease (51). In the present study, married men had higher systolic and diastolic blood pressure, lower HDL level, higher TG level, and higher WC than single men.

Troxel et al mentioned that the association between cardiovascular mortality and morbidity and marital status in women is less consistent than men. In the present study,

the association between marital status and MetS was not significant in women, regardless of definition. The paradox association, regarding the magnitude of their relation by using different definitions, was found in this study. When the ATP III applied, marriage was a protective factor, while it was a risk factor when the IDF applied. Hye Park et al also reported that risk of developing MetS was statistically higher among unmarried women (64).

This study has several limitations, first in this study the classification of Metabolic Syndrome relied on patient report of a physician diagnosis of diabetes, rather than measured fasting blood glucose. This issue can lead to underestimation of the prevalence of DM (65), and have an underestimation of the prevalence of MetS.

Second, we had no information on the ethnicity of participants in this study so we could not use the ethnic-specific cutoff point for central obesity, which should be used to define MetS by the IDF definition. Thus this issue can lead to misclassification of individuals as having MetS; however, according to census data by statistic Canada 86% of population were Caucasian in 1991, so this would likely not have had a major impact. Third, there was no information about the lipid lowering drugs so individuals who were treated for hypertriglyceridemia were not considered as having dyslipidemia. This limitation can lead to underestimation of the true prevalence of dyslipidemia, and subsequently underestimation of prevalence of MetS. Fourth, this study was based on the individuals for whom full anthropometric measurements and data on all components of MetS were available and we excluded individuals for whom those information was not available, thus there is possibility of selection bias in this study. Finally, it is a cross-sectional so a causal association cannot be inferred from these findings.

5. Conclusion

Demographic, socio economic factors, and lifestyle habits are significantly associated with MetS among the Canadian adults. The socioeconomic factors which are associated with Metabolic Syndrome vary by gender; level of educational appears to be the best measure in women versus employment status in men. Physical activity is associated with lower odds of MetS for both sexes; it might be expected therefore that intervention programs to increase the level of physical activity among the Canadian population may reduce the prevalence of MetS.

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How does the Metabolic Syndrome defined by two definitions predict Cardiovascular Disease mortality?

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Abstract

Background: No studies have compared the ability of ATP III and IDF to predict CVD mortality among Canadian adults using the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP III) and the International Diabetes Federation (IDF) definitions.

Objective: The purpose of this study was to determine the effect of definition on the prevalence of the component factors by using the ATP III and the IDF definitions and examine the relation between Metabolic Syndrome and CVD mortality.

Methods: The Canadian Heart Health Survey was a cross-sectional probability sample survey conducted in all 10 Canadian provinces between 1986 and 1992. Statistics Canada linked the CHHS data set to Canadian Mortality Database. The present study is based on 2553 men and 2644 women from three provinces (Alberta, Manitoba, and Saskatchewan) for whom full anthropometric measurements, mortality data, and data on all components of MetS were available. MetS was defined according to ATP III and IDF definitions. Cox-regression analyses using the STATA (version11) was conducted.

Results: In women who have the Metabolic Syndrome according to the IDF definition 81.9%, 76.6%, 71.7%, and 14.4% have low high-density cholesterol, high triglyceride, hypertension, and diabetes, respectively, versus 84.5%, 80.3%, 78.4%, and 19.3% according to ATP III ($p \leq 0.001$). In men, the comparable levels of prevalence are 71.7%, 85.1 %, 71.5%, and 10.5% according to IDF and 78.7%, 89.3%, 85.0%, and 13.1% according to ATP III ($p \leq 0.001$). Kappa agreements between the definitions are 70.8% for men and 82.3% for women ($p \leq 0.05$). The hazards of death due to CVD events in women with the syndrome according to the ATP III and the IDF definitions are 3.96(1.30-12.09)

and 2.56 (1.32-4.97), respectively. The comparable numbers for men are 2.21(1.16-4.02) and 2.50(1.50-4.17).

Conclusion: The prevalence of MetS is higher when the IDF definition is applied but the metabolic derangement of individuals identified is less severe. The ATP III definition predicts CVD mortality better in women, while the IDF definition predicts CVD mortality better in men.

Key words: Metabolic Syndrome, insulin resistance syndrome, insulin resistance, definition, Cardiovascular disease mortality.

1. Introduction

During the past decade, several definitions have been developed for Metabolic Syndrome (1-4) and several studies used these definitions to describe the prevalence of the Metabolic Syndrome in different countries (2). The results showed that the prevalence was varied and it was difficult to compare these studies because different definitions were used, the ways that they modified the definitions were different, and their study designs were different as well (1,2). Several studies compared the prevalence of the syndrome by applying different definitions and measured the degree of concordance between these definitions during the past years (5-11). Most studies aimed to compare the prevalence of MetS using ATP and IDF definitions, reported a higher prevalence based on IDF definition.

Several studies have examined the association between the Metabolic Syndrome and cardiovascular disease (CVD). Most studies have used the WHO and the ATP III definitions to examine this association (12-15), and fewer studies used the IDF (16-22) and the AACE definitions (19).

Among the above studies, four notable meta-analyses have reported that that risk of developing the CVD was higher in individuals with Metabolic Syndrome than those without the syndrome (12-15). Three meta-analyses included studies which used both the ATP III and the WHO definitions (12-14), and one meta-analysis only included studies which used the ATP III (15). Other studies which used the IDF, (16-22), and the AACE definitions (19) also reported a similar association.

One important scientific dilemma was that several definitions can lead to confusion among researchers and clinicians. Thus, researchers and clinicians should know which definition can be more useful and practical and there is also a need for a unified definition (6-10,23-28). One of the best ways to address the issues prevented by different definitions is to compare their predictive accuracy for disease, particularly CVD development. Indeed, one of the main reasons for proposing different definitions of Metabolic Syndrome was to identify individuals who were at a higher risk for developing cardiovascular disease. Thus, by comparing the predictive accuracy of the definition for developing CVD, researchers sought to determine which definition should be used in both clinical practice and research (19).

Several studies were conducted to examine the comparison. The results of three meta-analysis showed that the WHO definition could predict cardiovascular events better than the ATP III definition (12-14). The results of studies which compared the ATP III and the IDF definitions were varied. Some studies reported that the ATP III was superior in predicting CVD events than the IDF definition in both sexes (18,21).However the results of study by Katzmarzyk showed that they had the same ability in men (16). Benetos et al reported that the IDF was a better predictor than the ATP III (20). The result of a study by Qiao et al found that theta predicted CVD events better than the IDF in men, while in women the IDF was superior(17). However, these studies varied regarding the baseline population, follow up years, number of CVD events, how they modified the definitions, and different potential confounders which had been controlled in their analysis (19).

It has been known that CVD is one of the most important causes of death in Canada, and some predicted that earlier the risk of developing CVD is higher in individuals with the syndrome. The prevalence of the Metabolic Syndrome is high in Canada, but is varied among different studies (men 15.9%, women 19.2%) (29-31).Thus, there is a need for a precise definition which can identify individuals with the Metabolic Syndrome accurately in Canadian populations. Although several definitions have been developed, the most applicable in both clinical practice and research are the ATP III and the IDF definitions. To our knowledge, no studies have compared the ability of ATP III and IDF to predict CVD mortality among Canadian adults. This study determined the prevalence of Metabolic Syndrome by using the ATP III and the IDF definitions and examined the relation between Metabolic Syndrome and CVD mortality in Canadian adults.

2. Methods

Baseline study

The Canadian Heart Heath Survey (CHHS) was a cross-sectional study which was conducted between 1986 and 1992 in ten provinces. Details of the study have been published previously (32). Participants were non-institutionalized Canadians, aged 18-74. The health insurance registration files were used to choose participants. The study was conducted at two stages. Participants, who agreed to be involved in the study, were visited by a trained nurse at their home. The nurses measured blood pressure at the beginning and end of the visit. Participants were also asked to fill in a questionnaire which included the questions regarding CVD risk factors, and attitudes and opinions of participants about heart health related issues. Within two weeks, participants presented to

a survey clinic. During the clinic visit, the nurses measured blood pressure at the beginning and end of the visit, and took the blood sample. The means of four blood pressures, which were measured during the home interview and clinic visit, were calculated during the data analysis. The blood sample was sent to the Lipid Research Laboratory at the University of Toronto to measure the lipid profile, which included low density lipoprotein cholesterol (LDL), high density lipoprotein (HDL), and Triglycerides (TG). Participants wore indoor clothing without shoes to measure the anthropometric components. Standard protocols were applied to measure waist circumference (32). The level of narrowing waist circumference was measured at the end of normal expiration. WC was measured at the level of the floating rib if nurses could not find the level of narrowing waist circumference. Although height and weight were only measured in all ten provinces, waist circumference was measured in five provinces (Alberta, Manitoba, Ontario, Quebec and Saskatchewan). Blood glucose was not measured, however participants were considered diabetic if they have been told by a doctor that they had diabetes. Type I and II were not distinguished.

Age was considered into two categories ($<65, \geq 65$ year). Smoking status was considered in three categories including: never-smokers (participants who never smoked), former-smokers (participants who had stopped smoking), and current-smokers (participants who smoke at least one cigarette every day). Drinking status was categorized as former drinkers (participants who had stopped drinking), and current drinkers (participants who reported alcohol drinking during the past month). Participants who reported they never drank alcohol were excluded due to the small numbers in this category. Participants were classified into two groups regarding their physical activity status. If participants did not

engage in physical activity during the previous month of the study for at least half an hour, they were considered as sedentary individuals, otherwise they were considered active individuals. Socioeconomic variables (education level, income level, and employment status) were considered in the analysis. Level of education of participants divided into two categories: participants with less than secondary education, and participants with secondary education or university degree. Participants were categorized into three income adequacy levels: low, middle, and high (Details have been published previously) (32). Participants were asked regarding their employment status and they were categorized into three categories: fulltime or part time, retired, and other which included unemployment, laid-off, home makers, and students. The rationale for grouping participants into three categories regarding their employment status was to have sufficient numbers of deaths due to CVD in each group. Marital status was classified as single (which included never married, widowed, and divorced) or married (which included married and common-law marriage).

Follow-up study

Statistics Canada linked the CHHS data set to Canadian Mortality Database (CMDB). The CMDB record all deaths since 1950, and these are regularly updated by using death registrations which are reported by all Canadian provinces and territories. Record linkage was performed using computerized probabilistic match. There is a national health care system in Canada and CMDB covers the entire population, so the chance of missing death events for participants was limited. The present study is based on 2553 men and 2644 women from three provinces (Alberta, Manitoba, and Saskatchewan) for whom full

anthropometric measurements, bootstrap weights, and data on all components of MetS were available. In the study, participants were followed up from date of survey to December 31/ 2004. The CHHS was a complex survey design, so Statistics Canada calculated the bootstraps weights for the participants based on the PSU (probability sample unit) and strata, which enabled researchers to calculate an accurate value of standard error. During the linkage process the Statistics Canada changed the ID number of participants for confidentiality purposes. As a result, three data sets were released by the Statistics Canada including: mortality data set, bootstrap-weights data set, and the original CHHS with new ID numbers. Three data sets were merged together during the data analysis process according to the ID numbers. The cause of death was reported by the Statistics Canada according to Intentional Classification of Disease (ICD), 9^{th} (up to December 31 1999) and 10th (up to December 31 2004) codes revisions. Cardiovascular events were identified during the data analysis by the researchers (ICD-9: 390-448; ICD-10: 100-178). If there was no information regarding the death events, participants were considered alive.

The Metabolic Syndrome was defined using a modification of the criteria from the ATP III (33) and IDF Definitions (Tables 1a,1b) (4). No information was available about the ethnicity of participants, and according to Statistic Canada more than 85 % of Canadian populations were Caucasian in 1991. Thus, the European cutoff point was applied to define the central obesity in the IDF definition. There was no information available about lipid lowering drugs, so individuals who were under treatment for dyslipidemia with normal lipid profile were not have been identified as dyslipidemic.

Fasting blood glucose was not measured so diagnosis of diabetes was based on physician diagnosis of diabetes.

Table 1 a. ATP III definition of Metabolic Syndrome

Metabolic Syndrome :
At least three of the following:

- Central obesity(waist circumference ≥ 102cm for men and ≥ 88 cm for women)
- Triglyceride≥ 1.7 mmol/L
- HDL< 1.03 mmol/L(men) ; HDL<1.3 mmol/L(women)
- Blood pressure ≥ 130/85mmHg; or Drug treatment for hypertension
- Physician diagnosis of diabetes

* adopted from ATP III definition

Table 1b. IDF Definition of Metabolic Syndrome

Metabolic Syndrome :

Central obesity (defined as waist circumference exceeding specific values)*
Plus any two of the following four factors:
Raised triglycerides: ≥150 mg/dL (1.7 mmol/L)
Reduced HDL cholesterol: < 40 mg/dL (1.03 mmol/L) in men < 50 mg/dL (1.30mmol/L) in women
Raised blood pressure: systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Physician diagnosis of diabetes

*Ethnicity-specific values were not available; European cutoff point was applied: Men WC≥94; Women WC≥80

* adopted from IDF definition

Statistical analyses

The CHHS is a complex survey design. Standard statistical methods that assume that the data represent a simple random sample are not appropriate. To accommodate the complex survey design, our analysis was conducted using STATA (version11) (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP) that enabled researchers to perform Cox-regression analyses using the bootstrap weights to estimate the standard error (StataCorp. 2009. *Stata Statistical Software: Release 11*. College Station, TX: StataCorp LP). Twelve individuals were excluded from the analysis because there was a disconcordance regarding their gender between the CHHS and mortality data set. Four individuals excluded from analysis because the date of death was reported before the date of the survey. Individuals who died during the follow-up time due to non-cardio vascular causes of were excluded from the analysis (men 285 (10%), women 190 (6.7%)). Descriptive statistics were based on a weighted analysis in order to produce nationally representative and unbiased estimates. Follow-up time based on the date of survey and end date of follow up was calculated. The survey Cox-regression procedure, adjusted for age, the level of education, income adequacy, employment status, alcohol drinking status, smoking status, marital status, and LDL cholesterol, was used to estimate the association between Metabolic Syndrome and CVD mortality. Separate models were examined for men and women. Crude and adjusted hazard ratios and 95% CI were calculated. Interaction terms and confounding were examined as well. The assumption of proportional hazards was evaluated by graphic diagnostics tools.

Kappa agreement was calculated to analyze the concordance between the two definitions based on unweighted numbers. Kappa values were considered to be excellent ($\geq$0.8),

good (0.61-080), moderate (0.41-0.60), and weak (≤0.40). The SAS Proc Frequency was used to test the difference between proportion for each components involved in the definition of MetS.

3. Results

The characteristics of participants are summarized in tables 2a and 2b according to both definitions. 2553 men and 2644 women are included in the study. Individuals (both men and women) with the syndrome are older, have higher systolic and diastolic blood pressure, lower HDL level, higher TG and BMI than those without the syndrome. Compared to women, men with the syndrome are younger, have lower systolic blood pressure, lower HDL level and BMI, while their TG, diastolic blood reassure, and WC levels are higher.

Table 2a. Descriptive statistics (mean± se) for MetS-components (men).

	MEN (MEAN±SE) ATP III		MEN (MEAN±SE) IDF	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
AGE	38.02±13.82	47.18±13.69	37.63±13.72	45.56±13.78
Average SBP	122.41±12.29	135.90±12.65	122.36±12.35	133.08±13.43
Average DBP	77.59±8.65	86.02±8.54	77.53±8.81	84.36±8.53
HDL	1.21±0.27	0.93±0.18	1.22±0.28	0.96±.019
TG	1.40±0.80	2.78±1.88	1.35±0.79	2.63±1.70
WC	89.21±9.87	104.54±11.49	88.35±9.80	104.22±9.16
BMI	25.41±3.67	30.05±4.25	25.12±3.53	30.04±3.97

Table 2b. Descriptive statistics (mean± se) for MetS-components (women).

	WOMEN (MEAN±SE) ATP III		WOMEN (MEAN±SE) IDF	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
AGE	38.74±13.84	52.74±13.88	38.53±13.70	51.62±14.52
Average SBP	114.15±13.81	136.32±16.60	113.96±13.90	133.87±16.66
Average DBP	71.93±8.52	82.71±8.31	71.82±8.59	81.59±8.29
HDL	1.45±0.33	1.11±0.23	1.45±0.33	1.12±0.24
TG	1.15±0.57	2.42±1.08	1.13±0.56	2.31±1.04
WC	75.83±10.00	95.94±13.16	75.47±10.03	94.64±12.10
BMI	23.94±4.00	31.35±5.64	23.82±4.00	30.83±5.34

The prevalence of Metabolic Syndrome according to the IDF and the ATP III definitions are 21.9%, 17.1% in men and 16.7%, 14.2% in women, respectively. Cross tabulation of individual by the two definitions shows that 77.3% of women and 66% of men with the Metabolic Syndrome are identified by both definitions. The results show that 22.7 % of women and 34% of men who have been identified as individuals with the syndrome by the IDF definition, have been identified as normal individuals by the ATP III definition. The results also showed that 1.5% of women and 3.3% of men who have been identified as normal subjects according to the IDF definition, have the syndrome according to the ATP III definitions. Kappa agreements between the definitions are 70.8% for men and 82.3% for women ($p \leq 0.05$).

Table3a demonstrates the prevalence of the Metabolic Syndrome according to different risk factors. Indeed, a significant association has been reported between these factors and Metabolic Syndrome and CVD. As it is shown, the prevalence of the syndrome is higher according to the IDF definition than the ATP III definition for every risk factor. Table 3b shows the percentage mortality due to CVD or other causes for different risk factors. Higher numbers of deaths are observed for individuals who are older, retired, inactive,

current smokers, have stopped drinking alcohol, are married, or have lower level of education. The percentages of CVD deaths are higher in men with middle income and women with low income.

Out of 2883 men and 2834 women who participated in the study, 3.2% (183) and 5.6% (285) of men died due to CVD and other causes during the follow-up (15 years) . The comparable numbers for women are 1.9% (103) and 4.8% (190). Out of 737 men and 633 women who had the Metabolic Syndrome according to the IDF definition, 7 % (96) men and 5.8% (58) died due to CVD. Out of 613 men and 560 women who have the Metabolic Syndrome according to the ATP III definition, 6.9% (84) and 7.0% (52) died due to CVD.

Table 3a. Prevalence of Metabolic Syndrome by sex and different risk factors

		Men		Women	
		weighted %		weighted %	
		ATP III	IDF	ATP III	IDF
AGE	<65	16.0	20.7	12	14.2%
	>=65	32.1	38.4	36	42.9
Income adequacy	Low	16.9	22.4	20.6	23.8
	Middle	17.8	23.5	15.5	19.3
	High	15.1	19.0	7.9	9.1
Educational level	Elementary or Some secondary	26.7	31.3	25.5	26.9
	Secondary or University degree	13.7	18.6	10.3	13.3
Employment status	Full-time or Part-time	15.9	20.6	9.1	12.0
	Retired	33.7	40.7	34.2	39.6
	Unemployed or Laid off or Home maker or Student or Other	12.5	16.4	18.8	20.3
Exercise (≥ 1 time/week)	Yes	14.7	18.9	14.3	16.4
	No	20.8	26.7	13.9	17.2
Alcohol	Former drinker	21.2	31.3	26.0	25.9
	Current drinker	16.7	20.9	12.3	15.2
Smoking	Never smoker	12.9	16.9	12.9	16.7
	Former smoker	22.1	26.7	16.4	18.1
	Current smoker	14.8	21.7	14.1	15.6
Marital status	Single	9.6	13.3	14.5	17.6
	Married	20.3	25.6	14.0	16.4

Table 3b. Overall status of participants at the end of follow-up

		Men weighted %			Women weighted %		
		Other cause	CVD death	Alive	Other cause	CVD death	Alive
Age	<65	3.3	1.5	94.6	3.3	0.7	96.0
	>=65	23.9	22.5	53.6	18.3	12.6	69.1
Income adequacy	Low	6.3	2.3	91.3	4.1	2.5	93.3
	Middle	6.7	4.7	88.6	5.9	2.0	92.1
	High	3.5	1.8	94.8	3.0	1.1	96.0
Educational level	Elementary or Some secondary	11.8	7.5	80.7	8.5	4.7	86.8
	Secondary or University degree	3.2	1.6	95.2	3.5	1.0	95.5
Employment status	Full-time or Part-time	3.5	1.9	94.6	2.7	0.5	96.8
	Retired	21.8	16.1	7.2	13.9	10.3	75.8
	Unemployed or Laid off or Home maker or Student or Other	4.8	0.8	94.4	6.5	2.5	91.1
Exercise (≥ 1 time/week)	Yes	5.9	3.2	90.8	4.3	1.7	93.9
	No	5.1	3.3	91.7	5.8	2.4	91.8
Alcohol	Former drinker	9.8	4.9	58.3	7.7	5.7	86.5
	Current drinker	5.3	3.1	91.7	4.1	1.3	94.6
Smoking	Never smoker	2.7	1.2	96.1	5.1	1.7	93.2
	Former smoker	6.4	4.9	88.7	3.7	2.1	94.2
	Current smoker	8.1	2.2	89.7	6.3	2.4	91.3
Marital status	Single	3.6	2.1	94.3	5.9	1.6	92.4
	Married	6.4	3.7	89.9	4.4	2.1	93.5
Overall	Mortality	5.6	3.2	91.1	4.8	1.9	93.2

Table 4 describes the prevalence of the components of the Metabolic Syndrome according to both definitions in both sexes. As it is shown, ATP III definition identifies people with a more adverse metabolic profile. In women who have the Metabolic Syndrome according to the IDF definition 81.9%, 76.6%, 71.7%, and 14.4% have low

high-density cholesterol, high triglyceride, hypertension, and diabetes, respectively, versus 84.5%,

80.3%, 78.4%, and 19.3% according to ATP III ($p \leq 0.001$). In men, the comparable levels of prevalence are 71.7%, 85.1 %, 71.5%, and 10.5% according to IDF

and 78.7%, 89.3%, 85.0%, and 13.1% according to ATP III ($p \leq 0.001$).

Table 4. Prevalence of MetS-Components by ATPIII and IDF definition stratified by sex.

	MEN				WOMEN			
	IDF		ATP III		IDF		ATP III	
	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome	Normal	Metabolic Syndrome
Low HDL*	20.8%	71.7%	22.3%	78.7%	31.7%	81.9%	32.7%	84.5%
TG≥1.7	20.0%	85.1%	23.0%	89.3%	10.7%	76.6%	12.0%	80.3%
HTN**	27.8%	71.5%	27.6%	85.0%	13.2%	71.7%	13.8%	78.4%
DM	1.9%	10.5%	1.9%	13.1%	3.5%	14.4%	3.0%	19.3%
Elevated WC***	24.8%	100%	8.8%	69.6%	26.9%	100%	11.5%	76.8%

*Low HDL for men: HDL <1.03, women: HDL<1.3
** Blood pressure ≥ 130/85mmHg or anti hypertensive treatment
***Elevated WC by ATP III for men: WC≥102; for women WC≥88
***Elevated WC by IDF for men: WC≥94; for women: WC≥80
**** The difference of proportions of the two definitions is statistically significant ($p \leq 0.001$) for all components.

Table 5a, 5b present the hazard ratios of CVD mortality associated with the Metabolic Syndrome. According to the multivariable models, the hazards of dying due to CVD events in women who have the syndrome according to the ATP III and the IDF definitions are 3.96 (1.30-12.09) and 2.56 (1.32-4.97), respectively. The comparable numbers for men are 2.21 (1.16-4.02) and 2.50 (1.50-4.17). Regardless of the definitions, in women, the hazards of death due to CVD are higher in those who are older, inactive, current smokers, former drinkers, and retired. In men, regardless of the definitions, the hazards of death due to CVD are higher in those who are older, current smokers, and of middle income.

Interaction terms between the Metabolic Syndrome and other risk factors was examined, which none of them was statistically significant. In women, regardless of definition, age was a confounding factor. In men, when the IDF definition and the ATP III definitions were applied, smoking and income were confounding factors, respectively.

Table 5a. Hazard ratios for CVD mortality associated with the Metabolic Syndrome by both definitions in women, final model.

	Categories	CVD mortality HR (95% CI)
WOMEN		
ATP III	No	Ref
	Yes	3.96(1.30-12.09)
AGE *	<65	Ref
	>=65	6.18(1.49-25.59)
EXERCISE	Yes	Ref
(≥ 1 time/week)	No	1.63(1.01-2.64)
SMOKING	Never smoker	Ref
	Former smoker	2.17(1.09-4.31)
	Current smoker	3.68(1.89-7.18)
ALCHOL	Former drinker	Ref
	Current drinker	0.39(0.20-0.78)
EMPLOYMENT	Full-time or Part- time	Ref
STATUS	Retired	4.53(1.12-18.38)
	Unemployed or Laid off or Student or Home maker or Other	2.09(0.51-8.55)
WOMEN		
IDF	No	Ref
	Yes	2.56 (1.32-4.97)
AGE *	<65	Ref
	>=65	6.40(1.63-25.21)
EXERCISE	Yes	Ref
	No	1.68(1.05-2.68)
SMOKING	Never smoker	Ref
	Former smoker	2.17(1.08-4.35)
	Current smoker	3.74(1.89-7.40)
ALCHOL	Former drinker	Ref
	Current drinker	0.35(0.17-0.75)
EMPLOYMENT	Full-time or Part- time	Ref
STATUS	Retired	5.03(1.27-19.97)
	Unemployed or Laid off or Student or Home maker or Other	2.20(0.57-8.53)

*confounding factor

Table 5b. Hazard ratios for CVD mortality associated with the Metabolic Syndrome by both definitions in men, final model.

	Categories	CVD mortality HR (95% CI)
MEN		
ATP III	No	Ref
	Yes	2.21(1.16-4.02)
AGE	<65	Ref
	>=65	20.58 (10.61-39.89)
SMOKING *	Never smoker	Ref
	Former smoker	1.93(0.98-3.72)
	Current smoker	2.26(1.08-4.76)
EDUCATIONAL LEVEL	Elementary or Some secondary	Ref
	Secondary or University degree	0.70(0.47-1.03)
INCOME	Low	Ref
	Middle	1.74(1.00-3.01)
	High	1.49(0.65-3.34)
MEN		
IDF	No	Ref
	Yes	2.50(1.50-4.17)
AGE	<65	Ref
	>=65	20.14(10.20-39.78)
SMOKING	Never smoker	Ref
	Former smoker	1.81(0.93-3.54)
	Current smoker	2.20(1.02-4.71)
EDUCATIONAL LEVEL	Elementary or Some secondary	Ref
	Secondary or University degree	0.68(0.48-0.96)
INCOME ADEQUACY *	Low	Ref
	Middle	1.81(1.05-3.11)
	High	1.51(0.66-3.48)

*confounding factor

4. Discussion

One of the main concerns among researchers and clinicians is having a unified definition which can identify precisely individuals with the Metabolic Syndrome (6-10,23-28). To our knowledge it is the first attempt to examine the association between the Metabolic Syndrome and CVD mortality in Canadian adults by using the ATP III and the IDF definitions, and compared the predictive power of these two definitions for the CVD mortality.

The results show that the prevalence of the Metabolic Syndrome is lower in women than men which is consistent with the result of other studies (11). The results also showed that the prevalence of the Metabolic Syndrome was lower according to the ATP III than the IDF definition. This finding has also been observed in several other studies (5-11). There could be two main reasons for having a lower prevalence of the syndrome according to the ATP III definition: the use of the European WC cut-off value (94, 80 cm), not American, in the IDF definition; or the indication of WC as a main obligatory component in the IDF definition (5).

As observed in several other studies (7,11,24), the concordance between the IDF and the ATP III definition is good in this study (Kappa statistics for men: 70.8% Kappa statistics for women: 82.3%). These findings are not surprising because the essential components of these definitions are the same (7,11,24).

In the present study, the ATP III definition identifies people with a more adverse metabolic profile including: blood pressure, TG, LDL cholesterol, and HDL cholesterol. The similar results also observed by Olijhoek et al (10). These results raise the question

regarding the prognostic implication of these two definitions. To answer this question, we compared the definitions regarding their predictive accuracy for the CVD mortality.
In this study, the CVD mortality is higher in individuals with the syndrome than those without the syndrome. These results also have been observed in several studies (12-22). In four notable meta-analyses by Ford et al, Galassi et al, Gami et al, and Mottillo et al the pooled relative risks (RRs) for developing the cardiovascular events in individuals with the syndrome according to the ATP III were 1.74, 1.6, 1.35, and 2.35 respectively(12-15). Three of these studies separately reported the pooled RRs for men and women. Galassi et al reported that the RR for developing the CVD events were 1.5 in men and 2.1 in women(13), and the RRs which reported by Gami et al and Mottillo et al were 1.89 and 1.94 in men , and 2.63 and 2.55 in women, respectively (14). In the present study the hazard ratios for CVD mortality are 3.96 in women and 2.21 in men with the Metabolic Syndrome according to the ATP III definitions. Observing higher HRs in the present study compared to other studies might be due to the inclusion of diabetic individuals in the present study. Indeed, in a Meta –analysis by Ford et al, the authors observed that those studies which included diabetic individuals had higher pooled RRs for developing CVD events compared with those studies which did not included individuals with diabetes (2.2 vs 1.58). In fact, individuals with established diabetes have more CVD risk factors which can lead to developing higher CVD events. In addition to this explanation, the base line populations, end point definitions, methods for analysis, duration of follow-up, confounders which have been considered, and the way that the Metabolic Syndrome definitions have been modified in the present study are different from other studies. All these issues might explain why higher HRs have been observed in

the present study (19). Similarly, hazards of CVD mortality for individuals with the syndrome as per the IDF definition are higher in the present study compared to other studies (men HR=2.50, women HR=2.56) (16-21). The same explanation might justify the difference between the results of this study and other studies.

In the present study, regardless of definitions, the hazard of CVD mortality in women with the Metabolic Syndrome is higher than men with the syndrome, as seen elsewhere (13,14). Although there is no clear explanation for this observation, several theories have been proposed (15). Mottillo et al discussed that central obesity had a greater adverse effect on the risk of CVD events in postmenopausal women than men. Also, level of LDL increases and LDL becomes denser in postmenopausal women, which increases the risk of CVD events in women more than men (15). Mottillo et also discussed that the elevation of TG could lead to more coronary artery disease in women than men (15). Huxley et al, in a meta-analysis, reported that coronary heart disease mortality was higher in diabetic women than diabetic men by 50%.(34). A greater adverse effect of diabetes in women than men could be due to several reasons. Several studies showed that diabetic women had a more adverse metabolic profile (34,35) and diabetic women were less likely to receive medications (statins, aspirin and anti- hypertensive medication) than diabetic women (34). Also, unfavorable cardiac risk factors had more impact on diabetic women than diabetic men (35). Thus, higher hazards of CVD events in women than men might be due to the inclusion of subjects with diabetes in the present study.

The results show that the ATP III definition predicts CVD mortality better in women, whereas the IDF definition can predict CVD mortality better in men. As explained earlier, having different end points, considering different confounding factors, using

different modified definitions, and not stratifying results by gender lead to discrepancies among different studies regarding the predictive accuracy of the different definitions (22). Thus, comparing the results is difficult.

Our results show that the ATP III definition (3.96) can predict the CVD mortality better than the IDF definition (2.56) in women. Similar results were observed in studies among non-diabetic Swedish adults (18) and Korean adults (21). In another non-population based study, Saley et al also observed that the ATP III definition could predict the coronary artery events better than the IDF definition (36). Results of the present study show that the ATP III definition identifies women with adverse metabolic profile, and IDF definition fails to identify non-obese women have a high risk of developing the CVD events. In addition, hypertension and low HDL level had the strongest association with CVD events compared to other components in women (37,38). Regitz-Zagrosek, in addition to low HDL level, reported that high TG level had a greater effect in developing CVD events than other components in women (39). Thus, based on these results the criteria of the IDF definition in women should be modified because, as explained earlier, it fails to identify women who have a high CVD mortality risk.

Our results showed that the IDF definition better predicts CVD events than the ATP III definition in men (2.21 vs 2.50). Results that are both consistent (16,20,22)and inconsistent with this finding have been reported (17). Several studies reported that among the components of Metabolic Syndrome, hypertension and abdominal obesity had the strongest association with development of CVD in men (37,39). Also, our results confirm the importance of abdominal obesity as a key factor in developing of CVD events. Katzmarzyk et al in a study in non-Hispanic American men pointed out that the

IDF definition failed to identify a large proportion of not abdominally obese men (WC<94), who had other risk factors and were at a high mortality risk. Thus, they suggested that there is a need to modify the WC threshold (16). However, the results of the present study show that the presence abdominal obesity (WC ≥94, women WC≥80) in combination with other risk factors can accurately predict CVD mortality in Canadian adults. The comparison must be taken with caution because the characteristics of the population are different.

The present study has several strengths. First, the present study is based on large sample size and a population which represents the general Canadian population. Second, our study has a large number of deaths and a long follow-up period, which increases the power of the study (19). Several important confounders have been considered in the present study. However, the present study has several limitations. Diagnosis of diabetes was based on physician diagnosis which can lead to an underestimation of its prevalence and subsequently the prevalence of the syndrome (40). Also, including individuals with diabetes leads to higher hazards of developing of CVD mortality in subjects with the syndrome. There is lack of information regarding the ethnicity of participants which can lead to misclassification of individuals as having MetS. There is no information available about lipid lowering drugs which lead to underestimation of prevalence of dyslipidemia. Individuals who do not have full anthropometric measurements are excluded, which raise the concern of selection bias. Individuals who died due to other causes were also excluded from analysis which might raise some concern regarding the accuracy of the analysis. However, individuals who die due to other causes can not be considered as censored because other causes of death are the competing events but censoring means

that events will happen at a later time. In addition, the goal of this study is to compare the predictive accuracy of the definition for development of the CVD. To ease the confusion regarding the analysis, the competing- risk procedure is performed, and the results show that the final models and hazard ratios are slightly different (data is not shown).

Conclusion

The prevalence of MetS is higher when the IDF definition is applied but the metabolic derangement of individuals identified is less severe. The ATP III definition predicts CVD mortality better in women, while the IDF definition predicts CVD mortality better in men.

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4. Conclusions and future research

The present thesis examine, the prevalence of the Metabolic Syndrome by the IDF and ATP III definitions, the degree of concordance between the definitions, the associated risk factors for the Metabolic Syndrome , the association between the syndrome and CVD mortality, and the predictive accuracy of the definitions for CVD mortality.

Several definitions have been developed during the past decades (3), and it has been well documented that individuals with the Metabolic Syndrome at a higher risk of developing cardiovascular disease, regardless of definition (21,22,40,87-94). Moreover, the main reason to identify individuals with the Metabolic Syndrome is to identify individuals who are at a risk of developing CVD events, however labeling many individuals with a diagnosis of the Metabolic Syndrome leads to burden on patients and public health care system (3,27,91). Although several studies have conducted in the USA and Europe on the Metabolic Syndrome, there is little information available for Canadian adults. The results of this study provide useful information for clinicians and researchers to assess the importance of the syndrome, to identify individuals who are at a risk of CVD events, and to identify associated risk factors. Thus, public health professional and clinicians can implement interventional programs to reduce the prevalence and incidence of the Metabolic Syndrome which would be expected subsequently reduce CVD mortality in Canadian populations.

As explained previously, the primary intention of our studies was to include all individuals for whom full anthropometric measurements were obtained which included only five provinces (Alberta, Manitoba, Ontario, Quebec and Saskatchewan). However,

Statistics Canada completed the linkage of the CHHS data set with the mortality data set and provided the necessary bootstrap weights for only three provinces (Alberta, Manitoba, and Saskatchewan). As a result, the sample size was reduced for our third objective. On the other hand, the research question of first paper is also covered briefly in third paper. Obviously, the results are similar because the analysis was conducted on subpopulation. In this section, results regarding prevalence of the syndrome, the degree of concordance between definitions, and the predictive accuracy of the definitions will be discussed together, while the associated risk factors will be discussed separately.

I. Degree of concordance between two definitions

The results show that the prevalence of the Metabolic Syndrome to be higher in men (ATP III; 17.9%, IDF: 23.8 %) than women (ATP III; 15.3%%, IDF: 17.3%), which is consistent with several studies (11). In two Canadian studies, conducted by Arden et al (32)and Brien et al (36), in which ATP III definitions have been applied the prevalence of the Metabolic Syndrome is 17 % and 17.5 % in men and 13.2% and 11.2% in women. However, in a recent Canadian study, Riediger et reported that the prevalence of MetS was 15.9 in men and 19.5 in women (43). Based on these results, we conclude that there is a need for public health initiatives to reduce the prevalence of MetS in Canadian adults with more emphasis on women.

Although the essential components of both definitions are the same, the prevalence of the syndrome is higher when the IDF definition applied, as has been observed by others (3,11,23-27). This result can be understood by the examining differences in the definitions. In fact, in the IDF definition abdominal obesity (WC) is a required

component and its cut-off value is lower compared to the ATP definition (23). In the present study the European cut-off value has been applied because there is the lack of information regarding the ethnicity of our population and according to the Statistics Canada 86% of the Canadian population was Caucasian in 1991(Statistics Canada) . There is lack of information regarding the WC threshold for Canadian people. Thus, we recommend that defining the WC threshold in Canadian population should be subject of future research.

The results also show that individuals who are identified by the IDF definition have a less adverse cardiovascular metabolic profile with respect to blood pressure, LDL, and HDL. However, a higher prevalence of the syndrome is observed by using the IDF definition (men; ATP III; 17.9%, IDF: 23.8 %, women; ATP III; 15.3%%, IDF: 17.3%). There is also a body of research that suggests that abdominal obesity is the first component which develops before other components of the Metabolic Syndrome (100) and many obese individuals who are metabolically normal might develop insulin resistance later in their life (101). These results raise the questions as to which definition can identify accurately individuals who are at a higher risk of developing CVD events, and whether applying the IDF definition would label more individuals as unhealthy. Several studies attempted to answer these issues by comparing the concordance between definitions (3,11,23,25,27,29,31,37-39), and comparing their predictive accuracy in development of CVD events (21,22,40,87-94).

The results of this study show that the degree of concordance between the IDF and the ATP III definition is good (men: 72 %, women: 80%, $p \leq 0.05$), which is consistent with several other studies (11,25,29). However, the degree of concordance between the

definitions does not provide information regarding the prognostic value of these two definitions. To investigate this issue, the association between the syndrome and CVD mortality, and the predictive accuracy of definitions for CVD mortality need to be investigated.

II. Predictive accuracy of definitions

The results show that regardless of definition individuals with the syndrome have a higher mortality due to CVD events than those without syndrome (men: ATP III=2.21, IDF=2.50; women ATP III =3.96, IDF=2.56) . These findings confirm the importance of the Metabolic Syndrome in mortality from CVD, which has been also observed in several other studies (21,22,40,87-94). Several studies have been conducted in Europe, America, and Asia, but there is little information available for Canadian population. We suggest that the comparison between the definitions regarding their accuracy to predict CVD mortality should be considered for the future research in Canadian population.

As discussed earlier, several studies compared the prognostic value of different definitions (21,22,40,87-94). But the results of these studies should be compared with caution. Indeed, baseline population, duration of follow up, and definition of end points are different. In addition, each study modifies the definitions differently and different confounders are considered in their analyses which lead to difficulty in the interpretation of the results (89). Overall, these issues strongly suggest that there is a need for unified definition which can be used by all researchers and clinicians. In addition, most studies compares the prognostic implication of the ATP III and WHO definitions (21,22,87,88), and there is less information available regarding the comparison of the ATP III and IDF definitions (40,89-93). Also, to our knowledge no study compares the predictive accuracy of these two definitions in Canadian adults. Thus, the present study provides useful information regarding the health consequences of Metabolic Syndrome in Canadian population.

Higher hazards of death due to CVD events are observed in the present study compared to the results of other studies for both sexes (men: ATP III=2.21, IDF=2.50; women: ATP III =3.96, IDF=2.56) (21,22,40,87-94). In addition to differences between the present and other studies (89), it has been well documented that including diabetic individuals in our study leads to observing higher CVD events in subjects with the Metabolic Syndrome (87). Thus, these reasons might explain the difference between the results of this study and other studies.

The results show that although the prevalence of the Metabolic Syndrome is higher in men (ATP III; 17.1 %, IDF: 21.9 %) than women (ATP III; 14.2 %, IDF: 16.7%), the hazard of death due to CVD is higher in women (ATP III =3.96, IDF=2.56) than men (ATP III=2.21, IDF=2.50). Several theories have been developed to explain why women with the syndrome more likely to die due to CVD events (88). It has been discussed that central obesity has greater adverse effects in developing CVD in women than men. Also, high TG level cause more coronary artery disease in women than men, and diabetic women have higher coronary heart disease mortality than diabetic men (88,102,103). These results suggest that the intervention programs, which reduce prevalence and incidence of the Metabolic Syndrome in Canada, should focus more on women. Also, Riediger et al recently reports one in five on Canadian adults have MetS, which confirm the importance of intervention programs to reduce the prevalence of MetS in Canada (43).

Although the ATP definition identifies individuals with a more adverse metabolic profile in both sexes, the prognostic implication of the ATP III and IDF definitions are different between men (ATP III=2.21, IDF=2.50) and women(ATP III =3.96, IDF=2.56). The

ATP III definition identifies women with a more adverse metabolic profile, and predicts CVD mortality better than the IDF definition. These results might suggest that cardiovascular metabolic profile is more important than abdominal obesity in women, as the IDF definition is highly influenced by the presence of abdominal obesity. In addition, most studies report stronger associations between low HDL level and high level TG with CVD mortality compared to other components of the Metabolic Syndrome in women (95,104,105). These results might suggest that the IDF criteria should be modified for Canadian women with more emphasis on cardiovascular metabolic profile and less emphasize on abdominal obesity. In men, the ATP III definition identifies men with a more adverse metabolic profile but the IDF definition predicts CVD mortality better. Several studies report that among the components of the Metabolic Syndrome, the strongest associations are observed between hypertension and abdominal obesity and CVD events (104,105). These results suggest that abdominal obesity, as explained by Cameron et al and Sims et al, is a key component and the first component which develops before other components in men (100,101). However, concluding which definition is superior in Canadian adults should be with caution. Indeed, there is little information available in Canada. Also, the results regarding the predictive accuracy of the IDF and the ATP definitions for CVD events are varied (40,89-93).

III. Associated risk factors

Obesity and CVD are important issues among Canadian population. 60% of Canadian are overweight and obese and almost 30% of women and 31% of men die each year due to CVD in Canada ([1] Statistics Canada, CANSIM Table 102-0529: Deaths, by cause, Chapter IX: Diseases of the circulatory system (I00 to I99), age group and sex, Canada, annual (number), 2000 to 2006. Released May 4, 2010). As discussed earlier, the association between Metabolic Syndrome and CVD events are well documented in the present and several other studies (21,22,40,87-94). Thus, identifying associated risk factors for Metabolic Syndrome is an important issue in Canada. In fact, researchers will be able to implement intervention programs to reduce the prevalence and incidence of the Metabolic Syndrome by knowing the risk factors (9). However, there is little information available in Canada regarding the risk factors of Metabolic Syndrome. The association between several well known risk factors and Metabolic Syndrome is examined in this thesis.

The present results show that the prevalence of the Metabolic Syndrome is age dependent and reaches its peak between the age of 45 and 55 in both men and women. The increasing risk of developing the Metabolic Syndrome by age might be due to increasing the abdominal obesity or insulin resistance by age (48,106). These results suggest the importance of weight reduction in individuals with the syndrome. The American Hearth Association recommends that individuals with the syndrome should be physically active and their diet should be low in saturated and trans fats, cholesterol, sodium, and carbohydrate (3,9).

The results also show that the risk of developing the Metabolic Syndrome in physically active individuals is less than sedentary individuals (men; ATP III: OR= 2.0(1.5-2.8); IDF: OR=1.6(1.3-1.9), women; ATP III OR = 2.2(1.3-3.8), IDF= 2.0(1.2-3.5). Also, higher numbers of death due to CVD are observed for sedentary individuals (men; ATPIII: HR= 20.8 %; IDF: HR =26.7 %, women; ATP III=13.9%; IDF=17.2%). Our results in combination with the results of other studies (49,55,64,66) confirm the importance of physical activity in individuals with the Metabolic Syndrome. The American Hearth Association recommends individuals with the syndrome should be engaged in moderate-intensity activities for at least 30 min for five days per week (9). Thus, applying this recommendation will have undeniable benefits for Canadian adults with the syndrome.

The results of the present study show that the consumption of alcohol consumption have a protective effect for the development the Metabolic Syndrome only in women (ATP III: OR=0.5(0.4-0.7), IDF: OR=0.6(0.4-0.9)). The association between alcohol consumption and the syndrome is complex and contradicting associations have been reported (55,57-59). In the present study the classification of alcohol consumption relied on self-report questioners and there is no information regarding the quantity and types of alcoholic beverage which might lead to bias (107). All these issues suggest that interpretation of the results should be interpreted with caution.

The association between socioeconomic status and Metabolic Syndrome is varied between studies and also is different between men and women. Moreover, there is not an agreement which measure of socioeconomic status are better predictors for the

development of the Metabolic Syndrome (48,49,55,59,65,77-80). The results of present study show that education level in Canadian women (University degree; ATP III: OR=0.2 (0.1-0.5); IDF:OR= 0.3(0.1-0.6), Secondary education ; ATP III OR=0.5(0.3-0.7) , IDF OR=0.6(0.4-0.9)) employment status (retired: ATP III: OR=2.1(1.1-3.8), IDF: OR=1.8 (0.9-3.9)) in Canadian men have significant associations with developing the Metabolic Syndrome . No significant association is observed between income level and risk of developing the Metabolic Syndrome. Our results confirm the importance of education in women (80) and employment in men (49) as protective factors for development of the Metabolic Syndrome. In fact, they can reduce development of each components of the syndrome (48,65). Riediger et al also confirmed that Canadian people with low level of education and income have higher risk to develop MetS (43).

The association between smoking and the Metabolic Syndrome is statistically significant only in unadjusted analysis. However, smoking is a risk factor in men (current smoker: ATP; III OR=1.8 (1.2-2.7), IDF; OR= 1.9(1.3-3.0)) and protective factor in women (current smoker: ATP III; OR=0.7 (0.5-1.2), IDF; OR= 0.9 (0.5-1.6)). Observing the different magnitude of association between smoking and the Metabolic Syndrome may be due to different effect of smoking on abdominal obesity (56) and cardiovascular metabolic profile (49,51-54). Although the present results do not demonstrate a significant association between smoking and the Metabolic Syndrome, smoking is a well know risk factor for cardiovascular disease. Thus, we suggest that, as it was discussed by the American Hearth Association, smokers who have the Metabolic Syndrome should quit smoking (9).

In married men higher odds of developing of Metabolic Syndrome (ATP III; OR=2.1(1.7-2.5), IDF; OR=1.8(1.4-2.3)) and in married women both higher (IDF; OR=1.1(0.8-1.6) and lower odds (ATP III: OR=0.96(0.7-1.2)) of developing the syndrome are observed in unadjusted analysis. However, these associations are not significant in adjusted analysis in this study. It has been discussed that being married could lead to a lower cardiovascular mortality and morbidity (49,69). On the other hand, to our knowledge there is little information available regarding the association between the marital status and the Metabolic Syndrome. We suggest that investigation of this association should be considered for future research.

IV. Future research

It has been discussed that the primary goal of clinical management of individuals with Metabolic Syndrome is to reduce the risk of atherosclerotic disease by reducing LDL cholesterol level, controlling hypertension, and preventing diabetes (9). Theses goals can be achieved through lifestyle modification or drug therapies. In terms of lifestyle modification, weight reduction by reducing caloric intake and increasing physical activity has been suggested. However, there is a need for strategies which help individuals with the Metabolic Syndrome to achieve and sustain these goals for long term. Statins for treatment of dyslipidemia and Angiotension-Converting Enzyme (ACE) inhibitors for treatment of hypertension have been suggested. To our knowledge there is not enough evidence available regarding the primary use of these drugs in individuals with the Metabolic Syndrome, and also more investigation are needed in terms of cost

effectiveness of using theses drugs (9). More research should be done to find the most appropriate therapies for individuals with the Metabolic Syndrome.

As we discussed earlier, there is little known about the association between the Metabolic Syndrome and CVD events by using all definitions, the predictive accuracy of these definitions, and associated risk factors for Metabolic Syndrome in Canadian population. Thus, we suggest that these subjects should be considered for future research in Canadian population. These information help researchers and clinicians to identify individual with the syndrome accurately and also design a good interventional program to reduce the prevalence of the syndrome.

It has been reported that there are number of metabolic changes which occur in individuals with Metabolic Syndrome such as elevations of CRP, inflammatory cytokines (IL-6), fibrinolytic factors (plasminonogen activator inhibator-1), clotting factors (fibrinogn), and reduction of adiponectin. Although, measurement of these factors is not easily available in clinical practice, there is a need for more investigation regarding the association between these proinflammatory and prothrombotic factors and Metabolic Syndrome because it will provide more information about the pathogenesis of the syndrome. It has been shown that there are numbers of different ways which measure body fat distribution such as; using dual-energy x-ray absorptiometry (DXA), CT or MRI, measuring adipose tissue biomarkers (leptin, adiponectin), measuring liver fat (using resonance spectroscopy). Also, there are some other anthrogenic factors which can measure dyslipidemia such as; apolipoprotein B, small LDL particles, triglycerides/ HDL-c ratios. Additional research is needed to better refine which of these measurements should be applied in the definition (9).

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