Université de Montréal

Association between Diet Quality and Metabolic Syndrome in Overweight and Obese Postmenopausal Women

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Association between Diet Quality and Metabolic Syndrome in Overweight and Obese Postmenopausal Women

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Résumé

Objectifs : Le *syndrome métabolique* (MetS) est un ensemble de composantes (obésité, résistance à l'insuline, intolérance au glucose, dyslipidémie, hypertension) qui sont associées à une augmentation du risque de diabète de type 2 et de maladies cardiovasculaires. Aux États-Unis, la fréquence du MetS atteint des proportions épidémiques avec une prévalence de 25% de la population. Les études nutritionnelles traditionnelles se sont concentrées sur l'effet d'un nutriment alors que les études plus récentes ont déterminé l'effet global de la qualité alimentaire sur les facteurs de risque. Cependant, peu d'études ont examiné la relation entre la qualité alimentaire et le MetS.

Objectif: Déterminer l'association entre la qualité alimentaire et le MetS et ses composantes.

Méthodes: La présence du MetS a été déterminée chez 88 femmes post-ménopausées en surpoids ou obèses, selon la définition du *National Cholesterol Education Program Adult treatment Panel III* alors que la qualité alimentaire a été évaluée selon le Healthy Eating Index (HEI). La sensibilité à l'insuline, la composition corporelle et le métabolisme énergétique ont été mesurés.

Résultats: Le HEI corrélait négativement avec la plupart des mesures de masse grasse et du poids mais pas avec la sensibilité à l'insuline, l'hypertension et la plupart des marqueurs lipidiques. Cependant, l'HEI corrélait positivement avec LDL-C/ApoB et négativement avec le métabolisme énergétique.

Conclusion: Les résultats démontrent que l'HEI est associé avec les mesures de gras corporel et la grosseur des LDL.

Mots clés: Obésité, qualité alimentaire, métabolisme lipidique, syndrome métabolique.

Abstract

Background: The *metabolic syndrome* (MetS) is a constellation of different metabolic components including central obesity, insulin resistance, abnormal glucose homeostasis, dyslipidemia and high blood pressure which identify individuals at high risk of type 2 diabetes and cardiovascular events. In the US, the prevalence of MetS has reached epidemic proportion and up to 25% of the population is affected.
Traditional nutritional studies have focused on a single nutrient. Recently, measures of overall diet quality have been proposed as an alternative to assess diet-related diseases. However, few studies have addressed the relationship between diet quality and the MetS.

Objective: To investigate the association of diet quality with the MetS and its components.

Methods: The presence of the MetS was determined in 88 postmenopausal overweight or obese women using the National Cholesterol Education Program Adult treatment Panel III definition while diet quality was assessed with the Healthy Eating Index (HEI). We also measured insulin sensitivity, body composition and energy metabolism.

Results: The HEI correlated negatively with most measures of body fat and body weight but not with insulin sensitivity, blood pressure and most markers of lipid metabolism. However, HEI correlated positively with LDL-C/ApoB and negatively with energy metabolism.

Conclusion: Our results demonstrated that HEI is associated with fat distribution and LDL size.

Key words: Obesity, diet quality, lipid metabolism, metabolic syndrome.

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List of Abbreviations

AHA/ NHLBI	American Heart Association/National Heart, Lung, and Blood Institute
AHEI	Alternate Healthy Eating Index
AM	Ante meridiem
BMI	Body mass index
BP	Blood Pressure
CA	Canada
CB1	Cannabinoid receptor type 1
CE	Cholesterylester
CERFM	Faculty of Medicine Ethics Committee
CETP	Cholesterylester transfer protein
CI	Confidential Interval
Cm	Centimetre
CRP	C-reactive protein
CSFII	Continuing Survey of Food Intake by Individuals
CT	Computed tomography
CVD	Cardiovascular Diseases
DECODE	Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe
DGI	Dietary Guideline Index
DLW	Doubly labelled water

DPP	Diabetes Prevention Program
DQI	Diet Quality Index
DQI-I	Diet Quality Index International
DQI-R	Diet Quality Index Revised
DQS	Diet Quality Scores
DXA	Dual Energy x Ray Absorptiometry
EDTA	Ethylene-diamine tetracetic acid
EGIR	European group for Insulin resistance
EHC	Euglycemic-hyperinsulinemic clamp
FBQI	Food Based Quality Index
FFA	Free Fatty Acids
FFQ	Food Frequency Questionnaire
FPI	Food Pyramid Index
G	Gram
GE	General Electric
GIR	Glucose infusion rate
h	Hour
HDI	Healthy Diet Indicator
HDL-C	High density lipoprotein Cholesterol
HEI	Healthy Eating Index
HEI-90	Original Healthy Eating Index
HEI-Ca	Canadian HEI
HFI	Healthy Food Index

HMG-CoA Reductase	3-hydroxy-3-methyl-glutaryl-CoA reductase
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
IDF	International Diabetes Federation
IDL	Intermediate density lipoprotein
IFG	Impaired Fasting Glycaemia
IGT	Impaired Glucose Tolerance
IL-6	Interleukin 6
IR	Insulin Resistance
IRAS	Insulin Resistance Atherosclerosis Study
IST	Insulin suppression test
kcal/day	Kilocalorie per day
kg/m2	Kilogram per square meter
LDL-C	Low density lipoprotein-cholesterol
LDL-C/ApoB	Ratio of low density lipoprotein cholesterol to Apolipoprotein B
MAI	Mediterranean Adequacy Index
MAR	Mean adequacy ratio
MCP1	Monocyte chemotactic protein-1
MDQI	Mediterranean Diet Quality Index
MDS	Mediterranean Diet Score
meq/L	Milliequivalent per liter

MetS	Metabolic Syndrome
Mg	Milligram
Mg/dL	Milligram per decilitre
Mg/g	Milligram per gram
min	Minute
MMHG	Millimeter mercury column
mmol/L	Millimole per liter
MONET	Montreal Ottawa New Emerging Team
MRI	Magnetic Resonance Imaging
NAR	The Nutrient Adequacy Ratio
NCEP ATPIII	National Cholesterol Education Program Adult treatment Panel III
NF-κB	Nuclear Factor Kappa B
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral Glucose Tolerance Test
OR	Odd Ratio
PAEE	Physical Activity Energy Expenditure
PAI-1	Plaminogen Activator Inhibitor 1
QUICKI	Insulin sensitivity Check Index
RDA	Recommended Dietary Intake
REE	Resting Energy Expenditure
RISC	Relationship between Insulin Sensitivity and Cardiovascular disease)

ROS	Reactive oxygen species
SAT	Subcutaneous adipose tissue
SD.	Standard Deviation
SD-LDL	Small dense -low density lipoprotein
SiOGTT,	Simple index assessing insulin sensitivity from OGTT measurements
TDZ	Thiazolidinediones
TEE	Total energy expenditure
TG	Triglycerides
TIDE	Thiazolidinedione Intervention With Vitamin D Evaluation
TNF-α	Tumour necrosis factor alpha
TSH	Thyroid stimulating hormone
U/L	Unit per liter
UK	United Kingdom
USA	United States of America
VAT	Visceral adipose tissue
VLDL-C	Very low density lipoprotein-cholesterol
WHO	World Health Organization
WHR	Waist to hip ratio
WI	Wisconsin
ß-cells	BETA Cells
µg/ min	Micro gram per minute

µg/h	Microgram per hour
µM/ml	Micro Mol per milliliter
µU/m^2/min	Micro Unit per square meter per minute

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TO MY DEAREST IN THE WORLD

MY MOM AND DAD

Fahimeh & Morteza

FOR THEIR GREAT HEARTS

&

TO MY SPECIAL FRIEND AND HUSBAND

Mohsen

FOR ALL HE IS

1 Introduction

The metabolic syndrome (MetS) is defined as a cluster of different metabolic disorders such as obesity, insulin resistance, dyslipidemia, and high blood pressure. The MetS is considered as an important risk factor for type 2 diabetes and cardiovascular diseases (CVD) [1]. It has been shown that the prevalence of CVD in people with MetS is 50-60% higher than those without MetS [2]. In addition, among the subjects without CVD or diabetes, those with MetS have greater risks of CVD and type 2 diabetes than those without MetS [3]. Furthermore, the San Antonio Heart Study [4] has identified the Mets as a predictor of diabetes. According to the Third National Health and Nutrition Examination Surveys (1988-1994 and 1999-2002 [5, 6]), the MetS is highly prevalent in the US and is an important burden for the US health care sector.

The association of diet with CVD and obesity has been investigated by several traditional nutritional epidemiological studies. These studies focused on the effects of single nutrients, dietary components, or food on the disease processes [7]. However, these studies could not show the overall role of dietary quality or dietary patterns on disease protections. Therefore, during the last decade several observational and interventional studies have reported that dietary patterns are stronger predictor for all-cause mortality and CVD than a single nutrient or food component [8-11]. In 1970, the development and improvement of dietary patterns resulted in the emergence of several diet indices that have been validated by assessing the correlation of the index scores with health outcomes [7, 12, 13]. Although the associations of overall dietary quality with all-cause mortality, chronic disease risk, and biomarkers of CVD have been discussed in several studies [9-12], only few studies have investigated the role of diet in MetS [14]. Among all diet indices, the Healthy Eating Index (HEI) has been validated by several studies and has been found to be a useful tool for estimating the overall dietary patterns [9, 10, 15]. Moreover, recent studies have indicated that HEI correlates with chronic diseases and obesity [16, 17]. Importantly, this index has been specifically validated for the Quebec population [18].

The aim of our study was to investigate the association of diet quality, which is evaluated by the Healthy Eating Index (HEI), with MetS and its components in overweight and obese postmenopausal women who participated in the Montreal Ottawa New Emerging Team (MONET) Weight-loss Weight Regain (WLWR) study.

2 Literature Review of Metabolic Syndrome

2.1 History

Currently, there exist multiple definitions for the metabolic syndrome, and these definitions have changed considerably over time. The first description of this syndrome was proposed in 1920 when the Swedish physician Kylin described the metabolic syndrome (MetS) as a cluster of hypertension, hyperglycaemia, and gout [1, 19]. Two decades later, Vague denoted that a particular obesity phenotype, namely upper body adiposity (android or men type obesity), was associated with metabolic abnormalities including diabetes and cardiovascular disease (CVD) [1, 19]. During the 1988 Banting lecture, Reaven used the term "Syndrome X" to define a cluster of abnormalities using insulin resistance as the central pathophysiological feature [1, 19] owever, he did not include obesity as a component of the syndrome [1, 19]. In 1989, Kaplan renamed it "The Deadly Quartet", which was later substituted by the term "Insulin Resistance Syndrome" [1, 19]. Under this definition, the MetS is characterized by abdominal (visceral and retroperitoneal) obesity and a cluster of other cardiovascular risk factors including impaired glucose tolerance (IGT), increased triglycerides (TG), decreased high density lipoprotein cholesterol (HDL-C), elevated blood pressure and hyperinsulinemia with underlying insulin resistance [1]. Recently, the scientific community agreed that the term "Metabolic Syndrome" was the most useful and widely accepted description of this cluster, which is a risk factor for CVD and diabetes (if not already present) [19].

2.2 Current Definitions

The MetS is a cluster of different conditions, and not a single disease with a specific cut off point. Therefore, multiple definitions have been developed so far in the literature for this syndrome. Currently, there are six independent definitions of the MetS [19], which are presented as follow and will be briefly discussed thereafter.

- World Health Organization (WHO) [20]
- The European Group for the study of Insulin Resistance (EGIR) [21]

- The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) [22]
- The American Association of Clinical Endocrinology [1, 23]
- The International Diabetes Federation (IDF) [24]
- The American Heart Association/National Heart, Lung and Blood Institute [25]

The four most currently used definitions are summarized in Table 1.

Table 1. Definitions of the metabolic syndrome based on consensus statement

Definition	WHO [20, 26]	EGIR [21]	NCEP ATPIII [22]	IDF [24]
Criteria	Insulin resistance + 2 factors below	Insulin resistance + 2 factors below	3 or more factors below	Central obesity + any 2 factors below
Insulin Resistance	• Type 2 diabetes or • Impaired fasting glucose or • Impaired glucose tolerance • Evidence of insulin resistance	• Insulin Resistance • Fasting hyperinsulinemia (> 75th percentile)		
Plasma glucose	• Type 2 diabetes or • Impaired fasting glucose or • Impaired glucose tolerance • Evidence of insulin resistance	• >6.1 mmol/L (110 mg/dl) but non-diabetic	• ≥ 6.1 mmol/L (110 mg/dl)	• FPG ≥ 5.6 mmol/L (100 mg/dl) or • Type 2 diabetes
Obesity	• BMI > 30 kg/m^2 or • WHR > 0.9 Men • WHR > 0.85 Women	• Waist Circumference Men ≥ 94 cm (37 in) Women ≥ 80 cm (31.5 in)	• Waist Circumference Men > 102 cm (40 in) Women > 88 cm (35 in)	• Central obesity • Specific ethnic waist circumference values
Dyslipidemia	• TG ≥ 1.7 mmol/l (150 mg/dl) • HDL-C Men < 0.9 mmol/l (35 mg/dl) Women <1.0 mmol/L (39 mg/dl)	• TG > 2.0 mmol/l (178 mg/dl) or treatment • HDL-C <1.0 mmol/l (39 mg/dl) or • treatment	• TG ≥ 1.7 mmol/L (150 mg/dl) • HDL-C Men <1.03 mmol/l (40 mg/dl) Women < 1.29 mmol/l (50 mg/dl)	• TG ≥ 1.7 mmol/L (150 mg/dl) • HDL-C Men <1.03 mmol/l(40 mg/dl) Women < 1.29 mmol/l (50 mg/dl)
Hypertension	• ≥ 140/90 mmHg or • Treatment	• >140/90 mmHg or • Treatment	• Systolic >130 mmHg or • Diastolic > 85 mmHg	• Systolic >130 mmHg or • Diastolic > 85 mmHg or • Treatment
Others	• Urinary albumin excretion rate ≥ 20 µg/min or • Albumin/creatinine ratio ≥ 30mg/g			

WHR: Waist to hip ratio

The World Health Organization (WHO) Definition

The WHO was the first to release a definition for the MetS in 1998-1999 [1, 20, 26]. Under this definition, insulin resistance is a required component for diagnosis. Insulin resistance can be defined as one of the following: (a) type 2 diabetes, (b) impaired fasting glucose (IFG), (c) IGT or (d) for those with normal fasting glucose values (< 110 mg/dl), glucose uptake below the lowest quartile for background population under hyperinsulinemic-euglycemic conditions [27]. The inflammatory or haemostatic variables such as hyperuricaemia, coagulation disorders, and plasminogen-activating inhibitor [19] are associated with the MetS and highlighted in WHO. However, these variables are not necessary for the recognition of insulin resistance.

There are some limitations for the WHO definition [1, 19], such as the use of the euglycemic-hyperinsulinemic clamp to measure insulin sensitivity. The utilization of this technique is virtually impossible in clinical practice or epidemiological studies. Finally, the use of waist to hip ratio (WHR) was criticized since for a similar WHR one subject can be obese while another is not.

The European Group for the Study of Insulin Resistance (EGIR) Definition

Following the publication of the WHO definition in 1999, the EGIR group proposed a modified version of it to be used only in non-diabetic subjects. The EGIR proposed to measure fasting insulin levels to estimate insulin resistance and IFG as a substitute for IGT. Since this definition does not require the euglycemic-hyperinsulinemic clamp, it is considered as a simpler method to use in clinical practices and in epidemiological studies [1, 19]. However, significant problems remain about the standardization of insulin assay, which considerably limits both application and comparison between studies.

The National Cholesterol Education Program Adult treatment Panel III (NCEP ATPIII) Definition

In 2001, the NCEP ATPIII definition was presented as a part of educational programme for the prevention of coronary heart disease [1]. The goal of this definition was to facilitate diagnosis in clinical practice. The authors hoped that the simple definition could lead to an easier identification and thus implementation of preventive measures for CVD and type 2 diabetes [19]. This definition has two major differences as compared to the others. First, it does not include insulin resistance as a required component. Second, it is not "glucose centric". Thus, all components are treated with equal importance. It is notable that the NCEP ATPIII definition uses waist circumference as a measure of obesity (though with higher cut points than the EGIR) [1, 19]. Unlike the WHO, the NCEP ATPIII definition does not mention any other factors such as inflammatory and haemostatic variables. This definition has been widely used due to its simplicity since its components are easily and routinely measured in most clinical settings. On the other hand, some studies have shown that NCEP ATPIII fails to identify some patients with insulin resistance [22].

The International Diabetes Federation (IDF) Definition

In May 2004, the IDF released its statement on the MetS. The main goals were to examine how the current definitions of the MetS could be improved and to reach a consensus statement for a new, unifying and worldwide working definition. They also wanted to discuss the treatment of subjects with MetS and the prevention of diabetes and CVD [1, 19, 25]. The IDF wanted to provide a definition that

a. was easy to use in clinical practice, while avoiding the need of measurements available in research settings,

b. facilitated the comparisons across countries and populations, and

c. highlighted areas where more research was needed.

Furthermore, the IDF decided that the definition should have been less "glucose centric". Moreover, since abdominal obesity was highly correlated with insulin resistance, its presence became a necessary diagnosis requirement [25]. The definition of abdominal obesity is based on waist circumference with specific ethnic cut off points. In South Asians, Chinese and Japanese, the cut off values for men and women are ≥ 90 and 80 cm, respectively, while they are ≥ 94 and 80 cm for Europeans men and women, respectively. Thus, for Caucasians these cut-off points are lower than the ones proposed by the NCEP ATPIII (≥ 102 cm for men and ≥ 88 cm for women). The European cut off points are also used for Sub-Saharan Africans, Eastern Mediterranean and Middle East populations, while for South and Central Americans the Asian recommendation is used (see Table 2).

The IDF is the only definition that provides ethnic specific cut off values for waist circumferences. These have been developed based on expert consensus rather than strong scientific evidences, which explain the various cut-off points proposed by each organisation.

Table 2. Specific ethnic waist circumference values (adopted from IDF consensus worldwide definition of metabolic syndrome) [24]

Country/Ethnic group	Waist Circumference	
Europids Except for the USA, the ATPIII values (102 cm men, 88 cm women) are likely to be used	Men	≥ 94cm
	Women	≥ 80cm
South Asians: based on a Chinese, Malay and Asian-Indian population	Men	≥ 90cm
	Women	≥ 80cm
Chinese	Men	≥ 90cm
	Women	≥ 80cm
Japanese	Men	≥ 85cm
	Women	≥ 90cm
Ethnic South and Central Americans	South Asian recommendations until more specific data are available	
Sub-Saharan Africans	European recommendations until more specific data are available	
Eastern Mediterranean and Middle East (Arab) populations	European recommendations until more specific data are available	

These cut off points have been modified in the Canadian Guidelines [28]

The American Association of Clinical Endocrinology (AACE) Definition

More recently, the AACE released a modification of the NCEP ATPIII definition as a position statement on the "insulin resistance syndrome" [23]. The AACE definition considered insulin resistance as a core feature and its goal was to identify individuals with

insulin resistance. In diabetic subjects, glucose rises while insulin concentrations decline. This can lead to a false estimation of insulin sensitivity when surrogate indices are used. Since the goal is to measure insulin resistance easily and reliably, diabetic subjects are excluded. The AACE statement does not provide a specific definition for the MetS, and allows diagnosis to rely on clinical judgments [1, 19].

The American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) Definition

In contrast to the IDF, the AHA/NHLB decided to keep the NCEP ATPIII criteria with some minor modifications. The only difference between the AHA/NHLB and the NCEP ATPIII is the reduction of the threshold for impaired fasting glucose from 110 to 100 mg/dl, which corresponds to the American Diabetes Association criteria for this parameter [25].

2.3 Prevalence of the Metabolic Syndrome

The prevalence of the MetS will clearly vary depending on the definition applied, the ethnicity, and the age of the study population. The 1988-1994 cross-sectional National Health and Nutrition Examination Survey (NHANES) was done on 8814 men and women aged 20 years or older [6]. The objective of this study was to estimate the prevalence of the MetS in USA as defined by the NCEP ATPIII report. In this study, the unadjusted and age-adjusted prevalence of the MetS were 21.8% and 23.7%, respectively. The prevalence among participants aged 20-29 years was 6.7% while this number increased to 43.5% and 42% for those aged 60-69 and 70 years or older, respectively.

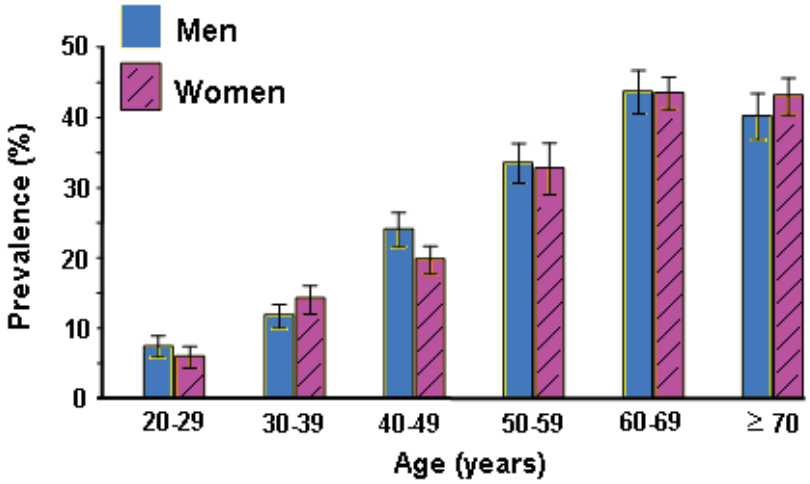

Figure 1. NHANES III: Prevalence of metabolic syndrome by age [6]

The highest age-adjusted prevalence was observed in Mexican-Americans (31.9%) while African-American and Mexican-American women had 57% and 26% higher prevalence than men, respectively.

Based on the 2000 census data, about 47 million of the US residents or 22% (24% after adjustment) have the MetS and approximately 73.9% of them are overweight or obese. There are some differences between previous estimations of the MetS prevalence in the US and Europe, in part because of the definitions used and the populations studied [6]. It has been suggested that the prevalence of the MetS tends to be higher than what estimated from 1988-1994 NHANES data due to the increase in the prevalence of obesity in the US [6].

A study by Earl Ford on 3601 American adults aged ≥ 20 years from the 1999-2002 NHANES [6] (Figure 1) showed that the unadjusted prevalence of the MetS was 39% and 35% according to IDF and NCEP ATPIII definitions, respectively [5]. Based on the IDF definition, the unadjusted prevalence of the MetS was 39.9% and 38.1% among men and women, respectively, while it was 33.7% and 35.4% among men and women according to

NCEP ATPIII [21]. This study, as well as another one from Greece [29], showed that the IDF definition led to a higher prevalence of the MetS than the NCEP ATPIII definition. However, compared to the study from Greece, the IDF definition seems to better predict CVD in middle-aged subjects [30]. Importantly, comparison between the two surveys (1988-1994 NHANES and 1999-2002 NHANES) highlights the significant increase in the prevalence of MetS over these periods [21].

As shown in Table 3, there are also some differences between the prevalence of MetS using NCEP ATPIII and WHO criteria among non-diabetic adults [31]. Furthermore, the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE), in which 10269 subjects were enrolled, suggests that the WHO definition has higher hazard ratios for CVD mortality in men than other definitions [32]. Therefore, it is still unclear which definition is the most appropriate one.

Table 3. Prevalence of the metabolic syndrome (%) using NCEP ATPIII and WHO criteria among non-diabetic adults (30-79 years) in the Framingham Offspring study (1991-95) and San Antonio Heart studies (1992-96) [31]

	White N=3224		Non-Hispanic white N=1081		Mexican-American N=1656	
	Men	Women	Men	Women	Men	Women
NCEP ATPIII Waist circumference (cm) men ≥ 102 women ≥ 88	26.9	21.4	24.7	21.3	29	32.8
NCEP ATPIII BMI ≥ 30 kg/m^2	25.2	17.8	22.1	15	28.4	26.8
WHO BMI ≥ 30 kg/m^2	30.3	18.1	24.7	17.2	32	28.3

NCEP: National Cholesterol Education Program; WHO: World Health Organization; BMI: body mass index

2.4 Pathogenesis of the Metabolic Syndrome

The pathogenesis of MetS is poorly understood and is likely to be complex and multifactorial [19]. Three potential etiological categories of factors have been identified: (a) obesity and disorder of adipose tissue, (b) insulin resistance, and (c) a cluster of independent factors e.g., hypertension, molecules of hepatic, vascular, and immunological origins. In addition, other factors such as aging, proinflammatory state, hormonal changes, genetic profile, physical inactivity, and atherogenic diet (e.g. a diet rich in saturated fat and cholesterol) have been implicated in the development of the MetS. The role of these causal factors varies depending on the ethnic group [1] .

2.4.1 Obesity and abnormal body fat distribution

As shown in Figure 2, the prevalence of obesity is rising rapidly in USA [33-35]. According to the WHO [36], at least 1.1 billion adults are overweight among which 312 millions are morbidly obese. In the last decade, the obesity prevalence has shown a dramatic increase of 10-40% in European countries while 50% of adults in Western Europe are overweight or obese. Furthermore, in the US 65% of adults are overweight or obese that indicates a 40% rise in the prevalence of overweight and 110% increase in the prevalence of obesity compared to the last decade [37].

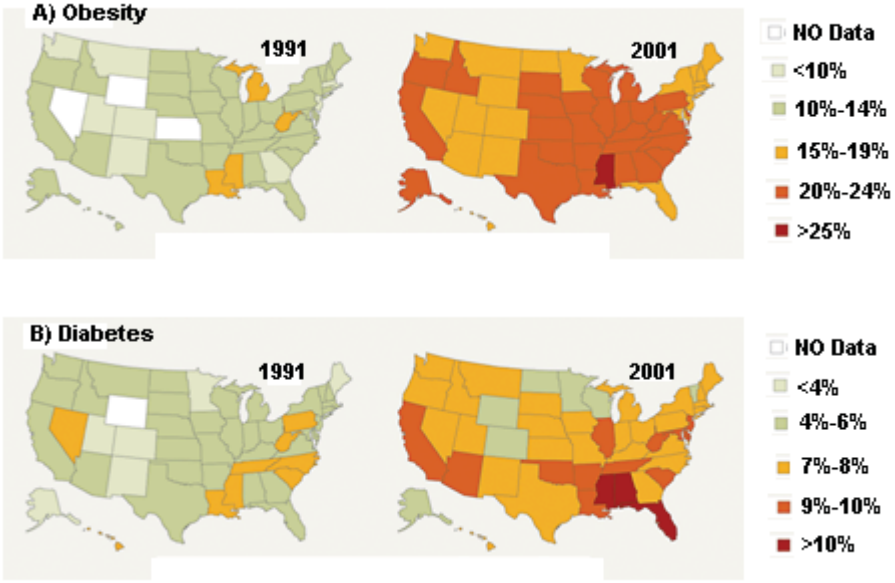

Figure 2. Prevalence of obesity and diabetes in adults 1991-2001 [38]

Obesity is most often defined based on body mass index (BMI) by using the following formula: weight (kg) divided by height squared (meter). As shown in Table 4, BMI is categorized into normal (20-25), overweight (25-30) and obese (≥ 30) [39]. Obesity can also be defined according to the percentage of total body fat, which is defined as ≥ 25% and ≥ 35% in men and women, respectively, or by waist circumference. Several

methods can be used to evaluate the percentage of total body fat, such as skin-fold thickness, bioelectrical impedance, Magnetic Resonance Imaging (MRI), Dual Energy X Ray Absorptiometry (DXA), underwater weighing (which used water displacement), and the BOD POD Gold Standard Body Composition Tracking System (which used air displacement). Some techniques also assess fat repartition including DXA, computed tomography (CT scan), MRI and waist circumference. Except for waist circumference, most of these techniques are rarely used in clinical practice because of inconveniences (as in radiation) and costs [40]. The recommendation for weight management can be made based on standardized BMI and waist circumference cut off points. The US National Institute of Health [40] and Scottish Intercollegiate Guidelines Network [41] have defined different waist circumference cut off points based on the severity of obesity. Thus, the cut off values of 94 cm in men and 80 cm in women represent moderate obesity, while severe obesity is defined as 102 cm in men and 88 cm in women. However, according to NCEP ATPIII, in the US abdominal obesity is defined as a waist circumference of ≥ 102 and ≥ 88 in men and women, respectively [40]. The Canadian clinical practice guidelines emphasize that for a given BMI, any waist increment increases the health risk associated with obesity (Table 4) [42].

Table 4. Health risk as a function of waist circumference and BMI [42]

	BMI category		
Waist circumference	Normal 18.5 - 24.9 kg/m^2	Overweight 25 - 29.9 kg/m^2	Obese class I 30 - 34.9 kg/m^2
Men: < 102 cm Women: < 88 cm	**Least risk**	**Increased risk**	**High risk**
Men: ⩾ 102 Women: ⩾ 88 cm	**Increased risk**	**High risk**	**Very high risk**

Ferranini et al. [43] showed that 35% of individuals with BMIs of 30-35 kg/m^2 and 65% of those over 35 kg/m^2 are insulin resistant. The San Antonio Heart study [44] showed that WHR and fasting insulin levels were significant predictors of the MetS. 32% of individuals presenting high BMI ($\geq$ 30 kg/m^2) and high waist circumference (102 cm in men and 88 cm in women) had developed the MetS as compared to 10% of subjects with low BMI and low waist circumference [42]. Furthermore, anthropometric indices remain significant predictors of the MetS after adjustment for fasting insulin, a surrogate measure of insulin resistance. The increased prevalence of the MetS, type 2 diabetes, and insulin resistance have been paralleled with the increase of obesity prevalence that suggests a role for obesity in promoting these diseases. According to NHANES, the prevalence of the MetS rises with increasing BMI [45]. Furthermore, the IDF [1] and the NCEP ATPIII [46] consider that the "obesity epidemic" is one of the main reasons for the rise in the prevalence of the MetS.

Obesity is also associated with multiple risk factors, which can alone or together favour the development of CVD. These factors include (a) atherogenic dyslipidemia (elevated levels of TG, very low density lipoprotein-cholesterol (VLDL-C), low density lipoprotein-cholesterol (LDL-C), apolipoprotein B-100 (ApoB) and low levels of high density lipoprotein cholesterol (HDL-C) [47]), (b) high blood pressure [48], (c) inflammation, and (d) coagulation and fibrinolytic abnormalities which can induce a prothrombic state [49-51].

Body fat distribution

Obesity can be due to increased adipocyte size (hypertrophy) or adipocyte numbers (hyperplasia) [52]. It is believed that bigger adipocytes are more insulin resistant and produce more deleterious molecules (such as TNF-α) than smaller adipocytes [52]. A large number of cross-sectional and prospective studies have confirmed the proposal of Jean Vague [53, 54], which suggested that excessive fat stored in trunk (or abdominal

obesity) could be metabolically more damaging than gynoid (also called lower-body, peripheral fat, and gluteofemoral fat) obesity. In fact, abdominal fat correlates better with insulin resistance and MetS than lower body obesity [55]. Therefore, in 1983 abdominal obesity was found as a key factor in promoting MetS [56].

An accumulation of abdominal body fat can occur intraperitonally (visceral fat) or subcutaneously. Excessive visceral fat (VAT) correlated more strongly with insulin resistance than other adipose tissue compartments [25, 57]. In addition, a recent study has found a strong and independent relationship between intra-abdominal fat (VAT) area and the MetS [58]. On the other hand, some studies [59, 60] have observed a significant association between excessive subcutaneous abdominal fat and insulin resistance. In addition, this adipose tissue depot has been found to predict the features of MetS [58]. Several studies have demonstrated that even after correcting for BMI, waist circumference is still significantly associated with cardiovascular and all-cause mortality [61] (see Figure 3). This indicates the important role of abdominal adipose tissue compared to peripheral adipose tissue [21, 26, 62]. Importantly, even individuals with a normal BMI can have excessive VAT and show the feature of MetS. In addition, Figure 4 summarizes the role of abdominal obesity in development of MetS and Type 2 diabetes.

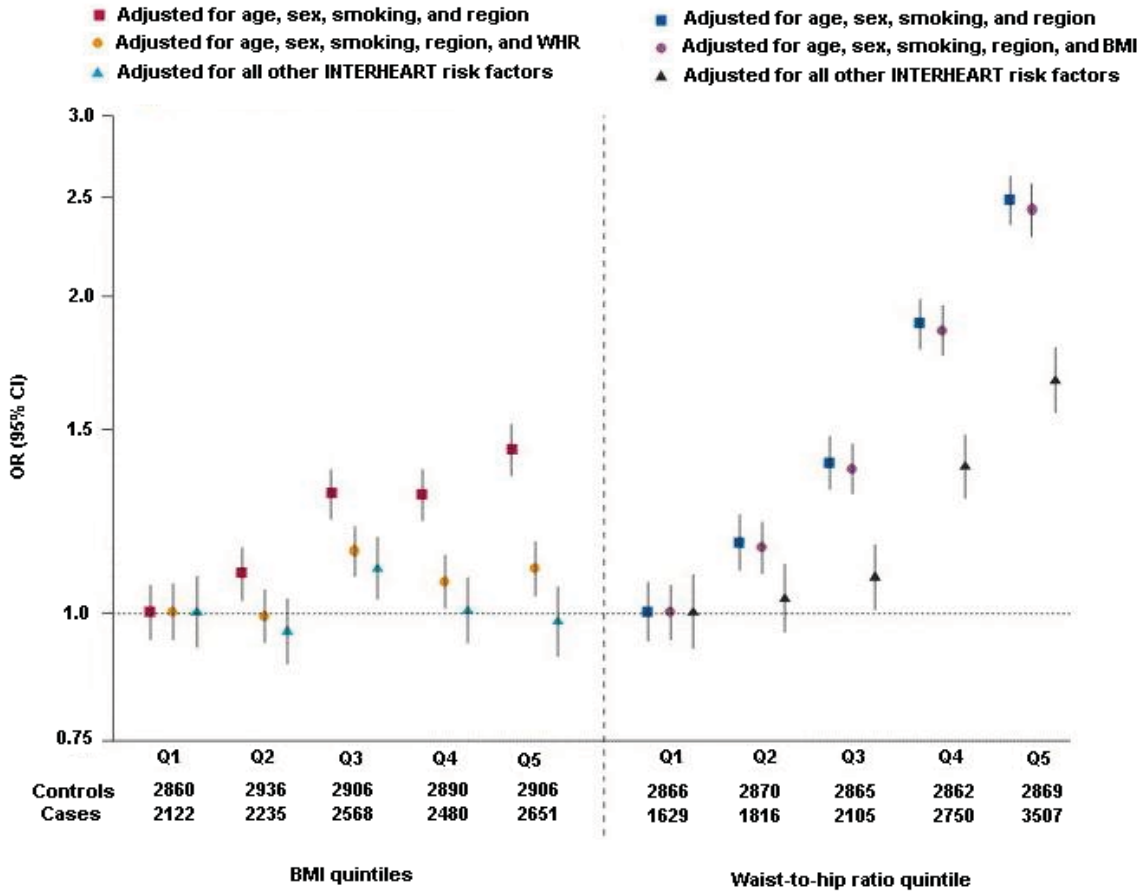

Figure 3. Association of BMI and waist-to-hip ratio with myocardial infarction risk. Vertical bars = 95% CIs [61]

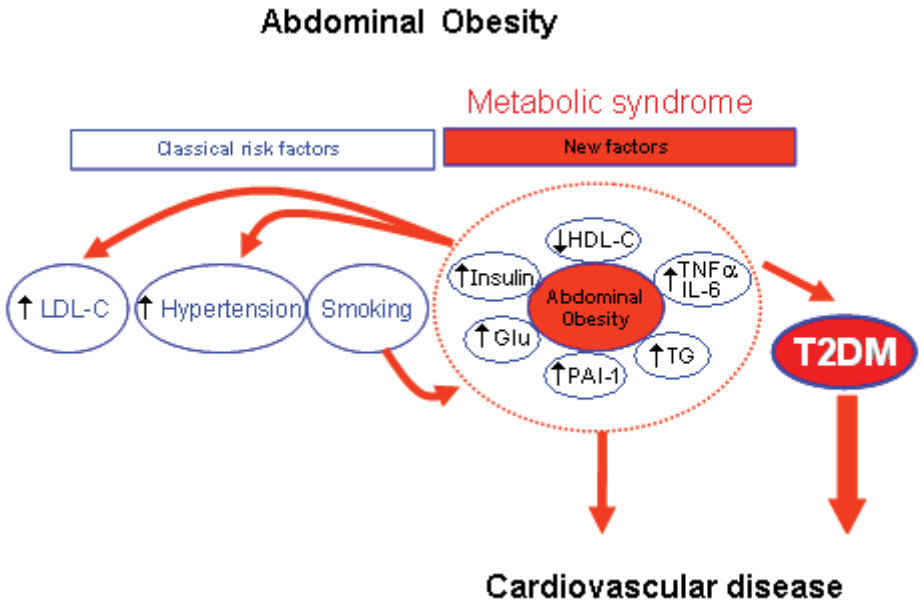

Figure 4. The role of abdominal obesity in development of MetS and Type 2 diabetes

Role of adipose tissue

In addition to the role of adipose tissue in heat insulation, mechanical cushioning, and TG storage [63], adipose tissue is a key endocrine organ that secretes active endocrine, paracrine and autocrine substances in response to different stimulus [64]. Thus, the association of obesity (particularly VAT) with metabolic risk factors could be explained through the following factors: (a) increased free fatty acids (FFA), (b) ectopic fat deposition, (c) altered postprandial lipid buffering, and (d) altered adipocytokine production.

Role of Free Fat Acids (FFAs) and ectopic fat deposition

FFAs are the primary energy source in the fasting state. They are derived from the biolysis of adipose tissue's triglycerides. This results in an increased FFA which is released by adipose tissue and leads to elevated circulating FFA levels. Since FFA uptake in different tissues is proportional to their concentrations, increased FFA levels lead to higher

tissue uptake of FFA [63]. This increased FFA influx enhances reactive oxygen species (ROS) production leading to oxidative stress. Elevated circulating FFA levels also promote fat accumulation in non-adipose tissues that is also called ectopic fat deposition. This can occur in muscle, pancreas, kidney, heart, and liver [39]. Ectopic fat deposition is toxic for most cells (lipotoxicity) including those from the heart and the pancreas, and can lead to lipoapoptosis or lipid-induced programmed cell death. Lipotoxicity can also cause insulin resistance, impaired insulin secretion, and type 2 diabetes [65, 66].

In the liver, increased fat deposition causes fatty liver, atherogenic dyslipidemia, and insulin resistance. Reduction of insulin action in the liver enhances glycogenolysis and increases hepatic glucose output, which accentuates hyperglycaemia in those patients. Liver fat accumulation is also associated with increased hepatic synthesis of plasminogen activator inhibitor-1 (PAI-1), fibrinogen, and inflammatory cytokines [67].

In pancreatic β-cells, the combination of excessive lipids (lipotoxicity) and hyperglycaemia (glucotoxicity) (that is called gluco-lipotoxicity) appears to be a deleterious combination favouring the progression to overt diabetes [68].

Role of postprandial lipid buffering

Abnormalities described in the previous section are exacerbated in the postprandial state due to lipid intake [69]. During this period, adipose tissue switches from a lipolytic to a lipogenic state. FFA derived from triglyceride rich lipoproteins are drained from the plasma wildly by adipose tissue during the postprandial period, while they are released softly during fasting period. The switch between the two states depends not only on the adipose tissue functional state but also on the environmental milieu (substrates and hormones). Because insulin plays a major role in lipid synthesis and degradation, insulin resistance in obese subjects leads to failure of the buffering function of adipose tissue [70], that results in higher plasma postprandial lipids levels. Postprandial lipidemia initiates

various processes leading to metabolic abnormalities such as high triglycerides, low HDL-C, liver abnormalities, inflammation, β-cell dysfunction and apoptosis [71].

Role of adipocytokines

Adipose tissue is an endocrine organ that secretes a large number of biologically important substances named adipocytokines. Adiponectin and leptin are anti-inflammatory while tumour necrosis factor alpha (TNF-α), interleukin (IL)-6, PAI-1, angiotensinogen, and resistin have proinflammatory characteristics. As shown in Figure 5, obese individuals present elevated amounts of IL-6 and TNF-α [72, 73]. Studies have shown that TNF-α can impair insulin action and inhibit endothelial vasodilatation [72, 74], while resistin is associated with obesity and type 2 diabetes [75]. In addition, in people with abdominal obesity and high plasma fibrinogen it has been found that high level of PAI-1 leads to prothrombic state [76].

Adiponectin is an antiatherogenic adipocytokine that modulates glucose and fatty acid metabolisms. In obese subjects, excessive adipose tissue is associated with decreased adiponectin production, which may alter insulin sensitivity [77-81]. This hormone also inhibits TNF-α and its downstream regulator, NF-κB, and thus may reduce the proinflammatory profile. Hypoadiponectinaemia is associated with high BMI, insulin resistance, dyslipidemia, endothelial dysfunction, and increased risk of CVD and type 2 diabetes [78, 79, 82].

Another anti-inflammatory adipocytokine is leptin, which controls energy homeostasis and is an appetite suppressant. Leptin enhances fatty acid oxidation and protects against fatty liver. However, most obese subjects show leptin resistance as reflected by the high plasma leptin levels.

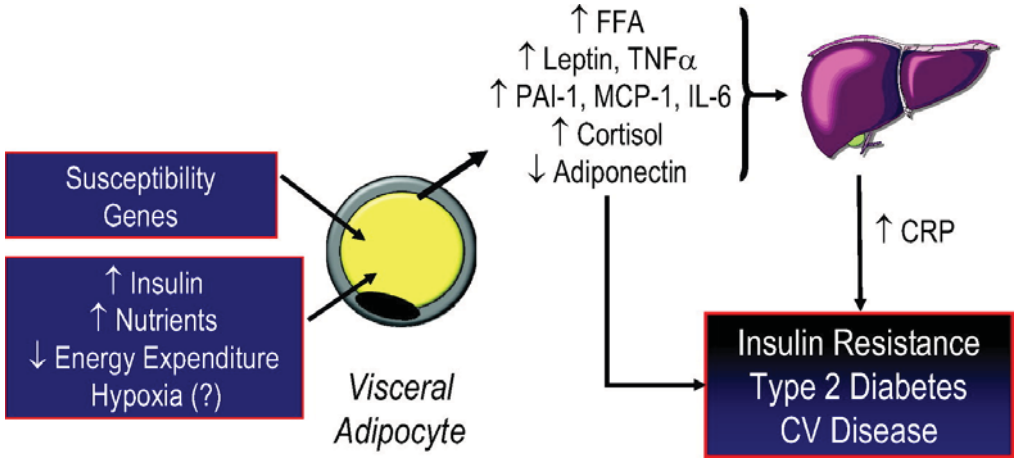

Figure 5. Role of visceral adipocyte in the development of insulin resistance, type 2 diabetes, and CVD [80]

2.4.2 Insulin Resistance

Insulin is a major anabolic hormone secreted by the pancreatic β-cells, which is essential for appropriate tissue development, growth, and maintenance of glucose homeostasis. Insulin has several roles in the body, such as decreasing postprandial glucose level due to increased glucose uptake into skeletal muscle and adipose tissue, and decreasing hepatic glucose production via inhibition of gluconeogenesis and glycogenolysis. Insulin also increases lipid synthesis in liver and fat cells and decreases fatty acid release from adipose tissue. Insulin regulates over 700 genes involved in metabolic and cellular functions [81]. Thus, altered insulin action may lead to elevated circulating glucose and FFA levels. Hyperglycaemia may promote cell damage (glucotoxicity) through multiple mechanisms including (a) increased production of ROS leading to oxidative stress, (b) increased formation of glycation end products [82], (c) increased hexosamine pathway, and (d) accumulation of intracellular diacylglycerol leading to the activation of protein kinase C, with diverse intra and extra cellular consequences [83]. Moreover, studies have shown that glucotoxicity may exacerbate insulin resistance and thus it may induce a vicious circle.

Several factors can contribute to the development of insulin resistance, such as genetic predisposition, ageing, sedentary life style, nutritional factors, obesity, hypertension and inflammation. Insulin resistance can trigger other components of the MetS such as obesity, type 2 diabetes, atherogenic dyslipidemia, hypertension, prothrombic and inflammatory state (Figure 6). Insulin resistance exists at any given level of body fat, and variation in insulin resistance may vary more than 10-fold even in apparently healthy normal weight subjects [84]. Interestingly, insulin resistance in normal weight subjects displays metabolic abnormality reminiscent of the MetS [85]. They have been identified as Metabolically Obese Normal Weight (MONW), an early phase of the MetS [86]. However, studies have shown that insulin resistance usually rises with the increase in body fat content [87]. It has been shown that basal and total 24-h rates of insulin secretion are 3-4 times higher in obese subjects compared to their lean counterparts [88]. On the other hand, variation of insulin sensitivity exists even within the obese population. A subset of obese individuals, who remain insulin sensitive, has been identified [88].

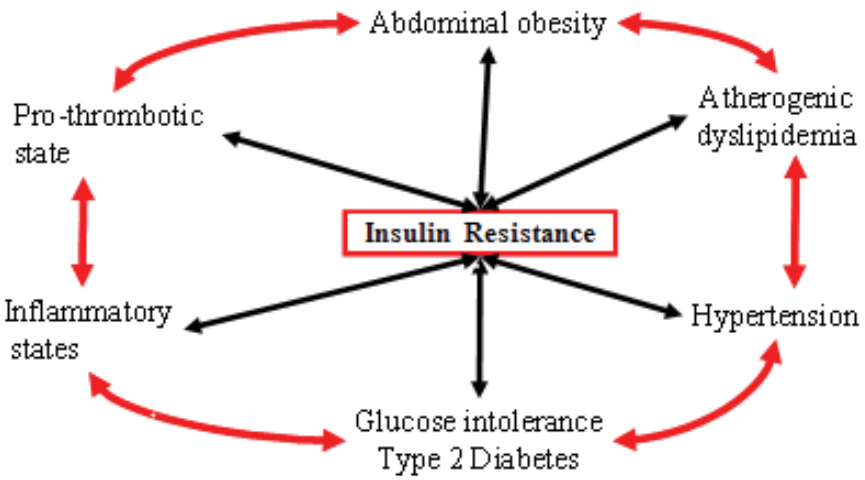

Figure 6. Metabolic Syndrome Components [6]

Insulin resistance is more common in some populations (e.g. South Asians) even with BMI $< 25\ kg/m^2$, and it contributes to the high prevalence of type 2 diabetes and premature CVD. Insulin resistance is present in the majority of people with MetS and it is one of the components of the MetS definitions in the WHO and EGIR as discussed previously. The association of insulin resistance or hyperinsulinemia with MetS components has been shown in a large number of studies. It is widely believed that insulin resistance is a central feature of the MetS and could be even more important than obesity [89, 90]. Bruneck et al. [91] have demonstrated that in subjects aged 40-79 years, the degree of insulin resistance assessed with the homeostasis model assessment (HOMA), which is a widely used fasting surrogate measure of insulin resistance, was correlated with the number of metabolic abnormalities. Karelis et al. have confirmed this association using the euglycemic-hyperinsulinemic clamp [92]. Several studies have shown that insulin resistance is strongly associated with most components of MetS, including atherogenic dyslipidemia and a proinflammatory state, while a weak association with hypertension and the prothrombic state has been reported [93-95]. The complexity of these links resulted from multiple causes that included (a) interaction of genes predisposing to insulin resistance with those modulating lipid metabolism, and (b) blood pressure and artery wall biology [96].

Reaven and Farquhar [97] began to define the insulin resistance syndrome and its links to both hypertriglyceridemia and CVD. In the following decades, several prospective cohort studies have shown the association between hyperinsulinemia or surrogate measures of insulin resistance, and risk of atherosclerosis even in non-diabetic subjects [88, 96]. For example, the San Antonio Heart Study reported that higher insulin levels were associated with a 2.5 fold increased risk of CVD even after controlling for blood pressure, medication, family history, age, BMI, plasma lipid levels, and tobacco and alcohol use [98]. The Helsinki Policemen Study, which included 1000 men followed up for a period of 9.5 years, has shown that plasma insulin levels were associated with coronary heart disease [99].

Similar results were obtained by Ducimetier et al. in 7000 non-diabetic middle-aged men [100]. Although some data suggest that insulin resistance and hyperinsulinemia are two independent risk factors for CVD, their associations have not been confirmed yet in large-scale clinical trials [101]. The need for prospective evaluation of insulin resistance as an independent CVD risk factor led the EGIR to design the Relationship between Insulin Sensitivity and Cardiovascular disease (RISC) study. Thus, 1500 healthy individuals in 13 countries were examined for insulin resistance and CVD risk, prospectively after 3 and 10 years. The study has shown that insulin resistance precedes the development of intermediate phenotypes (obesity, dyslipidemia, hypertension) while the association with atherosclerosis is still being evaluated [102]. However, there are increasing evidences that insulin resistance may be directly atherogenic. The Insulin Resistance Atherosclerosis Study (IRAS) showed a direct relationship between insulin resistance and the carotid artery intima thickness even after adjusting for several associated risk factors [103]. Hyperinsulinemia could be atherogenic by stimulating the division and migration of vascular smooth muscle cells of the vessel wall, and by promoting endothelial dysfunction. Supporting a role for insulin in this process, thiazolidinediones (TDZ) and other peroxisome proliferator-activated receptor (PPAR)-γ ligands, which increase insulin sensitivity, inhibit smooth muscle cell proliferation and migration [104, 105]. However, the effect of TDZ administration on CVD risk is still controversial. Thus, randomised controlled trials with type 2 diabetic patients receiving TDZ have demonstrated no reduction in CVD risk [106] or equivocal results [107], while meta analyses have suggested increased CVD risk [108-111]. Targeting insulin resistance to reduce CVD risk is currently tested in a huge randomized trial, namely the Thiazolidinedione Intervention with Vitamin D Evaluation (TIDE) study.

Methods to assess insulin sensitivity/resistance

There is no accepted cut off value that defines insulin resistance. As discussed previously, the absence of a standardized insulin assay is a major limitation. Insulin resistance affects various tissues at different levels. Thus, various methods and parameters

capturing different aspects of insulin resistance have been developed (including those specified below). One drawback is that since different methods are used to assess insulin resistance, the results obtained are not always comparable [112].

Hyperinsulinemic euglycemic clamp: This method is currently the accepted gold standard for investigating and quantifying insulin resistance [113]. The response of an individual to insulin is measured through infusion of a fixed dose of insulin to reach a hyperinsulinemic plateau, and through a variable glucose infusion aimed to maintain a constant serum glucose level (5.0-5.6 mmol/L or 89-90 mg/dL). To assess liver insulin resistance, low doses of insulin are more useful whereas high doses of insulin are better for assessing peripheral (muscle and fat) insulin resistance. Insulin resistance is calculated according to the rate of glucose infusion during the last 30 min of the test, which usually lasts for 2 to 3 hours. Stable isotopes can be used to measure more precisely the hepatic glucose production and the tissue utilisation. This test is done more in research than in clinical setting, because it is costly and rather complex to perform [76]. Despite the fact that it is considered as the gold standard, numerous technical variations exist such as the amount of insulin used, the length of the test, etc. [114].

Insulin Suppression Test (IST): After an overnight fast, somatostatin (250 µg/h) is infused intravenously to suppress endogenous insulin production. Simultaneously, glucose and insulin are infused over 150 min at constant rate. The resultant steady state plasma glucose concentration obtained during the last 30 min of the test represents an estimation of insulin sensitivity. The higher the glucose concentration goes, the more the individual is insulin resistant. The IST was the first test that utilized steady state plasma insulin levels to promote disposal of a glucose load. However, and similar to the clamp, the IST is impractical in large epidemiological studies. Moreover, there is a risk of hypoglycaemia in insulin-sensitive subjects. Finally, the IST can provoke glycosuria in type 2 diabetes subjects leading to an underestimation of insulin resistance. Since the clamp and the IST are expensive, complex to perform, and not applicable for routine clinical practice,

mathematical models have been developed to estimate insulin resistance using insulin and glucose levels either in the fasting state or during the OGTT.

Oral glucose tolerance test (OGTT): In the absence of fasting hyperglycaemia, OGTT is the recommended test for the diagnosis of diabetes. Glucose and insulin values collected during the OGTT are used to calculate various indices to estimate insulin sensitivity. For examples, Bastard et al. have proposed the simple oral glucose tolerance test (SiOGTT), which has been validated in various clinical situations [115]. Usually, OGTT-derived indices correlate better with the euglycemic hyperinsulinemic clamp than fasting based indices. Thus, the OGTT offers the ability to derive physiological information from a clinical test. However, the length (2-h) as well as the need for repeated blood sampling is a limitation.

Usually the OGTT is performed in the morning (7-8 am) as glucose tolerance shows a diurnal rhythm with a significant decrease in the afternoon. The patient should be fasting for the previous 8-14 h but water is allowed. Table 5 shows the criteria for the diagnosis of IFG, IGT and diabetes using this test. Ideally, diet and exercise should be standardized during the previous day (sufficient carbohydrate intake and no unusual exercise) to ensure adequate glycogen store. During an illness, the test should not be performed because the results may not reflect the patient's glucose metabolism in a healthy state. In addition, it is important to adjust the glucose load to the weight in a person with body weight less than 43 kg.

Table 5. Values for diagnosis of diabetes and other categories of hyperglycaemia [26]

	Serum glucose concentration mmol/L (mg/dL)		
	Venous	**Capillary**	**Plasma Venous**
Normal			
Fasting			<6.1 (< 110)
2-h post glucose load			<11.1(< 200)
Impaired Fasting Glycemia (IFG)			
Fasting and	≥ 5.6 (≥ 100) and <6.1 (110)	≥ 5.6 (≥ 100) and <6.1 (<110)	≥ 6.1 (≥ 110) and < 7.0 (< 126)
2-h post glucose load (if measured)	<6.7 (<120)	<7.8 (<140)	<7.8 (< 140)
Impaired Glucose Tolerance (IGT)			
Fasting (if measured) and	<6.1(<110) and	<6.1 (<110) and	<7.0 (< 126) and
2-h post glucose load	≥ 6.7 (≥ 120)	≥ 7.8 (≥ 140)	≥ 7.8 (≥ 140)
Diabetes			
Fasting or	≥ 6.1 (≥ 110)	≥ 6.1 (≥ 110)	≥ 7.0 (≥ 126)
2-h post glucose load	≥ 10.0 (≥ 180)	≥ 11.1 (≥ 200)	≥ 11.1 (≥ 200)

Fasting based indices

The first and the most well accepted model, which was proposed by Matthews et al. [116], is the HOMA. It is a mathematical model for estimating insulin resistance from plasma glucose and insulin values. Also a close alternative, namely the quantitative insulin sensitivity check index (QUICKI), has been proposed by using log transformed glucose and insulin values [117]. Both of these models correlate well with *in vivo* measures of insulin sensitivity. Although these two methods are widely available and have a predictive value in the development of type 2 diabetes, they have not been routinely used in clinical practices due to lack of evidence-based data that can guide the clinician to make decisions [76]. Table 6 shows the formula of these two mathematical models for insulin resistance assessment.

Fasting serum insulin level can also be used as a marker of insulin resistance since studies have shown that the two rise in parallel [118]. It has been found that fasting insulin level is a good surrogate in non-diabetic obese postmenopausal women [112]. Insulin cannot be used in diabetic patients because at some point plasma insulin falls and does not reflect insulin resistance any more. Furthermore, pharmacological treatments can bias plasma insulin values (e.g. insulin and sulfonylurea).

Table 6. Mathematical models for insulin resistance assessment [88]

HOMA-IR Homeostasis Model Assessment of Insulin Resistance	Fasting insulin (μM/ml) X fasting glucose (mmol/l)/22.5
QUICKI Quantitative Insulin-Sensitivity Check Index	1/[log fasting insulin + log fasting glucose (mg/dl)]

2.4.3 Dyslipidemia

Another component of the MetS is atherogenic dyslipidemia. As shown in Figure 7, this condition is defined as an aggregation of lipoprotein abnormalities including increased levels of serum TG, ApoB, and small LDL-C, as well as reduced level of HDL-C. All of these abnormalities are independently atherogenic. Dyslipidemia is strongly regulated by genetic variation, diet, alcohol intake and physical activity. Therefore, there is a considerable variation in the dyslipidemia phenotype in response to obesity and/or insulin resistance [46].

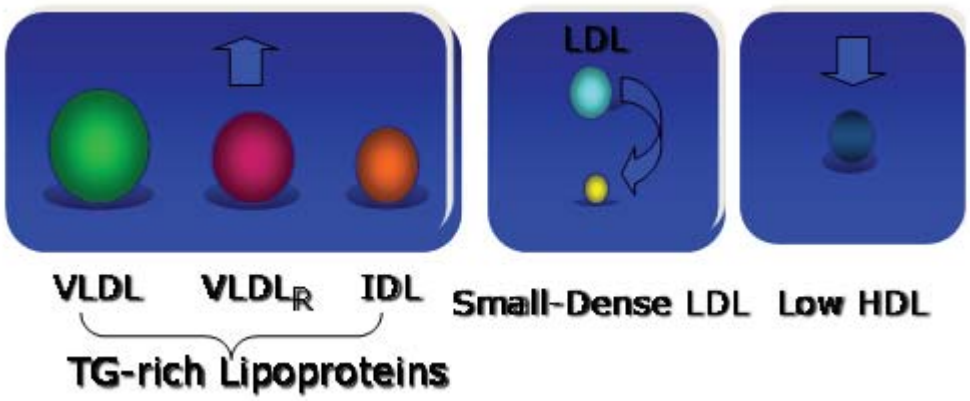

Figure 7. Atherogenic dyslipidemia

As shown in Figure 8, cholesterol metabolism is regulated mainly by five lipoprotein groups: (a) chylomicrons, (b) VLDL, (c) intermediate density lipoprotein, (d) LDL, and (e) HDL. VLDL is assembled in the liver from cholesterol and apolipoproteins. It transports cholesterol and triglycerides within the body. Two forms of VLDL exist, namely VLDL1 and VLDL2, which are assembled and secreted from the liver. VLDL1 is larger and contains more TG compared to VLDL2. VLDL 1 is pro-atherogenic through two main effects: 1) it is converted to LDL in plasma and 2) it decreases HDL level. Over-secretion of VLDL 1 has been associated with insulin resistance and type 2 diabetes [119].

LDL transports cholesterol and triglycerides from the liver to peripheral tissues while HDL transports cholesterol mostly to the liver. The cholesterol delivered to the liver is either recycled into new lipoproteins or excreted into the bile and the intestine. ApoB is the primary component of LDL and is absolutely required for its formation. ApoB is also found in VLDL. Importantly, there is one ApoB molecule per LDL and VLDL. Usually, more than 90% of ApoB is bound to LDL-C. It is believed that ApoB can act as a ligand for LDL receptors, thereby allowing cholesterol to transport into the cell. Since there is only one ApoB per LDL particle, and since in healthy subjects more than 90% of ApoB is found in LDL particles, determination of whole plasma ApoB can be considered as a reasonable approximation of LDL-Number.

It is well known that high LDL-C levels are predictors of CVD [100, 120, 121]. There are extensive evidences for the observation that reducing LDL-C through inhibition of a key enzyme for cholesterol formation (HMG co-A reductase) reduces CVD risk [122]. Studies have identified seven distinct LDL subclasses based on their diameters [123, 124]. The LDL size is primarily inherited. Several case control and prospective studies have shown that smaller LDL particles are better predictors of CVD than absolute LDL-C or larger LDL-C particles [100, 120, 121, 125-127]. Furthermore, the LDL particle size has been found to be a significant predictor in the univariate analysis in three large studies: the Quebec Cardiovascular Study [126], the Harvard Physicians Health Study [128], and the Stanford Five City Projects [129]. Characteristics of small and dense LDL include (a) longer residence time in plasma and (b) enhanced susceptibility to oxidation. These factors are considered as the main links to CVD. The NCEP ATPIII [22] has identified the small dense LDL as an emerging cardiovascular risk factor.

There exists large inter-individual variation in cholesterol content per LDL particle. Thus, the measures for LDL-C and LDL-Number are not equivalent. In fact, the number of total and smaller LDL particles has been found as a significant and independent predictor of CVD risk after multivariate adjustment for lipid variables [130, 131]. Convincing evidences from the Cardiovascular Heart Study [130], the Women's Health Study [132] the Veterans Affairs High-Density Lipoprotein Intervention Trial [5], and the Paravastatin Limitation of Atherosclerosis in the Coronary Arteries [133] have found that LDL-Number is a stronger predictor of CVD than LDL-C. In addition, the Framingham Heart Study [134] showed a parallel increase in small LDL-Number and in the number of MetS components in both men and women. In addition, the number of increased small LDL particles was associated with the number of increased TGs and decreased HDL-C, but it was not reflected in the concentration of LDL-C. Therefore, to have a reliable estimate of atherogenecity both the number and the size of LDL particles should be considered.

Insulin plays an important role in the regulation of FFA and lipoprotein profile, and studies have shown the association of insulin resistance with dyslipidemia. As shown in Figure 8, at the level of the adipocyte, insulin resistance is considered as the initiating insult, which leads to increased intracellular hydrolysis of TGs and leads to release of FFAs into circulation [96]. Defective FFA uptake by adipocytes may also contribute to elevated circulating FFA levels. Increased FFA flux to the liver stimulates the assembly and secretion of lipoproteins [135]. Thus, fatty liver could cause atherogenic dyslipidemia by stimulating VLDL secretion that leads to high LDL-C and TG, small LDL particles, and low HDL-C [136, 137]. In addition, hyperinsulinemia enhances hepatic VLDL synthesis, which may directly contribute to increased plasma TG and LDL-C level. Alternatively, elevated TG and LDL cholesterol levels may result from reduced insulin action on lipoprotein lipase in peripheral tissue [138].

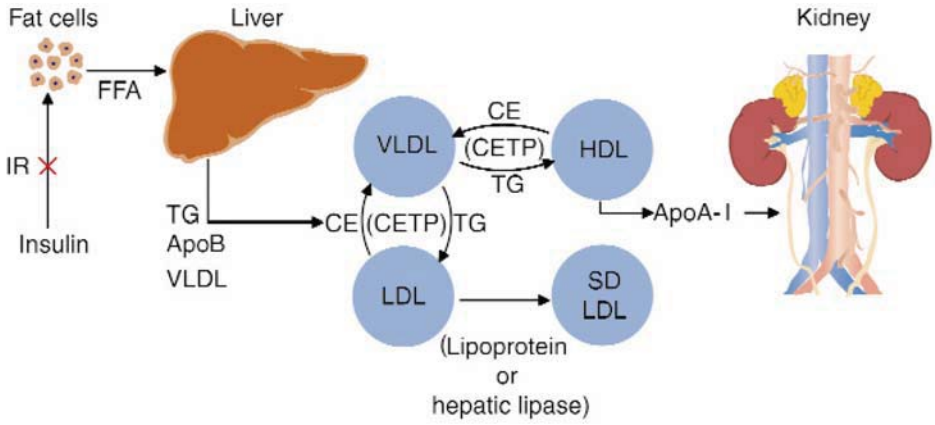

Figure 8. A simplified model relating insulin resistance to dyslipidemia and cardiovascular disease [96]

In addition to the changes in LDL and VLDL, diabetes patients also showed a significant reduction of HDL-C concentration. It has been suggested that in type 2 diabetes patients, insulin resistance may be responsible for reduced HDL-C level [67, 138]. This is due to the increase of HDL-C degradation, which exceeded its synthesis rate.

In summary, increased FFA release from adipocytes or defective uptake of FFA into adipocytes leads to increased circulatory FFA levels. These effects may explain the association between insulin resistance and dyslipidemia [96].

2.4.4 Hypertension

Hypertension is one of the components of the MetS. It has been shown that hypertension can promote the development of CVD [139]. Elevated blood pressure is also associated with obesity and glucose intolerance, and it commonly occurs in insulin resistant individuals. The strength of this association, however, varies considerably from one population to another. Epidemiological studies have highlighted the correlation between fasting insulin levels and systolic and diastolic blood pressure that is independent from age, weight, and serum glucose levels. Lind et al. [93] showed that 25% of hypertensive subjects were insulin resistant that suggested a role of hyperinsulinemia in the pathogenesis of arterial blood pressure. In addition, insulin resistance is found more frequently in salt-sensitive hypertensive subjects than in low salt-sensitive subjects. Furthermore, weight loss is associated with both blood pressure reduction and improved insulin sensitivity.

Four main reasons may explain the association between hypertension and insulin resistance: (a) abnormalities in insulin-mediated vasodilatation and blood flow, (b) the role of increased FFAs in inhibition of vasodilatation, (c) over activity of the sympathetic nervous system, and (d) the role of hyperinsulinemia in increased absorption of sodium and water by kidney tubular cells.

2.4.5 Other metabolic risk factors

The elevation of C-reactive protein (CRP), an inflammatory cytokine, leads to the proinflammatory state which is commonly present in people with MetS. Excessive adipose tissue leads to the release of inflammatory cytokines, which could promote an inflammatory state in obese individuals [5]. In fact, several studies have shown that there

is a significant relationship between plasma CRP and measure of adiposity and insulin resistance [5]. Moreover, the risk of having elevated CRP parallels the increase in the number of MetS components [140]. In high-risk subjects, increased physical activity is associated with lower sub-clinical inflammation [141]. Recent data suggest a link between lipoproteins and sub-clinical inflammation since hypolipidemic treatment in subjects with high CRP but normal LDL-C reduces CVD risk (JUPITER trial). Furthermore, there exist evidences of a significant relationship between ApoB and sub clinical inflammations [141].

The prothrombic state is considered as another risk factor in which plasma PAI-1 and fibrinogen have been increased. Since high cytokine levels could lead to an increase in fibrinogen, an acute-phase reactant protein like CRP, the proinflammatory and prothrombic states are considered to be interconnected metabolically [27]. Stimulation of PAI-1 secretion by insulin has been observed is cell culture as well as in humans following an intravenous insulin infusion, that suggests that hyperinsulinemia may directly inhibit fibrinolysis in insulin-resistant subjects [142]. High levels of VLDL can also stimulate PAI-1 synthesis and secretion by cultured cells. It seems that this process is sensitive to the PAI-1 genotype [143].

Advancing age is another metabolic risk factor. Several studies have shown that the MetS prevalence rises with advancing age [88]. Since ageing is commonly accompanied by a loss of muscle mass and strength as well as an increase in body fat, particularly in the abdomen, these abnormalities could favour the emergence of the MetS. Moreover, the lack of physical inactivity which occurs more commonly in elderly people promotes the development of obesity and insulin resistance. By using gold standard methods to measure strength, insulin sensitivity, and physical activities, studies have shown (a) the more association of a higher strength rather than a higher muscle mass with insulin resistance [144], and (b) the impact of objectively measured reduced physical activity on the prevalence of metabolic syndrome [145]. Table 7 shows metabolic measurements (not included in the definition) for which additional research is required to explore their association with and their role in metabolic syndrome.

In conclusion, MetS represents a cluster of risk factors (blood pressure, obesity, insulin resistance, high TGs, etc.), which together increase the cardio metabolic risks mainly including CVD and diabetes. Importantly, in clinical practice the MetS definition allows the identification of high-risk individuals for cardio-metabolic complications. Furthermore, since most of these risk factors are modifiable through changes in lifestyle, diet, and physical exercise, early identification of these subjects may allow early treatment of MetS and thus may reduce the burden associated with MetS.

Table 7. Additional metabolic measurements

IDF [24]	WHO [20, 26]
Abnormal body fat distribution: General body fat distribution (DEXA) Central fat distribution (CT/MRI) Liver fat content (MRS) Adipose tissue biomarkers: leptin, adiponectin	Hyperuricaemia
Atherogenic dyslipidemia: (beyond ⇑TG and low HDL-C) ApoB (or non HDL-C), small LDL particles	Coagulation disorders
Insulin Resistance:(other than elevated fasting glucose) Fasting Insulin/proinsulin levels HOMA-IR Insulin resistance by Bergman Minimal Model ⇑ free fatty acids (fasting and during OGTT) Insulin sensitivity (hyperinsulinemic/euglycemic clamp) (mg/min/kg)	⇑ PAI-1
Vascular dysregulation (beyond ⇑ BP) Measurement of endothelial dysfunction Microalbuminuria	
Proinflammatory state: ⇑ high sensitivity C-reactive Protein ⇑ inflammatory cytokines (e.g. TNF α, IL-6) ⇓ adiponectin plasma levels	
Prothrombic state: Fibrinolytic factors (PAI-1, etc.) Clotting factors (fibrinogen, etc.)	
Hormonal factors: Pituitary-adrenal axis	

3 Literature Review of Food Quality Indices

3.1 History of food quality indices:

Traditional nutritional epidemiological studies have examined the association between diet and diseases such as CVD, obesity, and MetS. These studies focused mostly on the impact of a single nutrient, dietary component, or food on the disease process [7]. This approach has highlighted the protective effect of vegetables and the deleterious effect of saturated fat on coronary heart disease and cancer [146, 147]. This approach, which is called "reductionist" [7], presents some advantages as well as limitations [148]. Focusing on a single nutrient helps to understand its role in the aetiology and pathogenesis of a disease, but it does not allow the investigation of the overall role of dietary quality or dietary patterns on disease protection or susceptibility.

According to Kant et al. [8], dietary patterns measure multiple dietary components as a single exposure. In several studies, dietary patterns have been derived by either of the following approaches: (a) using diet indices or scores that evaluate the compliance with dietary guideline, or (b) using data-driven methods based on factor or cluster analysis. In order to investigate the relation of dietary patterns with dietary biomarkers and chronic disease risk, several studies considered fruit, vegetable, wholegrain, fish, and poultry consumptions as the components of dietary patterns, regardless of the utilized approach.

The multidimensional nature of diet consumed by humans calls for the investigation of the association between dietary patterns and diseases as an alternative or complementary approach to the traditional method of investigating the effect of a single dietary component [147].

During the last decade, the effect of dietary patterns on all-cause mortality and CVD has been demonstrated through both observational and interventional studies [8]. Dietary patterns have been shown to be stronger predictors for survival than a single nutrient or food component [8]. Furthermore, several clinical trials have shown that

changing dietary patterns lowers blood pressure more efficiently than changing a single dietary component [8]. However, it has been suggested that dietary-derived patterns may be population-specific, which could be a limitation of this approach [149]. Therefore, investigating the effect of overall dietary habits can be complementary to the traditional method of investigating the effect of a single dietary component [14].

3.2 General overview on Diet Quality Scores (DQS)

In the 20th century, nutritional over-consumption and imbalance rather than nutritional deficiency have been implicated in the aetiology of chronic diseases. In fact, numerous studies have highlighted the strong association of the diseases including coronary artery diseases, stroke, diabetes, and certain forms of cancer, with the diets enriched in total fat, saturated fat, sodium, and cholesterol, as well as the diets low in fibre and complex carbohydrates. Therefore, in 1970 the goal of dietary guidelines was to improve dietary patterns, nutritional status, and public health. These guidelines propose to lower total and saturated fat, cholesterol, sodium and sugar, and to increase the consumption of fibre and complex carbohydrates as a key way to improve nutritional status [7].

Several indices of overall diet quality or diet quality scores have been validated by correlating the index score to health outcome [12, 13, 15, 150-152]. Most indices are based on current nutritional guidelines or recommendations [153]. As listed in Table 9, at least 20 distinct indices of overall diet quality exist in the literature. Among these indices, four are considered to be the “original ones” which include the Healthy Eating Index (HEI) [15], the Diet Quality Index (DQI) [12], the Healthy Diet Indicator (HDI) [154], and the Mediterranean Diet Score (MDS) [155]. Recently, the Mediterranean diet has received increasing attention because of the association of this type of diet with reduced risk of coronary heart disease and several forms of cancer [155-159]. The composition of these four scores is detailed in Table 14.

Compared to a monotonous diet, dietary variety also has a more beneficial effect on disease risk. This fact leads to the development of a Dietary Variety Score [160-165]. In this index, dietary variety is calculated based on the number of different foods or food groups consumed over a given period. Moreover, Kant and Thompson [150] modified this index and proposed to divide foods into nutrient-dense and nutrient-poor (energy-dense) foods in order to calculate a variety score for recommended foods. This approach has been successfully used to calculate the Recommended Food Scores [9].

3.2.1 Diet quality scores

Composing an index of overall diet quality involves choosing the variables or items (to be included), the cut-off values, and their scoring. This chapter is a general overview of the components of diet quality indices. Table 8 shows the key issues in the construction of diet quality scores [7].

Variables included in the index/ limitation of various indexes

Nutrients, foods, and food groups are considered as dietary variables in diet quality scores. Table 8 presents an overview of the index components of the diet quality scores, which are listed in Table 9.

Nutrients

Nutrients may include fat (total, saturated, polyunsaturated, etc.), cholesterol, complex carbohydrates, dietary fibre, protein, and alcohol. Different units have been used to estimate the amount of nutrient intake. Usually, the fat intake is based on the percentage of energy, while micronutrients are expressed in micrograms or percentage of the recommended dietary allowance. Thus, one of the criteria to obtain a good score from any indices is that an individual should consume at least two macronutrients. This is quite important because an imbalance in macronutrients consumption (fat, carbohydrates and protein) plays an important role in chronic diseases such as obesity and cancer [7].

Food items

The inclusion of food categories in a certain index is based on the knowledge at the time when the index was created. Fruit, vegetable, meat and meat products, cereals or grain, milk and dairy products are the main food groups that are present in most indices (see Table 8). But fish, legumes, nuts and soy products are only included in the more recent indices [11, 13]. Usually, food intake is evaluated by using the serving size or gram. depending on whether it is considered as a food or a nutrient respectively. Alcohol can be expressed by the number of glasses per day or by grams of ethanol per day. According to US Food and Drug Administration [166] seving size is " a standardized amount of a food, such as a cup or an ounce, used in comparing similar foods. Serving sizes are stated on the food label. Serving size on the food label is listed as a common household measure followed by the equivalent metric quantity in parenthesis, for example "1/2 cup (112 g)". Appendix 1 shows the serving size in all food categories.

Fat

Fat is considered as an important macronutrient and is present in most indices. However, various types of fat have different effects on disease risk. For example, saturated fat is associated with increased CVD while higher consumption of monounsaturated and polyunsaturated fatty acids is associated with reduced risk of CVD [167-171]. Thus, the fatty acid composition of the diet is considered as an important health determinant. Among the food quality indices, the DQI, HEI and HDI specifically estimate the amount of saturated fat intake.

Fruit and vegetables

All indices based on food items include fruits and vegetables. In some indices, fruits and vegetables are considered as one group while in others they are evaluated separately. The fact that all indices include these two items highlights their importance for a healthy diet.

Complex versus refined grains

The health benefits of whole grain compared to refined grains have been shown in several studies [47, 172-174]. Whole grain contains fibre, as well as other components such as micronutrients, antioxidants and non-nutritive dietary constituents (phyto-oestrogens in wheat bran and beta-glucans in oat), which have beneficial effects on disease risk [175, 176].

Dairy, meat, and alcohol

Consumption of dairy products is associated with reduced risk of several chronic diseases such as osteoporosis, hypertension, obesity and type 2 diabetes [177, 178]. However, some dairy products are associated with unfavourable effects because they are rich in saturated fat. Therefore, the ability of an index to distinguish between low and high fat dairy products is a strong advantage of that index.

The consumption of meat and alcohol in moderate quantities has been associated with a beneficial effect, while their high consumption may lead to some adverse consequences. This suggests a U-shape association of health with meat and alcohol consumption. Consequently, categorizing these variables with a cut-point is not appropriate. The best approach is to apply a recommended range for their intake amounts since insufficient and excessive intakes are not rewarded.

Cut points and scoring

The constitution of a diet quality index required that foods and nutrients become quantified accurately. Various methods have been used to achieve this goal. Using a cut off value seems to be the most straightforward method. Some indices (e.g. MDS) use the median intake for each variable independently of the recommended intake. One problem with this approach is that the medians will be different among various populations.

Furthermore, this does not reflect whether participants have healthy intakes of each variable. However, the advantage of this method is that half of the subjects will score positively while the other half will score negatively for each item.

Other indices are based on dietary guidelines with specific cut-off values for each variable. However, this method does not discriminate between various intake levels. To address this issue, some indices (e.g. DQI) include lower, intermediate, and upper boundaries. Other indices (e.g. HEI) score each item proportionally to the dietary guideline recommendation. In these indices, the degree to which an individual satisfies the dietary guideline recommendation is reflected in the total score.

Energy intake

Individuals who have high levels of energy intake may consume more food servings and food groups, and thus they can meet the dietary guidelines more easily in spite of unbalanced diets (e.g. high fat). Some indices have addressed this issue by scoring the number of servings and energy intake levels based on sex and age. These indices better reflect whether the diet is balanced or not.

Relative contribution of the individual index components to the score

The relative contribution of different items to the total score is another important but not frequently asked question. In most indices, all variables contribute equally.

3.3 Different approaches to evaluate diet quality

There are different approaches to evaluate diet quality [7] that are categorized based on: 1) dietary guidelines, 2) the Mediterranean diet, 3) food consumption, 4) nutrient intake, and 5) variety. Table 9 shows the most frequently used indices according to these categories.

Table 8. Overview of the attributes included in the existing diet quality scores [7]

Nutrients	
Total fat	DQI, DQI-R, DQI-I, DQI-a I–III, HEI, DGI
SFA	DQI, DQI-R, DQI-I, DQI-a I–III, HEI, HDI, MDQI, DGI
Ratio of MUFA or PUFA to SFA	DQI-I, AHEI, MDS, MDS-f, MDS-a I, MDS-a III
PUFA	HDI
Trans fatty acids	AHEI
Protein	DQI, DQI-I, HDI
Carbohydrate	DQI-a I–III
Complex carbohydrates	DQI, HDI
(Cereal) fibre	DQI-I, AHEI, HDI
Mono- and disaccharides	DQI-a III, HDI
Sucrose	DQI-a I
Cholesterol	DQI, DQI-R, DQI-I, DQI-a I–III, HEI, HDI, MDQI, DGI
Alcohol	MDS, MDS-f, MDS-a I, III, IV, AHEI, DGI
Sodium	DQI, DQI-I, DQI-a II, HEI, DGI
Calcium	DQI, DQI-R, DQI-I
Iron	DQI-R, DQI-I
Vitamin C	DQI-I
Ratio of carbohydrates to protein to fat	DQI-I
Foods	
Fruit and vegetables	DQI, MDQI, MDS-a I, HDI
Fruits (and nuts)	DQI-R, DQI-I, HEI, AHEI, MDS, MDS-f, MDS-a II–IV, FBQI, HFI, DGI
Vegetables	DQI-R, DQI-I, HEI, AHEI, MDS, MDS-f, MDS-a II–IV, FBQI, HFI, DGI
Legumes (and nuts and seeds)	MDS, MDS-f, MDS-a I–IV, HDI
Nuts (and soya)	AHEI, MDS-a II, MDS-a III
(Whole) cereals/grains (Coarse) bread	DQI-R, DQI-I, HEI, all MDS, MDQI, HFI, DGI FBQI, HFI
Meat (and meat products)	HEI, MDS, MDS-f, MDQI, MDS-a I–IV, FBQI, DGI
Ratio of white to red meat	AHEI
Red and processed meat	MDS-a III
Poultry	MDS-a IV
Fish	MDS-f, MDS-a II–IV, MDQI
Milk (and dairy products)	HEI, MDS, MDS-a I, FBQI, DGI
High fat dairy	MDS-a II, IV
Olive oil	MDS-a IV, MDQI
Potatoes	MDS-a IV, FBQI
Cheese	FBQI
Red wine	MDS-a III
Butter, margarine, animal fat	HFI
Sweets/sweet beverages	DGI
Dietary variety	DQI-R, DQI-I, HEI, DGI
Dietary moderation	DQI-R

DQI, Diet Quality Index; DQI-R, Diet Quality Index Revised; DQI-I, Diet Quality Index International; HEI, Healthy Eating Index; AHEI, Alternate Healthy Eating Index; DGI, Dietary Guidelines Index; MDS, Mediterranean Diet Score; MDQI, Mediterranean Diet Quality Index; HDI, Healthy Diet Indicator; FBQI, Food-Based Quality Index; HFI, Healthy Food Index.

Table 9.Overview of existing diet quality scores and studies in which they have been used and/ or evaluated [7]

Index	Authors (year)
Based on dietary guidelines	
Diet Quality Index (DQI)*	Patterson *et al.* (1994)
	Seymour *et al.* (2003)
	Dubois *et al.* (2000)
Diet Quality Index Revised (DQI-R)	Haines *et al.* (1999)
	Newby *et al.* (2003)
	Fung *et al.* (2005)
Diet Quality Index International (DQI-I)	Kim *et al.* (2003)
Other indexes adapted from the DQI	
DQI-a I	Drewnowski *et al.* (1996)
DQI-a II	Drewnowski *et al.* (1997)
DQI-a III	Lowik *et al.* (1999)
Healthy Eating Index (HEI)*	Kennedy *et al.* (1995)
	McCullough *et al.* (2000*a*)
	McCullough *et al.* (2000*b*)
	Dubois *et al.* (2000)
	Kennedy *et al.* (2001)
	Hann *et al.* (2001)
	McCullough *et al.* (2002)
	Weinstein *et al.* (2004)
	Fung *et al.* (2005)
Alternative Healthy Eating Index (AHEI)	McCullough *et al.* (2002)
	Fung *et al.* (2005)
Healthy Diet Indicator (HDI)†	Huijbregts *et al.* (1997*a*,*b*)
	Huijbregts *et al.* (1998)
	Dubois *et al.* (2000)
	Haveman-Nies *et al.* (2001
Dietary guidelines index (DGI)	Harnack *et al.* (2002)
Based on Mediterranean diet	
Mediterranean Diet Score (MDS)	Trichopoulou *et al.* (1995)
	Osler & Schroll (1997)
	Kouris-Blazos *et al.* (1999)
	Lasheras *et al.* (2000)
	Woo *et al.* (2001)
	Haveman-Nies *et al.* (2001
	Bosetti *et al.* (2003)
Mediterranean Diet Quality Index (MDQI)	Gerber *et al.* (2000)
	Scali *et al.* (2001)
MDS + fish (MDS-f)	Trichopoulou *et al.* (2003)
	Knoops *et al.* (2004)
	Trichopoulou *et al.* (2005*b*)
Other indexes adapted from the MDS	
MDS-a I	Haveman-Nies *et al.* (2002
MDS-a II	Schroder *et al.* (2004)
MDS-a III	Fung *et al.* (2005)
MDS-a IV	Pitsavos *et al.* (2005)
Food-based	
Food-Based Quality Index (FBQI)	Lowik *et al.* (1999)
Healthy Food Index (HFI)	Osler *et al.* (2001)
	Osler *et al.* (2002)
Food Pyramid Index (FPI)	Massari *et al.* (2004)
Nutrient-based	
Nutrient Adequacy Ratio (NAR/MAR)‡	Madden & Yoder (1972)

3.3.1 Approaches Based on Dietary Guidelines

3.3.1.1 Healthy Eating Index (HEI)

The focuses of earlier research were exclusively on nutrients by using the mean adequacy ratio of the diet or percentages of Recommended Dietary Allowances to estimate diet intake. In 1990, for the first time Patterson et al. proposed a diet quality index based on the US dietary guidelines [179]. In 1995, Kennedy et al. [15] expanded this index and provided a more comprehensive set of indicators for diet quality that led to the development of the HEI.

Overall structure of Healthy Eating Index

As shown in Table 10 [15], the HEI contains 10 components: grains, vegetables, fruits, milk, meat, total fat, saturated fat, cholesterol, sodium and variety. The score for each component ranges from 0 to 10, and the total diet score from 0 to 100. The serving size for each food group is based on the food guide pyramid [180]. The first five components (grain, vegetables, fruits, meat, and milk products) are based on serving sizes [180]. Legumes are assigned to the meat group up to the maximum score, and any additional intake is assigned to the vegetable group. On the other hand, soy products, which are considered as a meat substitute, are always assigned to the meat group. Components 6 and 7 are based on total and saturated fat consumption and are expressed as a percentage of total food and energy intake, respectively. Component 8 and 9 are based on cholesterol and sodium intake, and component 10 shows the amount of variety of the subject's diet.

Table 10. Components of Healthy Eating Index (HEI-90) [15]

Components	Range of score	Criteria for score 10	Criteria for score 0
1) Grain	0-10	6-11 servings	0
2) Vegetables	0-10	3-5 servings	0
3) Fruits	0-10	2-4 servings	0
4) Milk	0-10	2-3 servings	0
5) Meat	0-10	2-3 servings	0
6) Total fat	0-10	≤ 30% energy	≥ 45% energy
7) Saturated fat	0-10	< 10% energy	≥ 15% energy
8) Cholesterol	0-10	< 300 mg	≥ 450 mg
9) Sodium	0-10	< 2 400 mg	≥ 4 800 mg
10) Variety	0-10	16 different kinds of food items over 3 day period	≤ 6 food items over 3 days

Index scoring for components 1-5

Table 11 shows the recommended number of servings per day and per total calorie ingested, and thus it takes into account the total energy intake. A score of 10 belongs to an individual who consumed the recommended number of servings, while a score of 0 is assigned to an individual who did not have any servings for that certain item. In between, the score is calculated proportionally to the ingested amount of component. For example, a 40 years old woman with an energy intake of 2200 kcal/day should consume four servings of vegetables for a score of 10 while a 0 is assigned if she does not consume any vegetable at all. The consumption of 2 servings will give her a score of 5. For each component, when the optimum number of servings is achieved, neither further credits are given nor are any points deducted for additional servings.

Index scoring for components 6-10

Scoring of these components is based on their portion of total energy intake. A scored of 10 is assigned when total fat and saturated fat intakes represent less than 30% and 10% of total energy intake, respectively. A score of 0 is assigned when total and saturated fat intakes represent ≥ 45% and 15%, respectively. Cholesterol and sodium intakes are calculated based on milligrams of intake. A score of 10 is assigned when cholesterol and sodium intakes are less than 300 mg and 2 400 mg, respectively. A score of 0 is assigned when cholesterol and sodium intakes are ≥ 450 mg and 4 800 mg, respectively. These upper limits for total fat, saturated fat, cholesterol and sodium were determined from the 1989-1990 Continuing Survey of Food Intake by Individuals (CSFII) [181]. Both the UDSA Food Guide Pyramid [180] and the National Academy of Science's diet and health report have emphasized the role of dietary variety in a healthy diet [182], but few indices include this component [183, 184]. A score of 10 is obtained when 16 or more different foods are consumed during the 3-day study period, and a score of 0 is considered if 6 or less distinct foods are eaten.

Table 11. Recommended numbers of servings per day per energy intake [15]

K calories	Grains	Vegetable	Fruits	Milk	Meat
1 600	6	3	2	2	2
2 200	9	4	3	2	2.4
2 800	11	5	4	2	2.8

3.3.1.2 HEI adapted for Canadian

The HEI has been adapted for the Canadian population by Shatenstein et al. [18] based on Canada's Food Guide for Healthy Eating and Nutrition Recommendations for Canadians [185]. The index was validated against a self-administered semi-quantitative FFQ, which was designed in French and English based on the Block National Cancer Institute Health Habits and History Questionnaire to capture usual food consumption

among adults. The FFQ was pre-tested in a pilot study and was administered by mail to a random sample of 248 Quebecers, 106 men (43%) and 142 women (57%), aged 18-82 years within the Montréal area. A subgroup of 94 individuals gave four non-consecutive 1-day food records for validation of the FFQ.

As shown in Table 12 the HEI, which was adapted for Canadian population [18], includes nine components. Each component is worth 10 points except for the vegetable and fruit sub-scores, which are worth 20 points each. Dietary variety was also modified, because in the original HEI the variety sub-score counted the total number of different foods eaten during the 3 days, while the FFQ provided food intakes over a 12-month period. Therefore, the variety sub-score was made more reflective for Canada's Food Guide for Healthy Eating recommendation [185] by using a variant of the Dietary Diversity Score [151]. The Canadian HEI has a maximum score of 100 points.

Table 12. Criteria used in Canadian adaptation of the Healthy Eating Index (HEI-Ca) [18]

Components [a]	**Score range (points)**	**Criteria for maximum score by sex and age** [b]				**Criteria for minimum score**
		Female		*Male*		
		18-49	*>50*	*18-49*	*>50*	
Grain products (serving)	0-10	9	6	12	9	0 serving
Vegetables and fruits (serving)	0-20	7	5	10	7	0 serving
Milk products (serving)	0-10	2	2	2	2	0 serving
Meat and meat alternatives (serving)	0-10	2.5	2	3	2.5	0 serving
Total fat intake (%)	0-10	< 30% total energy from fat				≥ 45% total energy from fat
Saturated fat intake (%)	0-10	< 10% total energy from saturated fat				≥ 15% total energy from saturated fat
Cholesterol intake (mg/day)	0-10	≤ 300 mg cholesterol				≥ 450 mg cholesterol
Sodium intake (mg/day)	0-10	≤ 2400 mg sodium				≥ 4800 mg sodium
Dietary Variety	0-10	≥ 1 portion from each of four 4 groups of CFGHE				<1 serving from each of 4 food groups of CFGHE

Adapted from [18]

[a] The first four components are based on Canada's Food Guide for Healthy Eating (CFGHE) [185]; evaluation considers daily intakes

[b] Number of servings is based on approximate energy intakes (2200 kcal/day for women aged 18-49y, 1600 kcal/day for women > 50 y, 2800 kcal /day for men aged 18-49 and 2200 kcal/day for men > 50 y) adopted from Bowman and colleagues [186]

3.3.1.3 The HEI-05 and the HEI 2005

Recently, Gao et al. [187] and Guenther [188, 189] updated the original HEI. As shown in Table 13, the only difference between the HEI-05 and the original HEI is that three activity levels (sedentary, moderately and active) have been assigned for energy requirements. In addition, dietary variety is the sum of different foods consumed during the past 12 months instead of the past 3 days.

Similarly, there are two major differences between the HEI-2005 and the original HEI. First, the scoring system is based on the new food intake patterns developed specifically for the My Pyramid Food Guidance System [190]. Second, the standard for each component is based on the energy density approach. Thus, the food group standards are expressed per 1000 kcal while standards for nutrients and discretionary energy are based on percentage of total energy [191].

Table 13. Recommended daily intakes for the original HEI, [a] HEI-05, and HEI-2005, adapted from [191]

			HEI-05								
			Men, Ages 45-50[b]			Women, Ages 45-50[b]					
		Original HEI	Sedentary	Moderately Active	Active	Sedentary	Moderately active	Active			HEI-2005
		All Adults	2,200 kcal	2,400-2,600 kcal	2,800-3,000 kcal	1,800 kcal	2,000 kcal	2,200 kcal			All Adults
Components	Maximum points	Daily recommended intake	Daily recommended intake			Daily recommended intake			Components	Maximum points	Daily recommended intake
Adequacy											
Grains	10	6-11 svgs[c]	7 oz eq[d]	8 to 9 oz eq	10 oz eq	6 oz eq	6 oz eq	7 oz eq	Total Grains	5	≥3.0 oz eq/1,000 kcal
Vegetables	10	3-5 svgs	3 cups	3 to 3.5 cups	3.5 to 4 cups	2.5 cups	2.5 cups	3 cups	Whole Grains	5	≥1.5 oz eq/1,000 kcal
Fruits	10	2-4 svgs	2 cups	2 cups	2.5 cups	1.5 cups	2 cups	2 cups	Vegetables	5	≥1.1 cups eq/1,000 kcal
Milk	10	2-3 svgs	3 cups	3 cups	3 cups	3 cups	3 cups	3 cups	Dark green and orange vegetables and legumes	5	≥0.4 cup eq/1,000 kcal
Meat (and beans)	10	2-36 svgs	6 oz eq	6.5 oz eq	7 oz eq	5 oz eq	5.5 oz eq	6 oz eq	Total Fruits	5	≥0.8 cup eq/1,000 kcal
Moderation									Whole Fruits	5	≥1.3 cups eq/1,000 kcal
Total fat	10	≤30% of energy	≤30% of energy	≤30% of energy	≤30% of energy	≤30% of energy	≤30% of energy	≤30% of energy	Milk	10	≥2.5 oz eq/1,000 kcal
Saturated fat	10	<10% of energy	<10% of energy	<10% of energy	<10% of energy	<10% of energy	<10% of energy	<10% of energy	Meat and Beans	10	≥12 g/1,000 kcal
Cholesterol	10	≤300 mg	≤300 mg	≤300 mg	≤300 mg	≤300 mg	≤300 mg	≤300 mg	Saturated fat	10	≤7% of energy
Sodium	10	≤2,400 mg	≤2,400 mg	≤2,400 mg	≤2,400 mg	≤2,400 mg	≤2,400 mg	≤2,400 mg	Sodium	10	≤0.7 g/1,000 kcal
Variety	10	16 different food items over 3 days	Summary score based of foods consumed over past 12 months			Summary score based of foods consumed over past 12 months			Calories from SoFAAS[e]	20	≤20% of energy
Total points	100								Total points	100	

[a]HEI=Healthy Eating Index

[b]Recommended daily intakes for men and women > 50 years of age according to calorie plans appropriate for sedentary, moderately active, and active were also included in the HEI-05 (11)

[c]svgs=servings

[d]eq=equivalents

[e]SoFAAS=Calories from Solid Fats, Alcoholic Beverages, and Added Sugars

3.3.1.4 Alternate Healthy Eating Index (AHEI)

In 2002, McCullough et al. created the AHEI [9] by using dietary questionnaires from 38615 men of the Health Professional's follow-up study and 67271 women of the Nurses Health Study. The objective was to generate an index that would better predict chronic disease risk and better identify food choices and macronutrient associated with chronic disease risk [9, 192]. A major chronic disease was defined as the initial occurrence of CVD, cancer or non-traumatic death during 8-12 years of follow-up. They found an association between the AHEI score and reduced chronic disease risk. The investigators attributed this finding to the ability of the AHEI to capture certain dietary choices (e.g. white versus red meat consumption and the type of fat consumed). Moreover, the incorporation of n-3 fatty acids into the score might have improved the sensitivity of this score to CVD.

As shown in Table 14, the index contains 9 components: vegetables, fruits, nuts and soy, the ratio of white to red meat, cereal fibre, trans fat, the ratio of polyunsaturated to saturated fat, alcohol and duration of multivitamin used. A sub-score of 0-10 is allocated to each of the first eight components, where 10 represented a healthy diet and 0 indicated a poor diet quality. Intermediate intakes are calculated proportionally to the consumed amount (between 0 and 10). The consumed multivitamin is dichotomous and 2.5 and 7.5 points are assigned to non-users and users, respectively. The sum of all components can vary from 2.5 (poor) to 87.5 (best).

3.3.1.5 Diet Quality Index (DQI)

The DQI was developed by Patterson et al. [12] in 1994 to measure overall diet quality and its role in chronic diseases. The index is based on the US dietary recommendation while the serving size for each food group is based on the Diet and Health guidelines [193]. As shown in Table 14, the DQI is composed of eight components, namely total fat, saturated fat and cholesterol, fruits, vegetables, grains and legumes, protein, sodium and calcium. The scoring weight of each component is based on its

association with disease risks. Each component is scored from 0 to 2, where 0 represents an excellent diet and is assigned to individuals who meet dietary goals, 1 represents a fair diet, and 2 is assigned to individuals with poor diets. Accordingly, the total score ranges from 0 (excellent diet) to 16 (poor diet). It is believed that the index's score reflects diet quality. However, substantial misclassification can occur because a single nutrient or food is used as an indicator of diet quality.

3.3.1.6 Diet Quality Index Revised (DQI-R)

The DQI was revised by Haines et al. in 1999 [151]. The revised index reflects improved methods to estimate fruit, vegetable and grain servings, and it integrates the measures of diet variety and proportionality. The DQI-R contains 10 components and each one contributes to 10 points for a total of 100 (Table 14). Scoring of fruit, vegetable, and grain is based on the percentage of the recommended servings. The iron and calcium intakes are scored based on RDA and Adequate Intake Value, respectively. They are considered as continuous variables ranging in 0-100%. The dietary diversity score was developed to reflect differences in consumption across 23 food group categories, which were chosen to capture food diversity. Dietary moderation includes 4 components, namely added sugars, discretionary fat, sodium and alcohol [151]. The relative levels of total fat, saturated fat and cholesterol have not been included in the score since they all have been considered as independent components in DQI-R [54]. In this index, a low score is assigned when dietary recommendations are not met, while higher score reflects high quality diet. The points are assigned as follow: 10 points when recommendations are meet, 5 points for those within 30% of the recommendations, and 0 points for those 30% above upper threshold.

3.3.1.7 Diet Quality Index International (DQI-I)

This index was created by Kim et al. [194] to make cross-national comparison of diet quality between China and USA. It has been found to be an appropriate index for investigating diet quality across countries and for global monitoring of diet healthfulness.

The index is composed of four major components, namely variety, adequacy, moderation and overall balance, which represent the major aspects of a healthy diet. The selection component and the scoring system are provided by using the current worldwide and individual dietary guidelines [195, 196], the food guide pyramid [180], and several dietary indices [12, 15, 151, 197].

Variety is categorized into two different groups: overall variety and variety of protein sources [192, 194]. The overall variety score is based on the inclusion of at least one serving per day from each of the five food groups: meat/poultry/fish, eggs, dairy/beans, grains, and fruits and vegetables. The variety of protein sources is evaluated among the following 6 items: meat, poultry, fish, dairy, beans and eggs. The total variety score is obtained by adding the overall variety score (in the range of 0-15) and the variety score of protein sources (in the range of 0-5) [58]. The adequacy sub-score (in the range of 0-40) is determined from the consumption of a sufficient amount of the following dietary elements, namely vegetables, fruits, grains, fibre, protein, iron, calcium, and vitamin C, to maintain a healthy diet [192, 194]. The recommended intake of fruits, vegetables, grain and fibre is adjusted with the total energy intake according to age and gender.

The moderation sub-score (in the range 0-30) evaluates the intake of specific elements (total fat, saturated fat, cholesterol, sodium and empty calorie food) associated with an increase risk of chronic diseases. Accordingly, the maximum score is obtained with low intake of these elements. The last component of the DQI-I is the overall balance (in the range 0-10), which represents the proportion of macronutrients (the proportion is denoted by “carbohydrate: protein: fat”) and the fatty acid composition that contribute to energy intake.

3.3.1.8 Healthy Diet Indicator (HDI)

Hujibregts et al. [154] created the HDI to investigate the association of dietary pattern and mortality. They used the dietary history of 3045 men aged 50-70 from five

cohorts in Finland, Netherlands and Italy in 1970. After 20 years follow-up, they verified the vital status and calculated the mortality rate. In this dietary survey method, they estimated the usual food consumption pattern during 6-12 months, and they used the WHO guidelines for the prevention of chronic diseases [154].

As shown in Table 14, the HDI contains 9 components including saturated fatty acids, polyunsaturated fatty acids, protein, complex carbohydrate, dietary fibre, fruits and vegetables, pulses/nuts/seeds, monosaccharide/disaccharides, and cholesterol. However, the index excludes salt, alcohol [154, 192], total fat, and carbohydrate in order to avoid overlap. A score of 1 is assigned to intake within the recommended range of WHO guidelines [195]; Otherwise, a score of 0 is assigned. The summation of the 9 individual scores gives a final score, which varies from 0 to 9 [154, 192]. Studies have shown that the HDI is a strong tool for assessing diet quality and for evaluating future adverse health events [192].

3.3.1.9 Dietary Guideline Index (DGI)

The DGI was created by Harnack et al. [153] using data from 34 708 women of the Iowa Women's Health Study, a population-based cohort of postmenopausal women for whom diet was assessed in relation to cancer occurrence. The components and the corresponding scores of the DGI are shown in Table 14. This index contains 9 components in which the maximum and minimum scores of 2 and 0, respectively, could be assigned to each component according to its compliance with the dietary guidelines. Therefore, a total score of 18 across the 9 components defines full compliance with guideline whereas the total score of 0 indicates non-compliances.

3.3.2 Based on Mediterranean diet

3.3.2.1 Mediterranean diet score (MDS)

The MDS was developed by Trichopoulou et al. [155] in 1995 by using 91 men and women, who were over 70 years old and from three rural Greek villages. The goal was to investigate the influence of a specific dietary pattern on overall survival. The dietary habits were assessed with a validated extensive semi-quantitative food frequency questionnaire. The study showed that the role of overall dietary pattern in health is more important than individual nutritional components, and thus it highlighted the benefits of Mediterranean diet to the health and longevity of this population. As shown in Table 14, this index includes eight components: high consumption of vegetables, legumes, fruits, cereals (including breads, potatoes, starchy roots but excluding sugar and syrup), low consumption of meat and meat products, milk and dairy products, a high ratio of monounsaturated to saturated fat, and moderate alcohol consumption [155]. This index uses a median value as the cut point for each sex. A score of 0 and 1 is assigned to each component if the consumed amount is above and below the median, respectively. Therefore, the total score varies from 0 (poor diet) to 8 (excellent diet) [155]. The original MDS has been modified and used in several studies related to health outcomes.

3.3.2.2 Mediterranean Diet Quality Index

The MDQI has been used in two studies [198, 199] to set up the DQI and assess the dietary habits of Mediterranean southern France. As shown in Table 14, this index includes 7 components: saturated fat, cholesterol, meats, olive oil, fish (including white and fatty fish), cereals (including breads, pastas and rice as well as breakfast cereals), and fruit and vegetables. The number of cigarettes per day is not always included in the calculation of the index. For example, Gerber et al. [199] included the number of cigarettes in their study while Scali et al. [198] did not. Each nutrient or food group is divided into 3 sub-scores (0, 1 and 2) according to the recommendation guideline. These sub-scores are summed up for each subject that lead to a total score in the ranges 0-16 and

0-14 depending on whether the number of cigarettes are included or not [198, 199]. In both indices, a low score indicates a better diet.

3.3.2.3 MDS + Fish

This index has been developed by Trichopoulou et al. [155] in 2003. It contains 14 components, namely potatoes, vegetables, legumes, fruits and nuts, dairy products, cereals, meat, fish, egg, monounsaturated fat (mainly olive oil), polyunsaturated fat (vegetable-seeds oil), saturated fat and margarines, sugar and sweets, and non-alcoholic beverages. This index was modified by Knoops et al. [11] in 2004 to include only 8 components, namely legumes/nuts/seeds, grains, fruits, vegetables and potatoes, meat and meat products, dairy products, fish, and the ratio of monounsaturated to saturated fat. In both studies, the cut-off point is based on the median and is specific for each sex.

3.3.3 Other indices adapted from MDS

There exist multiple modified forms of the MDS [11, 200-202], and each form has its own components and scoring system. In addition, in 2007 the Mediterranean Adequacy Index (MAI) has been reported [203], in which 18 food groups and the specific score calculations were presented.

3.3.3.1 Food consumption

Other less frequently used indices have been developed based on food groups. These indices include the Food Based Quality Index (FBQI), the Healthy Food Index (HFI), and the Food Pyramid Index (FPI). The FBQI investigates the relationship between dietary characteristics and nutrient density of diets in accordance with the guidelines and food variety [204]. The HFI is based on dietary guidelines for a healthy diet and contains 6 components (butter, margarine, animal fat, vegetables, coarse bread, and fruit). Its score varies from 0 (poor diet) to 4 (excellent diet) [205]. Massari et al. developed the FPI to

examine the association between coronary heart disease risk factors and eating pattern. This index is an aggregated dietary index, which compares the ratio of fatty food to items with negligible fat contents [206].

3.3.3.2 Nutrient based scores

The Nutrient Adequacy Ratio (NAR) is a nutrient based index developed by Madden and Yoder in 1972. The NAR is the ratio of a nutrient intake relative to its RDA. The mean adequacy ratio (MAR) is computed by averaging the sum of the NAR. These indices have been used in several studies to evaluate diet quality scores [207]. Table 14 summarizes the components and scoring systems of the existing diet indices.

Clinical outcome of HEI

The HEI is the most frequently used index and has been validated in multiple studies. Kennedy et al. [15] showed that the HEI is a useful tool to estimate the overall diet pattern. Furthermore, the index sub-scores correlate positively with the consumption of most nutrients. The index scores correlate positively with biomarkers such as alpha- and beta-carotene, vitamin C, folate, and fibre [208, 209]. However, in spite of its strong association with individual diet components, the HEI was not associated with cancer risk both in men and women [210].

Studies have shown that the Canadian HEI adequately discriminates the overall diet quality based on dietary data from Food frequency questionnaire, and suggests examining the sub-scores within and between quartiles to improve diet quality [18]. More recently, the HEI was found to be a predictor of chronic disease [16]. Furthermore, a lower HEI score has been shown to be associated with overweight state and obesity [17]. Table 15 illustrates the association of dietary indices and scores with nutrient adequacy, biomarkers of health, disease outcome, and mortality.

Table 14. Overview of existing diet quality scores, their basis, index components, and scoring method [211]

Index	Basis	Index components	Cut-off values/scoring
DQI	Dietary guidelines: US recommendations from 1989 publication Diet and Health	Total fat; SFA; cholesterol; fruit and vegetables; complex carbohydrates; protein; sodium; calcium	Lower cut-off, intermediate range, upper boundary, based on the recommendations. Total score: 0 (excellent diet) to 16 (poor diet). Energy intake not taken into account. Equal weight for all items.
DQI-revised	Dietary guidelines: the 1992 Food Guide Pyramid, the 1995 Dietary Guidelines for Americans	Total fat; SFA; cholesterol; fruit; vegetables; grain; calcium; iron; dietary diversity; dietary moderation	Lower cut-off, intermediate range, upper boundary, based on the recommendations. Total score: 0 (poor diet) to 100 (excellent diet). Difference with original DQI: score of fruit, vegetables, grain, calcium, iron, dietary diversity, and dietary moderation is a continuous variable proportional to the recommended range of intake. Three levels of energy intake used. Equal weight for all items.
DQI-international	Dietary guidelines: worldwide and individual national dietary guidelines, the Food Guide Pyramid, other dietary indices	Overall food group variety; within-group variety; vegetable group; fruit group; grain group; fiber; protein; iron; calcium; vitamin C; total fat; SFA; cholesterol; sodium; empty energy foods; macronutrient ratio; FA ratio	Scoring is proportional to the extent to which the dietary guideline is met. Total score: 0 (poor diet) to 100 (excellent diet). Three levels of energy intake used for the recommended intake of fruits, vegetables, grains, and fiber. Different weight to different items.
MDS	Specific dietary pattern: Mediterranean dietary pattern	MUFA:SFA; legumes; cereals; fruit and nuts; vegetables; meat and meat products; milk and dairy products; alcohol	Median of the sample is used as a cut-off point, dichotomous, sex specific. Total score: 0 (poor diet) to 8 (excellent diet). Intake of components is adjusted for daily energy intake: 2500 kcal for men, 2000 kcal for women. Equal weight for all items.
MDS-adapted	Specific dietary pattern: Mediterranean dietary pattern	MUFA:SFA; legumes, nuts, and seeds; cereals; fruit and vegetables; meat and meat products; milk and dairy products; alcohol	Median of the sample is used as a cut-off point, dichotomous, sex specific. Intake of dairy products cut-off between P25 and P75. Total score: 0 (poor diet) to 7 (excellent diet). Intake of components is adjusted for daily energy intake: 2500 kcal for men, 2000 kcal for women. Equal weight for all items.
MDS and fish	Specific dietary pattern: Mediterranean dietary pattern	MUFA:SFA; legumes; cereals; fruit and nuts; vegetables; meat and meat products; milk and dairy products; fish; alcohol	Median of the sample is used as a cut-off point, dichotomous, sex specific. Total score: 0 (poor diet) to 9 (excellent diet). Intake of components is adjusted for daily energy intake: 2500 kcal for men, 2000 kcal for women. Equal weight for all items.
MDQI	Specific dietary pattern: Mediterranean dietary pattern	SFA; cholesterol; meat; olive oil; fish; cereals; fruit and vegetables; cigarettes	Lower cut-off, intermediate range, upper boundary, based on recommendations. Total score: 0 (excellent diet) to 14 (poor diet). Energy intake not taken into account. Equal weight for all items.
HDI	Dietary guidelines: 1990 WHO dietary guidelines for the prevention of chronic diseases	SFA; PUFA; protein; complex carbohydrates; dietary fiber; fruit and vegetables; pulses, nuts, and seeds; monosaccharides and disaccharides; cholesterol	Cut-off dichotomous, based on recommendations. Total score: 0 (poor diet) to 9 (excellent diet). Energy intake not taken into account. Equal weight for all items.

Table 14. Continued

HEI	Dietary guidelines: Dietary Guidelines for Americans, Food Guide Pyramid	Grains; vegetables; fruit; milk; meat; total fat; SFA; cholesterol; sodium; variety	Scoring is proportional to the extent to which the dietary guideline is met. Total score: 0 (poor diet) to 100 (excellent diet). Scoring depending on energy intake, intake is reflected as a proportion of the number of servings recommended for the appropriate energy intake level, based on sex and age. Equal weight for all items.
A-HEI	Dietary guidelines: Dietary Guidelines for Americans, Food Guide Pyramid	Vegetables; fruit; nuts and soy; ratio of white to red meat; cereal fiber; trans-fat; PUFA:SFA; duration of multivitamin use; alcohol (male/female)	Scoring is proportional to the extent to which the dietary guideline is met, except for the multivitamin use component (dichotomous). Total score: 2.5 (poor diet) to 87.5 (excellent diet). Energy intake not taken into account. Equal weight for all items, except for multivitamin use.
Canadian HEI	Dietary guidelines: Canadian Food Guide for Healthy Eating, Nutritional Recommendations for Canadians	Grain products; fruit and vegetables; milk products; meat and meat alternatives; total fat; saturated fat; cholesterol; sodium; dietary variety	Scoring is proportional to the extent to which the dietary guideline is met. Total score: 0 (poor diet) to 100 (excellent diet). Number of servings is based on approximate energy intakes, age and sex specific. Equal weight for all items, except for intake of vegetables and fruit (combined group, double score)
HFI	Dietary guidelines: current recommendations for a healthy diet and previous indices of overall diet quality	Butter, margarine, animal fat; vegetables; coarse bread; fruit	Dichotomous variables, based on recommendations. Total score: 0 (poor diet) to 4 (excellent diet). Energy intake not taken into account. Equal weight for all items.
DGI	Dietary guidelines: Dietary Guidelines for Americans (5th ed.), dietary recommendations by National Research Council's Committee on Diet and Health	Weight; physical activity; grains; vegetables; fruit; milk; meat; variety of grains; whole grains; variety of fruit; variety of vegetables; total fat; saturated fat; cholesterol; sweets/sweet beverages; sodium; alcohol	Lower cut-off, intermediate range, upper boundary, or lower cut-off and upper boundary, based on recommendations. Total score: 0 (poor diet) to 18 (excellent diet). Energy intake not taken into account. Equal weight for all items.

Table 15. Overview of the association of dietary indexes and scores with nutrient adequacy, biomarkers of health, disease outcome and mortality [7]

Authors (year)	Index	Subjects	Follow-up	Dietary method	Outcome measure	Results
Diet Quality Index (DQI) and adapted scores*						
Patterson *et al.* (1994)	DQI	5484 US adults	cs	24-h recall and 2-d record	Nutrient adequacy	Lower index scores positively associated with vitamin and mineral intakes and negatively associated with fat intake
Dubois *et al.* (2000)	DQI	2103 Canadian adults	cs	24-h recall	Nutrient adequacy	Correlation with MAR 0·001 (men −0·008; women 0·031)
Seymour *et al.* (2003)	DQI	63109 elderly women 52724 elderly men	4 y	68-item FFQ	CVD mortality, cancer mortality, all mortality	Medium-low *v.* high quality diet: 19 % (men) and 31 % (women) increase in all mortality, 86 % increase in CVD mortality in women only (multivariately adjusted). No association with cancer mortality
Haines *et al.* (1999)	DQI-R	3202 US men	cs	24-h recalls (2 repeated days)	Nutrient adequacy	Moving from lowest to highest group of scores: significant improvement in all components of DQI-R
Newby *et al.* (2003)	DQI-R	127 US men (40–75 y)	cs	Two 131-item FFQ (1-y interval) and diet records (2)	Biomarkers	Positive correlation of DQI-R from FFQ with alpha-carotene (0·43), beta-carotene (0·35), lutein (0·31), alpha-tocopherol (0·25). Inverse correlation with total cholesterol (0·22). Correlation of biomarkers with DQI-R from diet record was higher
Fung *et al.* (2005)	DQI-R	660 US women	cs	140-item FFQ	Biomarkers for CVD (and correlation of scores)	DQI-R not significantly associated with any of the biomarkers
Kim *et al.* (2003)	DQI-I	8269 Chinese adults 9218 US adults	cs	Three consecutive 24-h recalls Two 24-h dietary recalls	Nutrient adequacy	Many nutrients showed strong relationships with index score
Lowik *et al.* (1999)	DQI-a	1493 Dutch adult women (DNFCS)	cs	Two diet records	Nutrient adequacy and	DQI associated with improved intake of the nutrients included in the index
Healthy Eating Index (HEI) and adapted scores						
Kennedy *et al.* (1995)	HEI	7443 US subjects (>2 y)	cs	24-h recall and	Nutrient adequacy	HEI positively correlated with intake of nutrients
McCullough *et al.* (2000*b*)	HEI	62272 US women (30–55 y)	12 y	2-d record 116-item FFQ	Chronic disease risk	Lowest *v.* highest HEI-score quintile RR for major chronic diseases 0·97, RR for CVD 0·86. No association of HEI with cancer risk
McCullough *et al.* (2000*a*)	HEI	51 529 US men (40–75 y)	8 y	131-item FFQ	Chronic disease risk	Lowest *v.* highest HEI-score quintile: RR for major chronic diseases 0·89, RR for CVD 0·72. No association of HEI with cancer risk
Dubois *et al.* (2000)	HEI	2103 Canadian adults	cs	24-h recall	Nutrient adequacy	Correlation with MAR 0·287 (men 0·197; women 0·391)
Hann *et al.* (2001)	HEI	340 US women (21–80 y)	cs	3-d record	Biomarkers	Correlation of HEI with EI 0·21, alpha-carotene 0·40, beta-carotene 0·30, beta-cryptoxanthin 0·41, lutein 0·24, vitamin C 0·33, folate 0·26
Weinstein *et al.* (2004)	HEI	16 467 US adults	cs	24-h recall	Biomarkers	Crude correlation of HEI with serum folate 0·25, ery-folate 0·27, vitamin C 0·30, vitamin E 0·21, serum carotenoids 0·17 to 0·27. Correlations were attenuated, but still significant when adjusted for additional factors. No correlation with among other things TAG, cholesterol

Table 15. Continued

Authors (year)	Index	Subjects	Follow-up	Dietary method	Outcome measure	Results
Fung *et al.* (2005)	HEI, AHEI	660 US women	cs	140-item FFQ	Biomarkers for CVD	HEI not significantly association with any of the biomarkers, AHEI significantly inversely associated with most biomarkers
McCullough *et al.* (2002)	AHEI	38615 US men 67271 US women	8–12 y	130-item FFQ	Chronic disease risk	Highest *v.* lowest quintile: RR for chronic disease 0·80 in men and 0·89 % in women, for CVD risk: 0·61 in men and 0·72 in women. No association of HEI with cancer risk
Harnack *et al.* (2002)	DGI	34708 US post-menopausal women	13 y	127-item FFQ	Cancer incidence	Highest *v.* lowest quintile: 15 % reduction in all cancer risk. Similar association for colon, lung, bronchus, breast, uterus cancer. No association with ovarian cancer but when excluding non-diet factors from the index, associations were not significant
Mediterranean Diet Score (MDS) and adapted scores						
Trichopoulou *et al.* (1995)	MDS	182 Greek elderly	4 y	190-item FFQ	All mortality	17 % reduction in mortality for 1 unit increase in the 8-point score
Osler & Schroll (1997)	MDS	202 Danish elderly	6 y	3-d diet record and frequency checklist	All mortality	21 % reduction in mortality for 1 unit increase in the 7-point score
					Biomarkers	Plasma carotene significantly associated with score. No association of cholesterol, HDL, HDL/cholesterol, vitamin E with score
Kouris-Blazos *et al.* (1999)	MDS	141 Anglo-Celts and 189 Greek-Australian elderly	4 y	250-item FFQ	All mortality	17 % reduction in mortality for 1 unit increase in the 8-point score
Lasheras *et al.* (2000)	MDS	161 Spanish elderly	>9 y	FFQ	All mortality	No association in subjects <80 y In subjects >80 y: 31 % reduction in mortality for 1 unit increase in the 8-point score
Haveman-Nies *et al.* (2001)	MDS	828 US elderly	cs	126-item FFQ	Biomarkers	No association of serum albumin, Hb or BMI with MDS. Waist circumference significantly associated with MDS
		1282 European elderly		3-d record and frequency checklist		
Bosetti *et al.* (2003)	MDS	598 + 304 + 460 cases *v.* 1491 + 743 + 1088 controls	Rs		Upper aero-digestive tract cancer	60 % reduction in pharyngeal cancer risk, 74 % reduction in oesophageal cancer risk, 77 % reduction in laryngeal cancer risk
Haveman-Nies *et al.* (2002)	MDS-a I	1281 European elderly	10 y	3-d history and frequency checklist	All mortality	No significant association of MDS with all mortality
Trichopoulou *et al.* (2003)	MDS-f	25917 Greek adults	3·7 y	150-item FFQ	CHD, cancer, and all mortality	25 % reduction in all mortality, 33 % in CHD mortality, 24 % in cancer mortality for 2-unit increase in the 9-point score
Knoops *et al.* (2004)	MDS-f	European elderly: 1507 men and 832 women	12 y	Diet history	All cause and cause-specific mortality	Low-risk group (MDS ≥4): reduction in all mortality 23 %, CHD mortality 39 %, cancer mortality 10 %
Schroder *et al.* (2004)	MDS-a	3162 Spanish adults	cs	165-item FFQ	BMI, obesity	Significant inverse association of score with BMI and obesity risk
Fung *et al.* (2005)	MDS-a	660 US women	cs	140-item FFQ	Biomarkers for CVD	MDS-a significantly inversely associated with most biomarkers
Trichopoulou *et al.* (2005b)	MDS-m	74607 elderly Europeans	< 10 y	EPIC-FFQ	All mortality	8 % reduction in mortality for 2-unit increase in the 9-point score

Table 15. Continued.

Authors (year)	Index	Subjects	Follow-up	Dietary method	Outcome measure	Results
Pitsavos *et al.* (2005)	MDS-a	3042 Greek adults	cs	156-item FFQ	Biomarkers for CVD	Highest *v.* lowest score tertile: 11 % increase in total anti-ox. capacity, 19 % decrease in LDL-cholesterol level
Gerber *et al.* (2000)	MDQI	146 French adults	cs	162-item FFQ	Biomarkers	Significant inverse association between vitamin E, n-3 FA, beta-carotene and score. No association of cholesterol with score
Healthy Diet Indicator (HDI)						
Huijbregts *et al.* (1997*a*)	HDI	3045 European (Netherlands, Italy, Finland) men (50–70 y)	20 y	Diet history	All mortality	Large variation in intake between three countries Highest *v.* lowest group: HDI > 2 *v.* HDI < 2 for NL, F, and HDI > 4 *v.* HDI > 3 for I: 13% reduction in mortality (similar within each country)
Huijbregts*et al.* (1997b)	HDI	272 Dutch elderly (~ 70 y)	17 y	Diet history	All mortality	HDI > 2 *v.* HDI < 2: 44 % reduction in mortality risk in men. No association for women
Huijbregts *et al.* (1998)	HDI	1049 European men (70–91 y)	cs	Diet history	Cognitive impairment	19 % and 25 % reduction in cognitive impairment in Dutch (not significant) and Italian cohorts respectively
Dubois *et al.* (2000)	HDI	2103 Canadian adults (18–74 y)	cs	24-h recall	Nutrient adequacy	Correlation with MAR 0·079 (men 0·0·061; women 0·101)
Haveman-Nies *et al.* (2001)	HDI	828 US elderly	cs	126-item FFQ	Biomarkers	No association of serum albumin, Hb or waist circumference with HDI. BMI significantly associated with HDI
		1282 European elderly		3-d record and frequency checklist		
Food-based indexes						
Lowik *et al.* (1999)	FBQI	1493 Dutch adult women (DNFCS)	cs	Two diet records	Nutrient adequacy	Score positively associated with EI and nutrient density
Osler *et al.* (2001)	HFI	7316 (30–70 y)	15 y	26-item FFQ	CHD and all mortality	No significant association after adjustment
Osler *et al.* (2002)	HFI	7316 (30–70 y)	15 y	26-item FFQ	CHD incidence	No significant association
Massari *et al.* (2004)	FPI	7665 Italian adults	cs	32-item FFQ	Five CHD risk factors	Men: positive association between FPI and all five risk factors Women: only significant association for serum cholesterol and glucose

4 Rational

The presence of MetS significantly increases the risk of developing type 2 diabetes and CVD. Thus, identifying factors that promote the development of MetS or its components would likely diminish the risk of CVD and diabetes. Obesity is an important component of MetS. Furthermore, overweight or obese subjects are at increased risk of diabetes and CVD. In addition, overweighting and obesity have been shown to be significantly correlated with MetS, unlike normal BMI [44, 61, 62].

The association of HEI with obesity, chronic diseases, and some metabolic disorders has been validated by several studies [10, 16, 17, 187, 189, 209]. Importantly, the HEI has been validated for the Canadian population by another study [18]. Therefore, we determined that HEI was the most appropriate index to be used in our study.

Numerous studies have suggested that lifestyle including dietary patterns plays an important role in MetS. A few studies have shown a significant correlation of Diet Diversity Score with Mets in Tehranian adults [14]. Furthermore, another study has used HEI to evaluate the relationship of MetS with diet and physical activity in the US adolescents [212]. This study showed that a higher HEI score was significantly associated with a lower prevalence of MetS [212].

The objective of our study was to investigate the relationship of diet quality with MetS and its components. Our study included a population of overweight and obese postmenopausal women, who where at higher risks of metabolic complications due to their postmenopausal state.

5 Research design and method

5.1 Subjects

In this research, the samples were drawn from 137 non-diabetic, sedentary, and overweight or obese postmenopausal women aged 45-70 years, who had been recruited for the Montreal Ottawa New Emerging Team (MONET) Weight-loss Weight-Regain (WLWR) study. The recruitment of healthy, overweight, and obese postmenopausal women for this study was done by newspaper advertisement in the Montréal area from May 2003 to February 2006.

The study was approved by the Research Ethics Board - Faculty of Medicine (Comité d'éthique de la recherche de la Faculté de medicine, CÉRFM), Université de Montréal, and all participants gave an informed written consent before participation in accordance with the ethical guidelines of the Université de Montréal Research Ethics Committee. After reading and signing the consent form, each participant was invited to the Metabolic Unit of the Nutrition department for a series of tests. The women who were included in the study met the following criteria:

1) Cessation of menstruation for more than 1 year, and follicle-stimulating hormone level $\geq$ 30 U/L
2) No use of hormone replacement therapy (except for L-Thyroxine T4 (Synthroid®) at stable dosage with optimal plasma TSH levels)
3) Sedentary (less than 2 h /week of structured exercise)
4) Non-smoker
5) Free of known inflammatory diseases and cancer
6) Body mass index $\geq$ 27 kg/m^2

Based on physical examination and biological testing, it was shown that all participants had no history or evidence of:

1) Cardiovascular disease, peripheral vascular disease, uncontrolled thyroid disease, and stroke
2) Diabetes (fasting plasma glucose > 7.0mmol/L, and 2 h after a 75-gram OGTT plasma glucose > 11.0 mmol/L)
3) Orthopaedic limitations
4) Medication that could affect cardiovascular function and/or metabolism
5) Use of hormone replacement therapy, oestrogen, narcoleptics, steroids, lipid-lowering, and antihypertensive agents
6) Dyslipidemia or hypertension requiring immediate medical intervention (total cholesterol > 8.00 mmol/L, triglyceride > 4.5 mmol/L, and blood pressure > 160/100 mm Hg)
7) History of alcohol or drug abuse
8) Abnormal blood laboratory values (creatinine > 135 μmol/L, and haemoglobin < 120 g/L)
9) Use of (a) drugs or medications to stimulate weight loss, (b) psychoactive drugs, and (c) adrenergic agonists
10) Reported body weight fluctuation beyond 2 kg in the last 3 months

5.2 Study Design

In this study, two hundred fifty two participants were invited to the Metabolic Unit of Nutrition department, at 7:30 a.m. in the fasting state, for the inclusion protocol including OGTT, fasting blood samples, and physical examination. One hundred thirty seven participants, who were qualified for the inclusion protocol, went through a 4-week weight stabilization period (± 2 kg) that was verified by weekly weighting at the Metabolic Unit. Within the 4 consecutive weeks, patients underwent a series of tests including euglycemic-hyperinsulinemic clamp (EHC), body composition using DXA and CT-scan

for visceral adiposity, aerobic capacity, resting energy expenditure (REE), total energy expenditure (TEE) using doubly labelled water, psychosocial and socio-demographic questionnaires, and 3-day food record. All these tests were done at the inception of the 6-month weight-loss study by using caloric restriction with or without a resistance-training program.

Among the 137 subjects who were tested at baseline, 88 subjects had the complete data for the variables of interest (food intake, blood pressure, lipid profile, body composition, and glucose homeostasis) and hence were included in the analysis.

5.3 Methods

5.3.1 Blood samples

After an overnight fast (12 h), venous blood samples were collected for the measurements of total cholesterol, HDL-C, triglycerides, ApoB, and insulin. LDL–cholesterol was calculated by using the Friedewald equation [213]. All samples were analyzed on the day of collection by using the COBAS INTEGRA 400 (Roche Diagnostic, Montréal, Canada) except for insulin and ApoB, which were kept at -80 C until the analyses were performed.

Fasting insulin level was determined in duplicate by using radioimmunoassay with human insulin serving as the standard (Linco Research Inc, St-Charles, MO). The ApoB was assessed by using immunophelometry on an image analyzer (Beckman-Coulter, Villepinte, France). Because more than 90% of total ApoB (up to 13 mmol/L of triglyceride) was bound to LDL-C particles, we used the LDL-C/ApoB ratio to estimate the size of LDL-C particles [214].

5.3.2 Insulin sensitivity measurement and estimation

5.3.2.1 Euglycemic-hyperinsulinemic clamp

The aim of this test is to measure insulin sensitivity in peripheral tissues, which mainly include adipose tissue and muscle. To ensure appropriate glycogen concentration, the test was preceded by 3 days of dietary and exercise advices. The suggested diet provided more than 250 g of carbohydrates per day. Furthermore, the subjects were asked to refrain from any physical activities for 48 h prior to the test. After a 12-h overnight fasting, the study began at 7:30 a.m. according to the procedure described by DeFronzo et al [113]. The cannulation of an antecubital vein was done on each arm, one for plasma collection and the other for insulin infusion. The cannulation for plasma collection was done as close to the hand as possible. The arm was warmed up to 60° C in order to produce arterialized blood for sampling. Three blood samples were taken over a 40 min time interval to determine the basal plasma glucose and insulin values. After a priming dose, insulin infusion was kept constant (75 $\mu U/m^2/min$; Actrapid®, Novo-Nordisk, Toronto, Canada) for 180 min. This insulin level was chosen to ensure the complete suppression of hepatic glucose output.

Plasma glucose was measured every 5-10 min by using a glucose analyzer (Beckman Instruments, Fullerton, CA) and was maintained at the fasting level with variable infusion rate of 20% dextrose with 20 meq/L of potassium. Infusion of glucose and insulin was initiated simultaneously. Efforts were made to keep the plasma glucose and the 20% dextrose infusion stable during the last 30 min of the test (steady state). The fasting and steady state plasma glucose and insulin levels were determined by using the mean of the three values, which were taken over a 40 min time interval as mentioned above. The amount of glucose infused to maintain euglycemia during the last 30 min of the clamp (glucose disposal), was proportional to insulin sensitivity. The insulin sensitivity was expressed by using the following formula: glucose infusion rate (GIR) in the last 30 min of the clamp expressed as milligram per min per kilogram fat-free mass (mg/min/kg FFM, also known as MMT3).

5.3.2.2 Oral glucose tolerance test (OGTT)

According to the Canadian Diabetes Association guidelines [215], after a 12-h fast, a 2-h 75-g OGTT was performed. Blood samples were collected through a venous catheter from an antecubital vein in vacutainer tubes containing EDTA (SST gel and Clot activator) at 0, 30, 60, 90, and 120 min time instants. The plasma glucose and insulin levels were measured as described in the clamp test.

5.3.2.3 Fasting surrogate indices of insulin sensitivity

The most widely used index for estimating insulin resistance is the Homeostasis Model Assessment - Insulin Resistance (HOMA-IR), which utilizes the fasting plasma glucose and insulin values. This index was calculated according to the formula of Mathews et al. (Fasting insulin (μM/ml) × fasting glucose (mmol/L)/22.5) [216].

5.3.3 Blood pressure

Sitting blood pressure, which was measured by using Dinamap automatic machine (Welch, Allyn Inc), was determined by taking the average of the last 4 of the overall 5 readings (at the rate of 1 reading per min) in the left arm after the subject rested quietly for 10 min.

5.3.4 Body composition

Body weight was measured by using Dual-energy X–ray Absorptiometry (DXA) (Perspective Enterprises, Portage, MI, USA), which is described below. Moreover, the height was measured with a wall stadiometer. The values obtained were used to calculate BMI (body weight (kg)/height (m^2)) [217]. Waist and hip circumferences were measured with a non-extendable linear tape measure according to the standard method [218].

5.3.4.1 Dual-energy X–ray Absorptiometry (DXA)

Regional and whole body compositions (body weight, fat free mass, fat mass, peripheral fat mass, central fat mass, and percentage of fat mass) were measured by using DXA, which was calibrated daily by using a standardized procedure. The central body region was defined based on the following boundaries: (a) a horizontal line below the chin, (b) two vertical lines passing through the arm sockets along the edges of the ribs (separating the arms from the body), and (c) two diagonal lines beginning on the side of the trunk on top of the pelvis bone and meeting at the end of the soft tissue between the legs. The amount of peripheral fat tissue was determined by adding the quantity of fat, which was present in arms and legs and was outside the boundaries mentioned above. The same strategy was used to determine the amounts of peripheral and central lean body masses.

5.3.4.2 Computed tomography (CT)

Visceral adipose tissue (VAT), subcutaneous adipose tissue, total abdominal fat, and thigh subcutaneous fat were all measured by using a GE high-speed advantage CT scanner (General Electric Medical System, Milwaukee, WI, USA). The participants were examined while they were remaining in the supine position with both arms stretched above their head. The position of scan was established at the L4/L5 level according to a scout image of the body. The VAT area was quantified by delineating the intra-abdominal cavity at the most internal aspect of the abdominal and oblique muscle wall surrounding the cavity, and the posterior aspect of the vertebral body. The cross-sectional areas of adipose tissue were highlighted and computed by attenuation ranging from -190 to -30 Hounsfield units, and by using a commercially available software (GE Medical System) [219].

5.3.5 Energy metabolism

5.3.5.1 Resting Energy Expenditure (REE)

After a 12-h fast, the REE was measured by using indirect calorimetry. The concentrations of CO_2 and O_2 were measured by using the ventilated hood technique with a Sensor Medic Delta Track II (Datex-Ohmeda, Helsinki, Finland). The gas concentrations were used to determine the 24 h REE by using Weir's equation [220]. Measurements were performed while the subjects were lying in a supine position and were avoiding speaking, sleeping, and moving for 40 min. The first 10 min time interval was considered as the acclimatizing period and the last 30 min was used for the analyses. Before every measurement, the gas analyzers were calibrated for pressure and gas concentrations.

5.3.5.2 Total Energy Expenditure (TEE)

Daily TEE was determined from doubly labelled water (DLW) over a 10-day period [221]. The DLW experiments generated 5 urine samples per study as follow: one pre-dose sample was collected at baseline; two samples were collected (16-24 h later) after the $^{2}H_{2}{}^{18}O$ dose had initially equilibrated in the body, and two more samples were collected 10 days later. All samples were measured in triplicate for ^{18}O-water and ^{2}H-water. An Isoprime Stable Isotope Ratio Mass Spectrometer was connected to a Multiflow-Bio module for Isoprime, and a Gilson 222XL Autosampler (GV instruments, Manchester, UK) was used to make daily energy expenditure measurements. Data processing was performed by using the Mass Lynx 3.6 software. Stability tests were performed each day before sample's determination and gave a standard deviation of 0.026% for deuterium and a standard deviation of 0.004% for 18O.

5.3.5.3 Physical activity energy expenditure (PAEE)

PAEE was calculated from the following equation: PAEE = (TEE × 0.90) - REE [221], while assuming that the thermic effect of food was 10% of TEE [222].

5.3.6 Quantitative and qualitative food intake assessment

The Healthy Eating Index (HEI) was used to assess diet quality. This index was chosen because it was among the most frequently used and the best validated food quality scores in the literature. We used the Canadian HEI (HEI-Ca), which had been previously adapted for the Canadian population by Shatenstein et al. [18]. The HEI-Ca contains 9 components based on *Canadian Food Guide 1997* [185] as described before. Briefly, this index includes:

1) Number of servings of the 4 major food groups: grain products, vegetables and fruits, milk products, and meat and alternatives,

2) 3 components reflecting fat intake: total fat, saturated fat, and cholesterol,

3) 1 component addressing sodium intake, and

4) 1 component addressing the variety of food consumed.

Food servings and nutrient intakes were assessed with a 3-day food record at baseline. Studies have shown that some subjects underreported some of the food categories when using a 3-day food record [223]. However, the 3-day food record performed reasonably well compared to the double labelled water (DLW), which is the gold standard method to evaluate energy intake. Therefore, the 3-day food record can be used to evaluate food intake [223].

Subjects were instructed by a registered dietician to keep a record of their food intakes, including condiments and beverages, over two weekdays and one weekend day while maintaining their usual habits. Each food record was reviewed by the dietician, while being with the subject, to complete missing information. The dietician evaluated the serving size of each food eaten by the subject. She divided the amount of foods (gram) or beverages (milliliter) consumed by the subjects by the amount of one serving size as defined in the Canadian Food Guide (Appendix 1). Analyses were conducted with the Food Processor

SQL program (Food Processor SQL Edition, version 9.6.2, 2004, ESHA Research, Salem, OR, USA), by using the 2001 Canadian Nutrient Data File [224] and the US Department of Agriculture (USDA) databases [179]. The data entry of the food records was done by a registered dietician and was independently verified by a second dietician. Discrepancies between the two registered dieticians were discussed and modifications were made according to their mutual decision. The mean intake values (over the three day period) of food group servings, total and saturated fat, cholesterol, and sodium were calculated for each subject.

5.3.7 Cardio-metabolic assessment

5.3.7.1 Metabolic syndrome definitions

To investigate the relationship between HEI and cardio metabolic characteristics, we have chosen the most widely used definition of the MetS in North America, namely the NCEP ATPIII (Table 1).

5.3.7.2 Additional variables evaluated

The following variables have been selected based on their well-known associations with increased cardio metabolic risk:

- Variables associated with *body composition:* BMI, VAT, SAT, waist circumference, hip circumference, total fat mass, central and peripheral fat mass, fat free mass, and thigh subcutaneous fat
- Variables associated with *glucose homeostasis:* 2-h glucose, fasting insulin, and insulin sensitivity as determined by using the clamp (GIR) and the HOMA-IR
- Variables associated with *lipoprotein profile:* ApoB, LDL-C/ApoB, TG, LDL-C, and HDL-C
- Variables associated with *energy expenditure:* TEE, REE, and PAEE

5.3.8 Statistical analysis

The data are presented in the "Mean ± SD" format. The normality of the variable distributions was assessed with a Kolmogorov-Smirnov test, and all variables were shown to be normally distributed. An independent Student *t*-test was used to compare the HEI-Ca between women with 2 or less components and women with 3 or more components of the MetS. The associations between HEI and physical or cardio-metabolic characteristics were examined by using bivariate Pearson correlation. The SPSS software (version 16) for Windows was used for the statistical analysis. The significance was accepted if $p < 0.05$ held.

6 Results

Physical and metabolic characteristic of the study population

In this study, for the overall 88 obese and overweight postmenopausal women (subjects), the physical and cardio-metabolic characteristics are presented in Table 16 and Table 17, respectively. These subjects displayed wide variations in their body compositions, lipid profiles, and insulin sensitivities. As shown in Table 16, for this population the data "Mean ± SD" of the age and the BMI were obtained to be 58.2 ± 4.9 years and 32.5 ± 4.9 kg/m^2, respectively. As shown in Table 17, 68.2% (n=60) of these women had total cholesterol greater than 5.2 mmol/L, and 31.8% (n=28) had LDL-C greater than 3.4 mmol/L. The mean and standard deviation (Mean ± SD) of the total HEI for this population was calculated to be 83.5 ± 9. In addition, the data "Mean ± SD" for all components of HEI are shown in Table 18. Table 19 illustrates the HEI cut-off point and the numbers of subjects in each category. Seventy-seven subjects (87.5%) obtained the scores of ≥ 71.00, which corresponds to an excellent diet quality. Ten subjects (11.4%) obtained the scores between 62.00 and 70.00, which is defined as a good diet. Only 1 subject (1.1%) obtained a score between 53.00 and 61.00, which represents a fair diet quality. It is noticeable that no subject was found with a score of ≤ 52, which is the cut-off point for a poor diet quality.

As shown in Table 20, according to NCEP ATPIII definition only sixteen subjects (18.4%) had ≥ 3 components of the MetS. Among the seventy-one subjects (81.6%) who did not have the MetS, twenty-five subjects (35.2%) had two components, forty-three subjects (60.6%) presented one component, and three subjects had no component of the MetS. By design, the most common MetS component was obesity. Thus, eighty-two subjects (94.3%) of the population had waist circumferences more than 88 cm, while twenty-six (29.9%) of them displayed high TG (≥ 1.7 mmol/L). Furthermore, twenty subjects (23.0%) presented elevated HDL-C (<1.29 mmol/L), eight subjects (9.2%) had hypertension, and eight subjects (9.2%) had impaired fasting glucose.

Table 20 shows that the number of MetS components was not associated with the HEI score. As shown in Table 21, there was no significant difference in the HEI score between the subjects with number of factors ≤ 2 (without MetS) and the subjects with number of factors ≥ 3 (with MetS).

Relationship between Healthy Eating Index (HEI) and physical and cardio-metabolic characteristics

We examined the association between HEI and both physical and cardio-metabolic characteristics indices by using bivariate correlation. As shown in Table 22, the HEI correlated negatively with the measure of body fat (total fat mass, abdominal fat mass, and central fat mass) and the measure of body weight, while VAT did not show any significant correlation with HEI. On the other hand, as indicated in Table 23, HEI had no significant relationship with fasting plasma glucose, 2-h glucose, insulin sensitivity (HOMA and clamp), blood pressure, and most markers of lipid metabolism (total cholesterol, LDL and HDL-C, ApoB, and TG). It is noticeable that we found a significant positive association between HEI and LDL-C/ApoB. Furthermore, REE and TEE showed a significant negative correlation with HEI.

Table 16. Physical characteristics of overweight and obese postmenopausal women (n=88)

Physical characteristics	**Mean**	**S.D.**	**Range**
Age (yrs)	58.2	4.9	46.0 – 68.7
Weight (kg)	83.8	14.7	56.4 – 130.4
BMI (kg/m^2)	32.5	4.9	26.1 – 48.5
Waist circumference (cm) (n=87)	103.6	11.9	81.5 – 153.0
Hip circumference (cm) (n=87)	115.9	11.9	91.0 – 166.5
Fat free mass (kg)	45.1	6.6	32.6 – 64.0
Total fat mass (kg)	38.7	9.9	23.8 – 73.1
Fat mass (%)	45.7	4.8	37.6 – 57.9
Peripheral fat mass (kg)	19.0	4.9	11.5 – 34.9
Central fat mass (kg)	18.7	5.5	11.1 – 39.0
Abdominal fat mass (cm^2) (n=86)	649.0	147.7	442.9 – 1025.9
VAT (cm^2) (n=87)	183.4	48.8	82.7 – 343.6
SAT (cm^2) (n=87)	465.4	121.3	301.7 – 776.0
Thigh subcutaneous fat (cm^2)	312.9	107.3	145.2 – 678.0

S.D.: standard deviation, BMI: body mass index, VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue

Table 17. Cardio-metabolic characteristics of overweight and obese postmenopausal women (n=88)

Cardio-metabolic characteristics	Mean	S.D.	Range
Fasting glucose (mmol/L)	5.25	0.49	4.40 – 6.63
2-h glucose (mmol/L)	6.40	1.87	3.59 – 11.03
HOMA-IR (n=86)	3.53	1.56	1.11 – 9.50
MMT3 (mg/min/kg FFM) (n=85)	11.12	3.19	4.71 – 22.87
Total cholesterol (mmol/L)	5.49	0.76	3.27 – 6.94
LDL-C (mmol/L)	3.22	0.67	1.43– 5.09
HDL-C	1.47	0.34	0.98 – 2.66
TG (mmol/L)	1.73	0.73	0.49 – 3.84
ApoB (g/L) (n=87)	1.01	0.21	0.64 – 1.57
LDL-C/ApoB (n=87)	3.23	0.64	1.51 – 5.81
Systolic blood pressure (mmHg)	121	13	98 – 160
Diastolic blood pressure (mmHg)	76	8	60 – 100
TEE (kcal/day)	2525	404	1800 – 3572
REE (kcal/day)	1318	195	930 – 1850
PAEE (kcal/day)	954	288	381 – 1697
Healthy Eating Index	83.51	9.24	56.13 – 99.22

HOMA-IR: Homeostasis Model Assessment – Insulin Resistance, MMT3: Insulin sensitivity calculated by clamp, HDL: high density lipoprotein, LDL: low density lipoprotein, TG: triglycerides, TEE: total energy expenditure, REE: resting energy expenditure, PAEE: physical activity energy expenditure

Table 18. Healthy Eating Index (HEI) score and sub scores for overweight and obese postmenopausal women (n=88)

HEI Components	Mean	S.D.	Range
Grains	7.64	2.18	3.00-10.00
Fruits and vegetables	18.05	3.31	8.80-20.00
Milk products	7.16	2.81	0.00-10.00
Meat and alternatives	9.43	1.44	2.50-10.00
Total fat	7.81	2.51	0.00-10.00
Saturated fat	7.53	3.19	0.00-10.00
Cholesterol	8.37	3.20	0.00-10.00
Sodium	8.03	2.46	0.00-10.00
Dietary Variety	9.49	1.08	5.00-10.00
Total HEI	83.51	9.24	56.13-99.22

Table 19. Number of subjects according to HEI-Ca categories

HEI categories	Cut-off point for Total score	Number of subjects
Excellent	≥71	77
Good	62-70	10
Fair	53-61	1
Poor	≤ 52	0

Table 20. Healthy Eating Index (HEI) score according to the number of metabolic syndrome components in overweight and obese postmenopausal (n=88)

Number of metabolic syndrome components	HEI score	Number of subjects
0	86.87 ± 2.76	3
1	84.68 ± 7.85	43
2	80.23 ± 12.20	25
3	84.47 ± 7.81	14
4	89.63 ± 0.18	2
5	NS	0

Data presented as mean ± standard deviation

Table 21. Comparison of the Healthy Eating Index (HEI) between women with and without metabolic syndrome

	Without Metabolic syndrome ≤ 2 factors (n=71)	**With Metabolic syndrome ≥ 3 factors** (n=16)	***p* value**
HEI	83.21 ± 9.66	85.11 ± 7.48	0.461

Data presented as mean ± standard deviation

Table 22. Bivariate correlations of physical characteristics with Healthy Eating Index (HEI) (n=88)

Physical characteristics	**Coefficient correlation**	***p* value**
Age	0.16	0.150
Weight	**-0.28**	**0.010**
BMI	**-0.30**	**0.005**
Waist circumference (n=87)	**-0.24**	**0.023**
Hip circumference (n=87)	**-0.34**	**0.001**
Fat-free mass	**-0.22**	**0.043**
Total fat mass	**-0.26**	**0.013**
Fat mass (%)	-0.16	0.130
Peripheral fat mass	-0.19	0.080
Central fat mass	**-0.31**	**0.004**
Abdominal fat mass (n=86)	**-0.25**	**0.019**
VAT (n=87)	-0.15	0.181
SAT (n=87)	**-0.25**	**0.020**
Thigh subcutaneous fat	-0.18	0.092

BMI: Body mass index, VAT: visceral adipose tissue, SAT: subcutaneous adipose tissue

Table 23. Bivariate correlations of cardio metabolic characteristics with Healthy Eating Index (HEI) (n=88)

Cardio metabolic characteristics	**Coefficient correlation**	***p* value**
Fasting glucose	0.05	0.621
2h-glucose	0.05	0.642
HOMA-IR (n=86)	-0.09	0.408
MMT3 (n=85)	0.12	0.288
Total cholesterol	0.12	0.259
LDL-C	0.10	0.345
HDL-C	0.17	0.121
TG	-0.10	0.378
ApoB (n=87)	-0.12	0.257
LDL-C/ApoB (n=87)	0.25	**0.019**
Systolic blood pressure	-0.13	0.228
Diastolic blood pressure	-0.15	0.153
TEE	-0.22	**0.040**
REE	-0.24	**0.025**
PAEE	-0.12	0.282

HOMA-IR: Homeostasis Model Assessment–Insulin Resistance,

TG: triglycerides, TEE: total energy expenditure, REE: resting energy expenditure, PAEE: physical activity energy expenditure

7 Discussion

We did not find any differences in diet quality between subjects with and without MetS. This may be, at least in part, due to the fact that few subjects had MetS (18.3%). The low prevalence of MetS might have hampered the statistical power which is necessary to detect significant relationship between MetS and diet quality. In addition, MetS is a heterogeneous syndrome with variable components. As shown in Table 1, the definition of MetS chosen in our study is based on NCEP ATPIII [22]. According to this definition, an individual with three or more components including obesity, dyslipidemia, hypertension, and fasting plasma glucose $\geq$ 6.1 mmol/L is considered with MetS regardless of the components present. Thus, the HEI may correlate with some, and not all, of the components. This may explain the lack of correlation between HEI (that we used in our study) and MetS. However, it should be noted that HEI is associated with some components of MetS such as waist circumference.

We also examined the relationship between diet quality and individual components of MetS. The main finding of our study was that diet quality correlated negatively with most measures of body fat including total fat, abdominal fat, and central fat mass. Similar results have also been observed in American Youth [16] and Framingham [225] studies. More research will be needed to determine which dietary components contribute to the cardio-metabolic risk, and whether the overall dietary pattern is important or not.

Numerous studies have demonstrated the strong association between diet quality, specifically diets rich in saturated fat, and insulin resistance. Surprisingly, we did not observe any correlation between HEI and fasting plasma glucose, 2-h glucose, insulin sensitivity (HOMA and clamp), and most markers of lipid metabolism (total cholesterol, LDL and HDL-C, ApoB, and TG). One explanation may be that most subjects included in the study had an excellent diet score, while in other studies the HEI scores were notably lower (refer to Appendices 1 and 2). In general, the subjects who have an excellent diet quality consume less fat, and this may be one of the reasons why we do not see any association between markers of insulin sensitivity and diet quality.

The results of our study showed that most of our subjects had excellent HEI scores although they were overweight or obese. It has been shown that women generally have higher HEI diet quality scores, particularly in fruit and vegetable consumption, than men [18]. However, most of the subjects showed dyslipidemia in spite of their excellent diet quality. This observation suggests that diet quality alone is not sufficient to prevent metabolic alteration. Since the main cause of obesity is high-calorie intake, it can be concluded that having a high-quality diet is not a sufficient condition for having a healthy metabolic profile, and that a high-calorie intake may contribute to obesity and potentially abnormal metabolic profile. Thus, it is probable that a person may need to restrict his/her calorie intake and have a high-quality diet simultaneously, in order to lose weight and improve his/her metabolic profile as a result.

It should be noted that we found a significant positive association between HEI and the LDL-C/ApoB ratio. Since there is only one molecule of ApoB per LDL, the LDL-C/ApoB ratio has been used so far in the literature to estimate the LDL size [126, 132, 226]. Numerous studies have demonstrated that small dense LDL-C is more atherogenic and is associated with increased risk of CVD [127, 129]. Therefore, our results suggest that a higher diet quality is associated with a better lipid profile. However, it should be noted that the LDL/ApoB ratio remains an indirect measure of the LDL size. Although in more than 90% of patients ApoB is associated with LDL, we observe in some patients with high TG and cholesterol that some ApoB's bind to VLDL. However, subjects with high cholesterol and/or TG were excluded from our study. Further studies should be done to examine the relationship between diet quality and direct measure of LDL size.

One limitation of our study is that subjects with diabetes, hypertriglyceridemia, hypertension, and cardiovascular diseases were excluded, while all women were either overweight or obese. Thus, the study population was relatively healthy, that led to a small number of women with MetS. This situation had probably limited our ability to detect the interaction between diet quality and MetS. Further studies should be done to include a larger number of women with MetS as compared to our study population.

Another limitation of our study is due to the use of dietary journal. For example, although subjects had been taught by dieticians to estimate the portion sizes of the foods they consumed, the possibility remained that the subjects made mistakes in estimating their portion sizes. In addition, it was possible that the subjects did not report all foods that they consumed. For example, consumption of multivitamins, omega-3 pills, and some supplements for lowering cholesterol and TGs might had been forgotten by some subjects. All these issues could alter the results of this study.

Despite these limitations, our results were strengthened by using the gold standard techniques for the evaluation of various metabolic risk factors in a relatively well-phenotype cohort.

8 Conclusion and Future Work

Our results demonstrated that HEI is associated with fat distribution, as well as LDL size, in a cohort of overweight and obese postmenopausal women.

Further statiscal analyses could be performed by using the components of MetS as dependent variables and using HEI as the independent variable to examine the relationship between the MetS and diet quality.

Most of the women included in our study presented a relatively healthy profile as shown by the small number of subjects with the MetS. Thus, our future work may include the individuals with complications in order to investigate the association between diet quality and the MetS. It would also be useful to include more subjects in our future study in order to increase the power to do statistical analysis.

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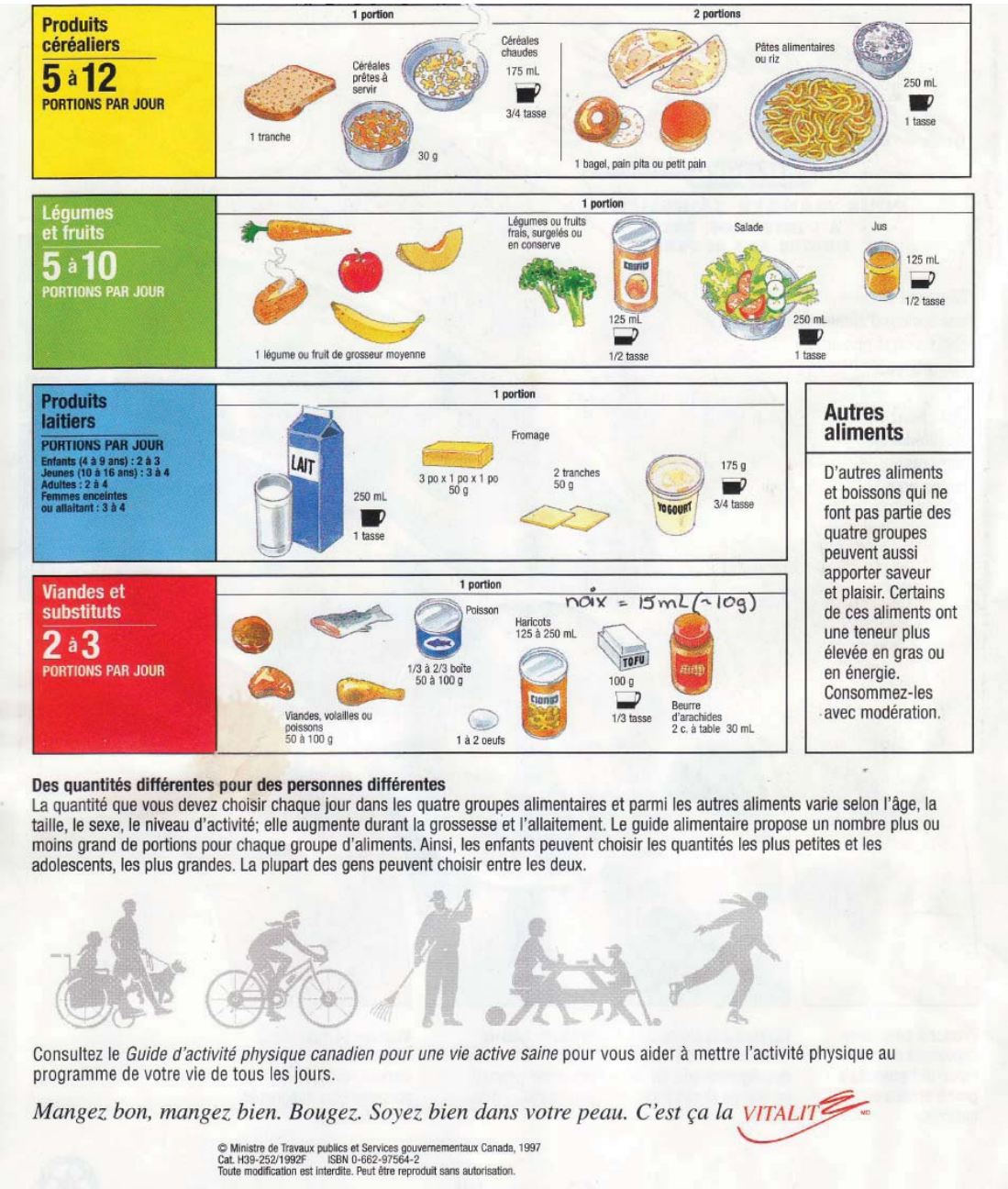
APPENDICES

Appendix 1. Canadian Food Guide, 1997

Appendix 1. Continued



Note: In our study, one serving of alcohol is equal to (a) 1.5 onces of distilled alcohol (e.g. Vodka, Jin, and Whiskey), (b) 4 onces of sec wine, (c) 2 onces of sec Sherry, or (d) 12 onces of beer.

Appendix 2. Tables for mean comparison of HEI

Table A-I. Scores of Healthy Eating Index Components (n=7643)* [15]

*weighted data for persons aged 2 years and older and 3 day dietary intake data.

HEI component	Mean	% observation at score 0	% of observation at score 10
Grain	6.2	< 0.5	11.1
Vegetables	6.1	0.8	17.1
Fruits	4.0	13.2	13.6
Milk	6.7	0.2	32.5
Meat**	7.5	< 0.5	32.2
Total fat	6.3	5.0	20.3
Saturated fat	5.1	18.7	19.5
Cholesterol	8.0	10.8	69.1
Sodium	7.0	9.6	36.2
variety	7.0	2.8	32.9
Total Score	63.9		

** included egg, nuts and some legumes

Table A-II. Diet Quality of Montreal-Area Adults Needs Improvement: Estimates from a Self-Administered Food Frequency Questionnaire Furnishing a Dietary Indicator Score [18]

HEI components	Highest possible score	Male(n=105)	Female(n=143)	All(n=248)
Grain	10	5.1±2.5	5.4±2.5	5.3±2.5
Vegetable and fruit	20	11.0±5.3	14.0±5.2****	12.7±5.4
Milk	10	7.5±2.8	7.5±2.9	7.5±2.9
Meat and alternatives	10	9.2±1.5	8.9±1.9	9.0±1.7
%total fat	10	7.3±2.8*	6.5±3.2	6.9±3.1
% saturated fat	10	6.1±3.7	5.9±3.8	6.0±3.8
Cholesterol	10	7.3±3.9	8.8±2.8***	8.2±3.3
Sodium	10	7.3±3.4	8.6±2.5**	8.1±3.0
Dietary variety	10	9.4±1.1	9.3±1.3	9.3±1.2
Total score	100	70.3±10.5	74.9±10.9***	73.0±11.0

* P<0.05

** P<0.01

*** P<0.001

**** P<0.0001

Table A-III. Healthy Eating Index Scores Are Associated With Blood Nutrient Concentrations in the Third National Health and Nutrition Examination Survey [209]

HEI components	CSFII 1989 n=3997	CSFII 1996 N=4800	NHANESIII 1989-94 N=26,348	NHANES 1999-2000 N=8070
Grains	6.1	6.7	6.7	6.7
Vegetables	5.9	6.3	5.7	6.0
Fruits	3.7	3.8	3.8	3.8
Milk	6.2	5.4	6.6	5.9
Meat	7.1	6.4	6.8	6.6
Total fat	6.3	6.9	6.5	6.9
Saturated fat	5.4	6.4	6.1	6.5
Cholesterol	7.5	7.9	7.8	7.7
Sodium	6.7	6.3	6.0	6.0
Dietary variety	6.6	7.6	7.7	7.7
Total Score	61.4	63.8	63.8	63.8

Table A-IV. Validation of Healthy Eating Index with Use of Plasma biomarkers in a clinical sample of women [208]

		Percentage obtaining score		
HEI Component	**Mean**	**Poor Score < 5**	**Needs Improvement Score 5 - 8**	**Good Score > 8**
Grain	7.2	18.5	40.9	40.6
Vegetables	8.4	10.0	24.1	65.9
Fruits	7.2	27.1	17.1	55.9
Milk	5.9	42.4	27.1	30.6
Meat *	8.9	6.5	17.1	76.5
Total fat	8.3	12.6	18.8	68.5
Saturated fat	8.1	17.1	12.1	70.9
Cholesterol	9.3	5.6	4.4	90.0
Sodium	8.0	13.8	22.9	63.2
Dietary Variety	5.9	37.4	38.5	24.1
Total Score **	77.3	1.8	49.4	48.8

*includes eggs,nuts and legumes
** to obtain value, criterion was multiplied by 10 (ie, for good score, score>80)

Table A-V. Predictors of Diet Quality among Overweight and Obese postmenopausal women [227]

Characteristics	N	DQI score Mean ± SD	HEI score Mean ± SD
Age group:			
50-55	43	7.8 ± 2.9	61.8 ± 13.6
56-65	76	8.3 ± 3.0	63.8 ± 11.8
66-75	45	8.0 ± 2.7	63.4 ± 11.6
P-value		0.63	0.70
BMI			
24-28	50	7.0 ± 2.9	65.7 ± 12.4
28-31	54	8.2 ± 2.6	63.2 ± 11.8
>31	60	8.9 ± 2.9	61.0 ± 12.2
P-value		0.003	0.13
% body fat			
34.1-45.0	50	7.3 ± 2.8	64.7 ± 13.1
45.1-49	56	7.9 ± 2.9	63.3 ± 12.3
>49	58	8.8 ± 2.8	61.7 ± 11.2
P-value		0.02	0.44
Educational level			
High school or less	18	9.5 ± 3.7	56.2 ± 11.7
College	82	8.2 ± 2.7	63.1 ± 12.0
PostBS. or advance degree	64	7.5 ± 2.5	65.1 ± 12.0
P-value		0.02	0.02
Smoking history:			
Never	86	8.5 ± 2.6	62.8 ± 12.5
Former	78	7.6 ± 3.1	63.6 ± 11.8
P-value		0.05	0.67

Table A-VI. Adherence to the Dietary Guidelines for Americans and risk of major chronic disease in women [210]

HEI Components	CSFII 1996* HEI score	NHS1984 HEI-F score	Criteria for max score 10 Women19-50	Women ≥51	
Grains	6.7	4.9±2.2	9.1	7.4	0
Vegetables	6.3	8.7±1.9	4.2	3.5	0
Fruit	3.8	7.2±2.9	3.2	2.5	0
Milk	5.4	6.1±2.9	2.0	2.0	0
Meat	6.4	8.3±2.0	2.4	2.2	0
Total fat	6.9	6.5±3.0	≤ 30		≥ 45
Saturated fat	6.4	5.2±3.5	< 10		≥ 15
Cholesterol	7.9	7.4±3.6	< 300		≥ 450
Sodium	6.3	5.0±3.2	< 2400		≥ 4800
Dietary Variety	7.6	5.0±3.1	16		≤ 6
Total Score	64	64.4±12.5			

*CSFII subset (n=428) was a subsample of women aged 37-66, with ≥ 12 yr of schooling. Pregnant and lactating women are excluded.

HEI scoring was adopted from Kennedy et al. [15]

Appendix 3. Consent form of the Weight-Loss Weight-Regain (WLWR) study

FORMULAIRE DE CONSENTEMENT

Titre du projet de recherche : FACTEURS MÉTABOLIQUES ET GÉNÉTIQUES PRÉDISANT LE REGAIN DE POIDS CHEZ LES FEMMES POST-MÉNOPAUSÉES ET OBÈSES

Investigateurs principaux : Dominic Garrel, MD. Ph.D., Martin Brochu, Ph.D., Rémi Rabasa-Lhoret MD. Ph.D., et collaborateurs du Département de nutrition et de kinésiologie de la faculté de médecine de l'Université de Montréal.

1. OBJECTIFS

Déterminer si un déséquilibre énergétique étant relié à une dépense énergétique trop faible ou à un apport énergétique trop élevé ou à une combinaison des deux, et la sensibilité à l'insuline contribuent à l'obésité chez les femmes. Un deuxième objectif sera de déterminer si la présence ou l'absence du gène de l'obésité influence la capacité à perdre du poids et à maintenir cette perte. Un troisième objectif sera de vérifier si l'entraînement musculaire associé à la consultation nutritionnelle peut maintenir l'amélioration du maintien et/ou de la perte de poids chez ce groupe de femmes. Un quatrième objectif sera de mesurer les niveaux de certaines hormones sécrétées par les tissus adipeux, le tractus gastro-intestinal, l'hypothalamus et l'hypophyse (ghrelin, acylation stimulating protein (ASP), leptin, adiponectin, resistin, NPY, orexin A et B, IGF-I et GH).

2. HISTORIQUE

L'obésité est un désordre chronique qui affecte entre autres les femmes plus âgées. Jusqu'à présent, il n'est pas clair si l'apport alimentaire excessif et/ou un faible taux de dépense énergétique contribuent au taux élevé d'obésité chez les femmes plus âgées. Certains facteurs hormonaux dérivés du tractus gastro-intestinal ainsi que des tissus adipeux semblent également jouer un rôle prépondérant quant au contrôle de l'appétit et à la dépense énergétique au quotidien. Une mutation génétique a récemment été découverte qui pourrait jouer un rôle important dans l'accumulation excessive de gras. Nous sommes intéressés à déterminer si les individus possédant cette mutation démontrent un taux de dépense énergétique plus bas, un niveau hormonal différent, une sensibilité plus faible à l'insuline, une capacité de dégradation et d'utilisation des graisses moins efficace comparées aux individus ne possédant pas la mutation. Nous aimerions démontrer que l'entraînement musculaire aura un effet sur l'augmentation de la masse maigre, du métabolisme basal, de la force musculaire ce qui représente une adaptation métabolique directe et indirecte qui pourrait maintenir la perte de poids et éviter le regain de poids. .

3. NATURE DU PROTOCOLE

L'étude est divisée en six parties :

A. Recrutement
B. Stabilisation du poids corporel (4 semaines
C. Restriction calorique (26 semaines)
D. Stabilisation du poids corporel (4 semaines)
E. Suivi (52 semaines)
F. Stabilisation du poids corporel (4 semaines)

A.Recrutement

Lors de la période de recrutement, vous serez soumis à certains examens pour déterminer si vous êtes en mesure de participer à l'étude (voir critères d'exclusion et description des tests). Une fois ces tests complétés, vous pourrez débuter l'étape suivante si votre profil correspond à celui requis pour l'étude.

B.Stabilisation du poids corporel (4 semaines) et série de tests

Cette période consiste à maintenir votre poids le plus stable possible avant les tests qui serviront à déterminer votre condition physique. Elle est nécessaire pour s'assurer que les tests sont représentatifs d'un état stable et que vous n'êtes pas encore en phase de changement. Ensuite, vous subirez une batterie de tests décrits plus loin nécessitant 7 visites au laboratoire, et une visite en milieu hospitalier. Avant de passer à l'étape suivante, vous serez assigné au hasard, soit au groupe avec exercice ou sans exercice.

C.Restriction calorique (26 semaines)

Il s'agit de la partie de l'intervention dont l'objectif principal est de vous faire perdre du poids, soit environ 10 % de votre masse grasse initiale. Votre alimentation sera contrôlée et la quantité d'énergie que vous allez consommer par jour sera limitée en fonction de votre métabolisme qui aura été évalué. Il s'en suivra une restriction énergétique d'environ 500 à 800 kcals par jour. Vous serez accompagnée par une nutritionniste pour tout ce qui concerne votre alimentation, en suivi individuel et en groupe.

D.Stabilisation du poids corporel (4 semaines) et série de tests

Le groupe exercice termine l'étude. Le groupe sans exercice sera divisé en 2 groupes : avec exercice et sans exercice.

E.Suivi (52 semaines)

Lors de la phase de suivi, vous devrez compléter une fois par mois un rappel alimentaire de trois jours ainsi que porter un petit appareil (TriTrac) de la dimension d'un téléavertisseur, qui mesurera votre niveau d'activité pendant la journée. Vous serez également pesée, et vous pourrez, au besoin, rencontrer la nutritionniste pour toutes questions lors de cette rencontre. Les professionnels de l'équipe de recherche demeurent à votre entière disposition pendant cette période.

F.Dernière stabilisation du poids corporel (4 semaines) et série de tests.

Les tableaux 1.1 et 1.2 et 1.3 résument la chronologie des évènements.

Tableau 1.1 L'APROCHE EXPÉRIMENTALE

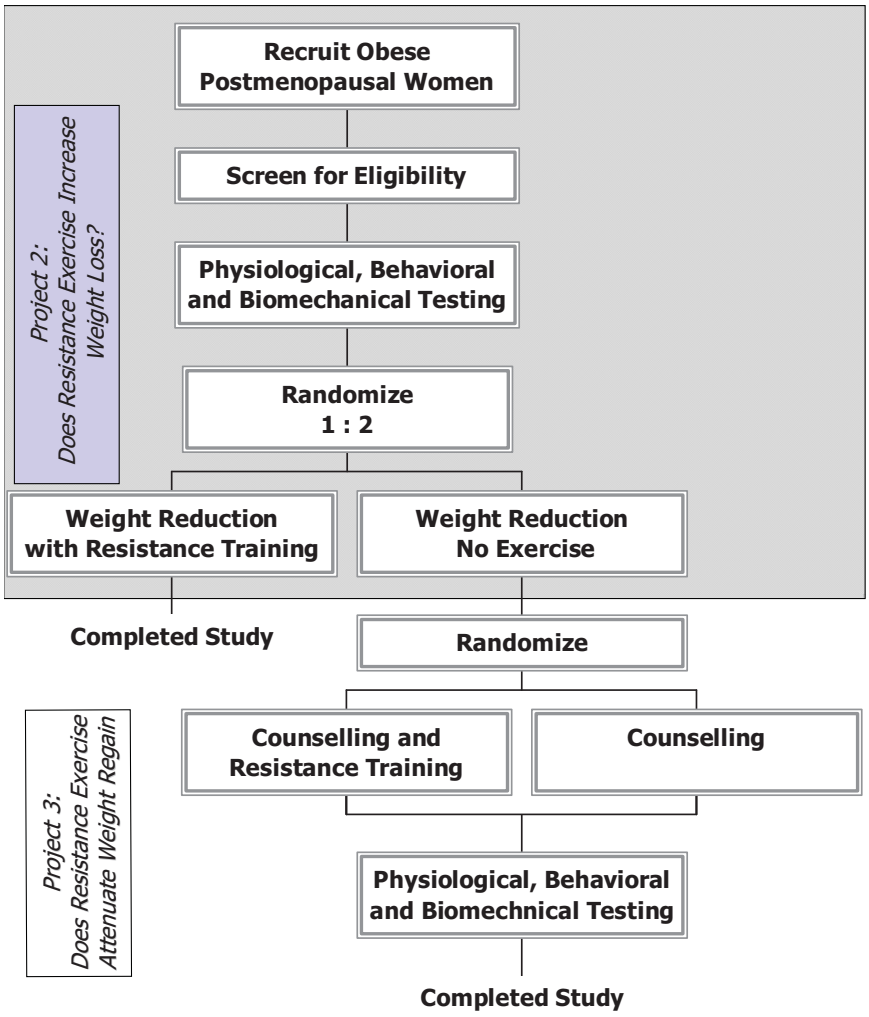


Tableau 1.2 : PLANIFICATION BI-ANNUELLE DU PROTOCOLE

DEVIS EXPERIMENTAL							
STABILISATION DU POIDS CORPOREL 4 SEMAINES	*SÉQUENCE DE 5 VISITES* 10 JOURS	RESTRICTION CALORIQUE (÷ en 2 groupes) 26 SEMAINES	STABILISATION DU POIDS CORPOREL 4 SEMAINES	*SÉQUENCE DE 5 VISITES* (÷ en 2groupes) 10 JOURS	SUIVI 52 SEMAINES	STABILISATION DU POIDS CORPOREL 4 SEMAINES	*SÉQUENCE DE 5 VISITES* 10 JOURS

Tableau 1.3 : HORAIRE DE LA SÉQUENCE DES 5 VISITES EN LABORATOIRE

Visite 1	**Visite 2**	**Visite 3**	**Visite 4**	**Visite 5**
-DÉPISTAGE	**tests**	**tests**	**tests**	**tests**
Laboratoire	*Laboratoire*	*Laboratoire*	*Laboratoire*	*Hôpital St Luc*
prise de sang examen médical électrocardiogramme	prise de l'eau doublement marquée composition corporelle : DXA,mesures anthropométriques Questionnaires Journal alimentaire 3 jours	collecte échantillon d'urine # 1 & 2 calorimétrie clamp euglycémique prélèvements sanguins diète 3 jours tomographie	échantillon d'urine # 3 & 4 test de VO2max retour questionnaires retour journal alimen.	tomographie en soirée
Durée 3 heures	Durée : 1 heure	Durée 6 heures	Durée 1 hre	Durée : 15 minutes

Veuillez prendre note que cette expérience demandera un dévouement en temps important de la part de tous les volontaires.

4. CRITÈRES D'EXCLUSION

- Souffrir de :
  - claustrophobie
  - diabète ou d'une mauvaise tolérance au glucose (glucose plasmatique à jeun > 125 mg/dL)
  - maladie thyroïdienne non traitée
  - maladie hépatique ou rénale (foie ou rein)
  - anorexie nerveuse
  - asthme nécessitant un traitement oral aux stéroïdes
  - hyperlipidémie (cholestérol < 6 nM/L; triglycérides >2 nM/L)
  - maladies cardiovasculaires ou maladies vasculaires périphériques
- Suivre présentement ou au courant des trois derniers mois :
  - un traitement à l'œstrogène
  - une thérapie de remplacement d'hormone
  - un traitement aux narcoleptique
  - un traitement chronique aux stéroïdes
  - un traitement avec des agents atténuant les lipides
- Avoir des antécédents d'abus de drogues ou d'alcool
- Avoir des valeurs de laboratoire anormales (hématocrites <32 ou >48, glucose à jeun >7,4 nM/L, créatine >2.0)
- Utilisation de médicament ou drogues pour la perte de poids, de médicaments ou drogues psychoactifs, et des agonistes adrénergiques peu importe la voie
- Être fumeur

5. DESCRIPTION DES TESTS POUR LE DÉPISTAGE

PRISE DE SANG ET DÉPISTAGE DU GÈNE DE L'OBÉSITÉ

Un petit échantillon de sang (environ ½ cuillerée à thé) sera prélevé pour premièrement mesurer le profil lipidique complet (cholestérol, triglycérides) de votre sang, et deuxièmement pour effectuer un test de dépistage du gène d'obésité. Ce test ne sera effectué qu'une seule fois au début de l'étude.

BÉNÉFICES

Vous serez informé si vous avez des valeurs de lipides dans la sang trop élevés ainsi que si vous êtes porteur du gène susceptible de causer l'obésité

RISQUES ET INCONVÉNIENTS

Des ecchymoses ou une décoloration de la zone de prélèvement sanguin sont les seuls inconvénients reliés à ce test

TEST DE TOLÉRANCE AU GLUCOSE

Ce test est utilisé pour diagnostiquer le diabète. Un petit échantillon de sang sera prélevé (½ cuillerée à thé). Par la suite, on vous demandera de boire une boisson

sucrée (glucose) à saveur d'orange. À chaque demi heure pendant deux heures, un petit échantillon de sang sera prélevé pour un total de 3 cuillerées à thé.
BÉNÉFICES
Vous serez informé de votre niveau de tolérance au glucose en relation avec le diabète.
RISQUES ET INCONVÉNIENTS
Les seuls risques impliqués lors de ce test inclus des ecchymoses ou une décoloration de la zone de prélèvement sanguin.

EXAMEN PHYSIQUE
L'examen physique ainsi que l'historique médical et d'obésité seront effectués par le médecin participant dans cette étude, lors de votre première visite à l'unité métabolique. Aucun risque et inconvénient ne sont associés à cet examen.
BÉNÉFICES
Vous serez informé de votre état de santé en détail.

ELECTROCARDIOGRAMME (ECG
L'électrocardiogramme va mesurer l'activité de votre cœur et nous serons en mesure de détecter toutes anomalies de votre coeur. Des électrodes seront installées à différents points sur votre thorax, et des mesures seront enregistrées. Un médecin sera présent durant le test.
BÉNÉFICES
Vous obtiendrez une évaluation précise de votre activité cardiaque.
RISQUES ET INCONVÉNIENTS
Peu de risques sont associé à cet examen. Un médecin sera présent durant le test et l'équipement médical nécessaire aux urgences cardiaques sera disponible. Le personnel de recherche est certifié en réanimation cardio-respiratoire.

6. DESCRIPTION DES TESTS DE MESURE

TEST DE TOLÉRANCE AU GLUCOSE
Ce test est utilisé pour diagnostiquer le diabète. Un petit échantillon de sang sera prélevé (½ cuillerées à thé). Par la suite, on vous demandera de boire une boisson sucrée (glucose) à saveur d'orange. À chaque demi heure pendant deux heures, un petit échantillon de sang sera prélevé pour un total de 3 cuillerées à thé.
BÉNÉFICES
Vous serez informé de votre niveau de tolérance au glucose en relation avec le diabète.
RISQUES ET INCONVÉNIENTS
Les seuls risques impliqués lors de ce test inclus des ecchymoses ou une décoloration de la zone de prélèvement sanguin.

DÉPISTAGE DES NIVEAUX D'HORMONES SÉCRÉTÉES PAR LES TISSUS ADIPEUX, LE TRACTUS GASTRO-INTESTINAL, L'HYPOTHALAMUS ET L'HYPOPHYSE

Les hormones du tissu adipeux, du tractus gastro-intestinal de l'hypothalamus et de l'hypophyse sécrètent des hormones (ghrelin, acylation stimulating protein, leptin,

adiponectin, resistin, NPY, orexin, IGF-I et GH) seront dosées à partir de l'échantillon de sang prélevé à la visite 1. Le dosage est effectué par radioimmunoessai (RIA), une méthode éprouvée pour la quantification des niveaux d'hormones plasmatiques.

BÉNÉFICES

Si vous le désirez vous serez informé des niveaux d'hormones susceptibles d'influencer la santé métabolique.

RISQUES ET INCONVÉNIENTS

Aucun associé à cette procédure.

MESURE DE LA CAPACITÉ AÉROBIE (V0²max)

Le V0²max sert à mesurer l'habileté de votre corps à consommer de l'oxygène pendant un exercice. Lorsque combiné avec un moniteur de fréquences cardiaques, nous pouvons également utiliser ce test comme un indicateur de votre forme cardiovasculaire. Ce test sera exécuté sur un ergo cycle (vélo stationnaire) maintenu à une vitesse constante. Le niveau de difficulté de l'exercice sera augmenté à chaque deux minutes. Le test sera arrêté lorsque vous serez fatigué. Votre consommation d'oxygène sera mesurée à chaque palier d'effort en mesurant votre souffle dans un appareil buccal en caoutchouc. Votre tension artérielle sera également mesurée. Ce test prendra environ une heure à compléter (approximativement 10-15 minutes d'exercice).

BÉNÉFICES

Vous obtiendrez une évaluation précise de votre capacité aérobie à l'aide d'une mesure directe. La capacité aérobie est un des déterminants important de la santé.

RISQUES ET INCONVÉNIENTS

Les risques associés à ce test sont; essoufflement, souffle court, fatigue, inconfort musculaire local. Un rythme cardiaque irrégulier ou même des complications cardiaques peuvent survenir lors d'efforts intenses.

Comme mesure préventive, vous serez suivi à l'aide d'un électrocardiogramme pour mesurer l'activité de votre cœur et le test sera arrêté si des anomalies se produisent. Un médecin sera présent durant le test et l'équipement médical nécessaire aux urgences cardiaques sera disponible. Le personnel de recherche est certifié en réanimation cardio-respiratoire. Malgré l'intensité associée à ce test, les risques de troubles cardiaques sont improbables. Les arrêts cardiaques sont extrêmement rares (< 1 décès en 10000 tests) chez les individus sans antécédents de maladies cardiaques.

MESURES ANTHROPOMÉTRIQUES

Il s'agit de mesures des dimensions de votre corps. Des circonférences, largeurs et longueurs seront mesurées ainsi que des plis cutanés dans le but de déterminer votre composition corporelle. Ces mesures seront ensuite comparées avec les valeurs obtenues sur le DXA.

BÉNÉFICES

Vous aurez une estimation de votre composition corporelle avec des mesures accessibles et pouvant être reproduites de façon peu dispendieuse.

RISQUES

Il n'y a pas de risque associé à ces mesures. Les seuls inconvénients sont les marques au crayon (lavable à l'eau) pour identifier les repaires anatomiques.

MÉTABOLISME DE REPOS

Même au repos, votre corps dépense de l'énergie (calorie). Ce test nous permet de mesurer la quantité de calorie que vous brûlez au repos. Cette mesure est effectuée de bonne heure le matin. Lorsque vous arriverez, vous vous coucherez dans un lit et un capuchon en plexiglas, alimenté en air frais, sera placé sur votre tête. L'air expiré sera analysé par échantillons et les pourcentages d'oxygène et de dioxyde de carbone seront déterminés. En mesurant le rythme d'expiration, nous déterminerons la quantité d'oxygène que vous consommez et l'appareil calculera le nombre de calories dépensées. Ce test nécessite votre présence en position allongée et calme dans un lit pour approximativement 40 minutes.

BÉNÉFICES

Vous obtiendrez une mesure précise de votre dépense énergétique au repos.

RISQUES ET INCONVÉNIENTS

Il n'y a aucun risque associé à ce procédé. Les seuls inconvénients sont associés aux personnes souffrant de claustrophobie, le capuchon étant un espace restreint, ainsi que l'importance de demeurer totalement inactif pendant toute la durée des mesures soit 40 minutes.

COMPOSITION CORPORELLE ET TOMOGRAPHIE (DXA)

Ce test déterminera la quantité de muscle et de graisse dans votre corps. Votre poids et grandeur seront mesurés. Ensuite, nous utiliserons une méthode nommée « dual photon x-ray » densitométrie (DXA) pour mesurer votre densité osseuse, pourcentage de graisse et de masse maigre. Vous devrez demeurer couché sur la table d'examen, habillé normalement, alors qu'un rayon x à faible densité balayera votre corps pendant 10 minutes.

TOMOGRAPHIE

La tomographie permet de déterminer combien de graisse se situe au niveau de l'abdomen et des cuisses. Pendant ce test, vous serez également allongé mais avec les bras étendus vers le haut au-dessus de la tête. Des mesures de deux secondes sur une surface de 5mm seront effectuées au niveau de l'abdomen, du nombril ainsi qu'à mi-cuisse par un appareil à rayon X. Le tout prend environ 15 minutes.

BÉNÉFICES

Vous obtiendrez une mesure précise de votre composition corporelle déterminée à l'aide de matériel de haute technologie ainsi qu'une évaluation non médicale de votre densité osseuse. La composition corporelle est un autre déterminant important de votre santé.

RISQUES ET INCONVÉNIENTS

Le seul risque se situe au niveau de l'exposition aux rayon X qui se chiffre à 0.03 millirem pour le DEXA, ce qui est moins que l'exposition ambiante naturelle pour une journée, et de 1.12 Rem pour la tomographie qui représente moins que le dosage maximum permis de 5 Rem par année. Veuillez considérer que cette exposition aux radiations est nécessaire pour les objectifs de l'étude et n'est pas requise pour des soins médicaux.

QUESTIONNAIRES

Vous devrez également répondre à des questionnaires alimentaires, psychologiques et sociodémographiques le tout prenant environ une à deux heures. Ces tests sont

réalisés avec papier et crayon ou lors d'un entretien. Les questions posées chercheront à évaluer ; votre consommation d'aliments, des qualités tels que la mémoire, l'appréciation de la vie, la satisfaction, la dépression ainsi que votre humeur.

« CLAMP » HYPERINSULINÉMIQUE-EUGLYCÉMIQUE

À votre arrivé nous prendrons votre poids et votre taille, vous irez à la toilette, puis vous serez installé dans un lit et un cathéter intraveineux (tube de plastique) sera placé dans une veine de votre bras. Un second cathéter, pour les prélèvements sanguins, sera placé dans une veine du dos de votre main qui elle, sera ensuite placée dans une boite chauffante pour la garder au chaud. On vous demandera par la suite de ne pas consommer de la nourriture ni aucune boisson quelconque autre que de l'eau jusqu'à la fin du test. Une demi-heure plus tard, nous commencerons à vous donner un liquide par l'intermédiaire du cathéter dans votre bras. Ce liquide est constitué de sucre marqué avec un isotope stable non radioactif. L'infusion du sucre marqué se poursuivra durant toute la durée du test. Une heure plus tard, nous débuterons l'infusion d'insuline. L'insuline est une hormone naturelle produite par votre organisme. Son action principale consiste à diminuer le niveau sanguin de sucre. Pour éviter une diminution du sucre, nous vous procurerons une quantité de sucre dissoute dans l'eau par l'intermédiaire du cathéter. Cette solution (sucre + eau) est utilisée couramment dans les hôpitaux lorsque l'alimentation est fournie par les veines. Pour les trois heures suivantes, de petits échantillons de sang (approximativement ½ cuillerées à thé) seront prélevés à chaque 5 minutes pour mesurer votre niveau sanguin de sucre afin de pouvoir ajuster la quantité de sucre administrée. Un total de 12 cuillerées à thé sera prélevé. Pendant la durée du test, vous pourrez visionner un film de votre choix. Après le test, un repas vous sera servi.

BÉNÉFICES

Ce test nous aidera à déterminer votre prédisposition au diabète ainsi que votre capacité à utiliser le sucre.

RISQUES ET INCONVÉNIENTS

Un isotope stable comme celui utilisé dans cette technique n'est PAS RADIOACTIF et ne présente aucun danger. Les prises de sang et l'infusion de liquide requièrent l'installation d'un tube dans une veine. Quelques inconforts mineurs peuvent être anticipés pendant la pose des tubes. Des ecchymoses, de l'inflammation et le blocage de la veine (thrombose) peuvent survenir lorsque les tubes sont installés. Il existe un faible risque d'infection. Le risque le plus important associé à l'infusion d'insuline (« clamp ») est l'hypoglycémie (taux de sucre bas). Un faible taux de sucre dans le sang peut générer de l'anxiété, augmenter votre rythme cardiaque et vous faire transpirer. Les conséquences potentielles sérieuses de l'hypoglycémie sont la perte de connaissance et convulsions. Un professionnel entraîné pour faire face à ces situations supervisera le test et les mesures fréquentes de votre taux de sucre minimiseront ces risques.

EAU DOUBLEMENT MARQUÉE

La méthode de l'eau doublement marquée est une technique relativement nouvelle pour estimer le nombre total de calories dépensées sur une base journalière (votre dépense énergétique journalière), et ce pendant 10 jours. Cette technique nous permet d'examiner votre dépense énergétique avant et après le programme de perte de poids. Par conséquent, cette technique sera utilisée trois fois pendant l'étude. Nous vous

demanderons de prendre un verre d'eau « lourde », qui aura été marquée par deux substances naturelles, le deutérium (^{2}Hydrogène) et le ^{18}oxygène. Ces substances ne sont pas radioactives. En mesurant le rythme d'élimination de ces substances dans des échantillons d'urine périodiques, il nous est possible de mesurer la dépense énergétique totale.

BÉNÉFICES

Vous serez informé du nombre précis de calories que vous utilisez pour effectuer vos tâches pendant une journée déterminée.

RISQUES ET INCONVÉNIENTS

Il n'y pas de danger associé à la consommation de cette eau.

ACCÉLÉROMÈTRE « RT3 TRI-AXIAL » :

Le « RT3 Tri-axial » est un accéléromètre de la taille d'un téléavertisseur que vous porterez à votre taille pendant trois jours, sur une base mensuelle, et ce pour la période de perte de poids et les 52 semaines d'observation. Cet appareil mesure les mouvements que vous effectuer dans les trois dimensions. Il permet de déterminer la quantité d'énergie (kcal) dépensée par vos mouvements sur la durée d'utilisation de l'appareil, soit 5 jours dans le cas de cette étude.

BÉNÉFICE : les résultats du « RT3 Tri-axial » vous permet de connaître la quantité d'énergie que vous dépenser selon votre activité journalière.

RISQUES ET INCONVÉNIENTS : aucun inconvénient n'est relatif au « RT3 Tri-axial ». Bien qu'il ne soit pas lourd (70 grammes avec batterie), il peut être incommodant de le porter avec soi à tout moment pour une période donnée. Il ne peut toutefois pas causer de douleur et ne peut être utilisé dans l'eau.

INTERVENTION NUTRITIONNELLE

On vous informera comment stabiliser votre alimentation ainsi que votre poids pour une période d'un mois avant les tests en laboratoire. Durant la période de perte de poids, un programme vous sera enseigné adapté à vos habitudes alimentaires. Une nutritionniste certifiée dispensera des cours sur des habitudes alimentaires saines lors de classes (pour approximativement 1 ½ heure par séance) qui seront tenue tout au long de la période de six mois associée au programme de perte de poids. Ces cours sont facultatifs.

RISQUES ET INCONVÉNIENTS

Vous serez supervisé par le personnel médical pendant toute la durée du protocole de recherche. Les tests vous seront expliqués en détails par le personnel en place avant aspect de l'étude. Le programme de perte de poids sera supervisé par un médecin, les classes seront dispensées par une nutritionniste certifiée, et les risques associés au programme de perte de poids sont minimes. Néanmoins, une incidence accrue de calculs vésiculaires lors de perte de poids rapide est présente. Cependant, ce phénomène se retrouve surtout en présence de régimes à très faible teneur en calories (<800 kcal/jour) ce qui n'est pas le cas dans notre programme. Il y a des chances de changement d'humeur pendant la perte de poids. Des études ont démontré autant des changements positifs (impression de bien-être) que négatifs (dépression et diminution de l'estime de soi) pendant des périodes de perte de poids.

BÉNÉFICES

La participation à cette étude vous offre la possibilité de subir un examen physique, d'obtenir de l'information sur votre tension artérielle et votre niveau de cholestérol, de passer un test aérobie maximal, ainsi que de recevoir des informations nutritionnelles et médicales reliées à l'étude. Vous aurez également l'opportunité de participer à un programme de perte de poids, ainsi qu'un programme d'entraînement superviser par des médecins, nutritionniste, entraîneur et kinésiologues spécialisés dans la perte et le maintien du poids.

EXERCICE / ENTRAÎNEMENT MUSCULAIRE

Vous serez assignée aléatoirement (au hasard) à l'un des deux groupes expérimentaux; soit "restriction calorique seul" ou "restriction calorique + entraînement musculaire en force". Les participantes qui auront été sélectionnées pour participer au groupe "entraînement musculaire en force" s'entraîneront 3 jours non consécutifs par semaine dans une salle de musculation (ex: lundi, mercredi et vendredi) sous la supervision d'un spécialiste en conditionnement physique, tel que décrit antérieurement (Poehlman et al. 2000).
L'intensité de l'entraînement sera entre 70% et 80%, soit environ 10 répétitions par exercice. Chaque séance d'entraînement comprendra une période d'échauffement d'intensité légère sur bicyclette (5 minutes), suivie par une période d'étirements statiques de 10 minutes ciblant les principaux groupes musculaires qui seront mobilisés pendant la séance d'entraînement. Toutes les séances d'entraînement seront comptabilisées afin de suivre votre progression et pour réajuster la prescription d'exercice au besoin.
Les charges d'entraînement seront établies et réajustées au besoin pour que le nombre de répétitions de chacune des trois séries de chaque exercice ne dépasse pas 10. Une période de repos de 60 à 90 secondes sera accordée entre chaque série. Selon notre expérience avec ce type de programme d'exercice, nous devrions avoir un taux d'abandon d'approximativement 15% à 20% à la fin de l'étude (Poehlman et al. 2000).
Les charges seront par la suite progressivement augmentées lors des semaines 2 et 3 afin d'atteindre 70% à 80% du 1-RM (charge maximale déplacée une seule fois), et ce pour le reste de l'étude. Cette stratégie est utilisée afin de permettre une meilleure adaptation des participantes à l'entraînement et afin d'éviter les blessures pouvant être causées par un entraînement trop intensif en phase d'initiation.
BÉNÉFICES
L'entraînement en musculation permet d'augmenter la force et la masse musculaire en plus d'améliorer la capacité fonctionnelle des participants.
RISQUES ET INCONVÉNIENTS
Certaines douleurs musculaires et articulaires peuvent survenir suite à un entraînement en musculation. Cependant, ces douleurs sont passagères et les périodes de repos prévues sont suffisantes pour assurer une récupération adéquate. Des blessures musculaires et articulaires plus importantes peuvent également survenir suite à une mauvaise utilisation des équipements. Cependant, sous la supervision de personnel compétent ces risques sont considérablement réduits.

7. PERSONNES RESSOURCES

Dominique Garrel, md, cspq
Professeur titulaire
Directeur du Département de nutrition

Personne ressource pour les questions concernant l'éthique :
Dr Vincent Castellucci
Président du Comité d'éthique de la recherche
Faculté de médecine
Université de Montréal

CONFIDENTIALITÉ
Toutes les données recueillies dans cette étude seront codées par numéros d'identification qui vous seront assignés et qui seront seulement connus par les responsables du projet. Votre nom ne sera pas divulgué avec aucun résultat. Les résultats des analyses de sang ainsi que des mesures physiques (grandeur, poids, tension artérielle) obtenus dans cette étude seront partagés avec vous et transmis à votre médecin traitant suite à votre consentement écrit.

COÛTS ET COMPENSATION
Vous devrez défrayer les coûts reliés à votre transport au laboratoire et à l'institut. Le stationnement à l'institut et au laboratoire est gratuit pour tous les participants tout comme le seront tous les tests effectués. Aucune compensation financière ne sera versée au participant.

ARRÊT DU PROJET
SI DES INFORMATIONS NOUVELLES RELIÉES À CETTE ÉTUDES OU CES COMPOSANTES VENAIENT À COMPROMETTRE D'UNE FAÇON OU D'UNE AUTRE LA SÉCURITÉ ET LA SANTÉ DES PARTICIPANTS OU NE RESPECTERAIT PAS LES RÈGLES D'ÉTHIQUE, CETTE ÉTUDE SERAIT ARRÊTÉE IMMÉDIATEMENT.

LIBERTÉ DE CONSENTEMENT
JE RECONNAIS QUE MA PARTICIPATION À CE PROJET EST TOUT À FAIT VOLONTAIRE ET QUE JE SUIS LIBRE D'Y PARTICIPER. JE CERTIFIE QU'ON ME L'A EXPLIQUÉ VERBALEMENT, QU'ON A RÉPONDU À TOUTES MES QUESTIONS, QU'ON M'A REMIS DES NOTES EXPLICATIVES COMPLÉMENTAIRES ET QU'ON M'A LAISSÉ LE TEMPS VOULU POUR PRENDRE UNE DÉCISION.
ET
JE RECONNAIS ÊTRE LIBRE DE ME RETIRER EN TOUT TEMPS SANS QUE CELA NUISE AUX RELATIONS AVEC MON MÉDECIN ET LES AUTRES INTERVENANTS ET SANS PRÉJUDICE D'AUCUNE SORTE. DE PLUS, JE

COMPRENDS QUE LES DONNÉES ET LES ÉCHANTILLONS ACCUMULÉS ANTÉRIEUREMENT SERONT UTILISÉS MÊME EN CAS DE RETRAIT

PARTICIPANT	TÉMOIN
SIGNATURE	SIGNATURE

JE CERTIFIE AVOIR EXPLIQUÉ AU SIGNATAIRE LES TERMES DU PRÉSENT FORMULAIRE DE CONSENTEMENT ET LUI AVOIR CLAIREMENT INDIQUÉ QU'IL RESTE À TOUT MOMENT LIBRE DE METTRE UN TERME À SA PARTICIPATION AU PRÉSENT PROJET.

CHERCHEUR	DATE
SIGNATURE	

TOUTES LES INFORMATIONS SERONT CONSERVÉES EN LIEU SÉCURITAIRE À L'UNITÉ MÉTABOLIQUE DU DÉPARTEMENT DE NUTRITION DE L'UNIVERSITÉ DE MONTRÉAL

J'AUTORISE LA TRANSMISSION DES INFORMATIONS CONTENUES DANS MON DOSSIER À MON MÉDECIN DÉSIGNÉ

PARTICIPANT	TÉMOIN
SIGNATURE	SIGNATURE
DATE	