Centre for International Health

A comparison of overall health between Asians and Australians from European backgrounds: A West Australian study of Chronic Disease, Diet & Metabolic Syndrome Risk Factors

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Declaration

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made.

This thesis contains no material which has been accepted for the award of any other degree or diploma in any university.

Signature: 

Date: ……...…11.02.2015……..……..

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ABCA1: ATP-binding cassette transporter A1

ABS: Australian Bureau of Statistics

AGEs: Advanced Glycation End Products

AMI: Acute Myocardial Infarction

Ang II: Angiotensin II

ATP: Adenosine Tri-Phosphate

ATPIII: Adult Treatment Panel III

AusDiab: The Australian Diabetes, Obesity & Lifestyle Study

BF%: Body fat percentage

BMI: Body Mass Index

BP: Blood pressure

CM: Chylomicron

CRP: C - reactive protein

CVD: Cardiovascular Diseases

CWT: circumferential wall tension

DBP: Diastolic blood pressure

DEXA: Dual Energy X-Ray Absorptiometry

DIAC: Department of Immigration and Citizenship

EGIR: European Group for the Study of Insulin Resistance

FBG: Fasting Glucose Plasma

FFA: Free Fatty Acids

FMD: Flow-mediated dilatation

FPG: Fasting Plasma Glucose

HC: Hip Circumference

HDL: High Density Lipoprotein

HDL-C: High Density Lipoprotein Cholesterol

HOMA: Homeostatic model of assessment

hs-CRP: High Sensitive C - reactive protein

HW: Hypertriglyceridemic Waist

ICAM-1: Intercellular Adhesion Molecule-1

IDDM: Insulin Dependent Diabetes Mellitus

IDF: International Diabetes Federation

IDL: Intermediate Density Lipoproteins

IFG: Impaired Fasting Glucose

IGT: Impaired Glucose Tolerance

IL: Interleukin

IPAQ: International physical activity questionnaire

IR: Insulin Resistance

LDL: Low Density Lipoprotein

METs: Metabolic equivalent score

MetS: Metabolic Syndrome

NCD: Non-Communicable Diseases

NCEP: National Cholesterol Education Program

NEFA: Non-esterified Fatty Acids

NHANES: National Health and Nutrition Examination Survey

NHS: National Health Survey

NIDDM: Non-Insulin Dependent Diabetes Mellitus

NO: Nitric Oxide

OGTT: Oral Glucose Tolerance Test

OR: Odd Ratio

PAI-1: Plasminogen Activator Inhibitor, model 1

PAR: Population Attributable Risk

PGI2: Prostacyclin

PREDICT: a web-based computerised decision support system

RAS: Renal Artery Stenosis

RCT: Reverse Cholesterol Transport

SBP: Systolic blood pressure

SD: Standard deviation

SEM: Standard error of mean

SMC: Smooth Muscles Cells

TBF%: Truncal body fat percentage

TF/L%: total fat-to-lean percentage

TF/L: Total fat-to-lean ratio

TG: Triglycerides

TLGS: Tehran lipid and glucose study

TNF: Tumour Necrosis Factor

TPA: Total Physical Activity

TSAT: Thigh Subcutaneous Adipose Tissue

UKADS: United Kingdom Asian Diabetes Study

VAT: Visceral or abdominal adiposity

VCAM-1: Vascular cell adhesion molecule, model 1

VLD: Very Low Density Lipoproteins

WC: Waist Circumference

WHO: World Health Organization

WHR: Waist/Hip Ratio

Abstract

Metabolic syndrome is a cluster of risk factors that increases an individual's risk to diabetes and cardiovascular diseases. Given the personal, social and economic consequences and the growing impacts of these wide spread chronic diseases, sufficient and accurate knowledge around metabolic syndrome plays a key role to define effective prevention and intervention programs. Despite many studies having been undertaken globally and offering various definitions for metabolic syndrome, there is still no general consensus about accurate definitions and their diagnostic criteria, in particular among different ethnic groups. Given this gap, we undertook a cross-sectional study investigating overall health condition and metabolic syndrome risk factors amongst three ethnic groups living in Western Australia as well as the effects of ethnicity on metabolic syndrome components.

The study population consisted of adult immigrants with European, Indian and Iranian origin who had lived in Australia for at least 5 years, and had an acceptable knowledge of written and spoken English. They had also one or more criteria including: body mass index (BMI) ≥ 25, waist circumference ≥ 94 cm for males and ≥ 80 cm for females, blood pressure≥ 130/85 mmHg (or taking medication), dyslipidemia (or taking medication) and diabetes mellitus. Participants were recruited from the community through different methods. Individuals with major systematic illness such as cancer and liver or renal failure, and women who were pregnant or lactating were excluded from this study.

After a primary screening, eligible volunteers received overall information about the study via phone conversation and email. Participants were also instructed to fast overnight between 10-14 hours before attending in out-patient clinic at Curtin University for clinical assessment. The variables of interest for the current study were anthropometric measurements, fasting blood glucose, fasting insulin, lipid profile, hs-CRP; systolic and diastolic blood pressure, and endothelial markers of VCAM-1, Adiponectin and E-selectin. The participants' dietary habits and the level of physical activity were also assessed using validated questionnaires.

To examine the main objectives, data from 97 participants (49 males and 48 females) with BMI 29.95±3.8 (kg/m^2) and aged 46.2±13.7 years were analysed. These participants included 35 Europeans (Males: 11, Females: 24), 29 Indians (Males: 16, Females: 13) and 33 Iranians (Males: 22, Females, 11), living in Western Australia.

According to the results, the highest overall prevalence of metabolic syndrome was shown by IDF definition (32%, Males: 30.6%, Females: 33.3%), followed by ATP III (28.9%, Males: 26.5%, Females: 31.3%), WHO (24.7%, Males: 18.4%, Females: 31.3%)) and EGIR (21.6%, Males: 18.4%, Females: 25%). The WHO definition aligns with the metabolic syndrome defined by ATPIII and IDF. In this study, the percentage of participants assessed as having metabolic syndrome risk factors by the WHO was lower than those with metabolic syndrome based on ATP III guidelines and IDF measures (see above); however, the highest percentage of participants with insulin resistance was identified by the WHO definition (66.7%).

The results highlighted that the Indian group tended to have the highest total body fat percentage among three ethnic groups after adjustment for age and BMI (European: 36.09±0.7%, Indian: 38.5±0.7%, Iranians: 36.9±0.7%). Similarly, for a given age and WC, the Indian group had the highest estimated mean percentage of truncal fat compared to two other groups (European: 39.5±1.0 %, Indian: 42.7±1.0 %, Iranian: 39.5±0.9%). Also, the results documented that for all ethnicities, in the same BMI, men had a lower total body fat, but a higher truncal fat compared to women. The results of comparing the adjusted measurements of total and truncal fatness in men and women of three ethnic groups suggest that the reference range of BMI and WC for detecting metabolic syndrome in both Indian men and women would be lower than those in the same gender of two other groups. Also, the cut-off points of BMI and WC in European women would be lower than that in Iranians women; however higher cut-off points need to be applied for European men compared to Iranian men.

According to the raw data, European and Iranian individuals participating in this study had the highest and the lowest mean values of total and truncal fatness, serum glucose, insulin and lipids, HOMA and blood pressure, respectively. These results were compatible with hs-CRP and E-selectin data analyses, indicating that Europeans may be at higher risk of cardiovascular events based on these biomarkers.

Subsequently, the initial patterns observed for most risk factors reformed when data were adjusted for potential confounders. Namely, Indian participants had the highest degrees of total and truncal fatness and insulin resistance (indicated by HOMA), and systolic and diastolic blood pressure in new analysis. However, there was no difference between the patterns observed for hs-CRP and E-selectin before or after adjustment for these variables. It was also found that the degree of associations between different cardiovascular risk factors and the biomarkers evaluated vary between ethnic groups. This may cause bias in predicting the risk of cardiovascular events in populations having a specific risk factor dominantly.

The current study indicated that different components of metabolic syndrome including general and central obesity, insulin resistance, dyslipidaemia and hypertension as well as serum biomarkers of hs-CRP, E-selectin and adiponectin can be affected by ethnicity. These findings support the hypothesis that ethnicity plays a significant role in developing metabolic syndrome risk factors. This also suggests that biomarkers of cardiovascular diseases may have different levels of accuracy across ethnic groups. This important point should be considered when these biomarkers are used to compare the risk of cardiovascular diseases among ethnic groups. Further studies with larger sample size are required to extend these encouraging outcomes.

Chapter 1

Introduction

1.1 Introduction

Metabolic syndrome is a cluster of risk factors that increases an individual's risk to diabetes, stroke and cardiovascular diseases that are important subgroups of chronic diseases. In turn, chronic diseases are responsible for main proportion of mortality and morbidity; and its human and financial related costs over the world. So, establishing related prevention programs is vital to decrease personal, social and economic consequences of a wide range of chronic diseases such as diabetes and cardiovascular diseases. In this way, sufficient and accurate knowledge around metabolic syndrome plays a key role to define effective prevention programs (Zimmet, McCarty, and de Courten 1997; Bonow and Gheorghiade 2004; Gu et al. 2005).

Despite many studies having been undertaken globally and providing five definitions for metabolic syndrome, there is still no general consensus about accurate definition and their diagnosis criteria. The primary research defining metabolic syndrome criteria and their cut off points have been mainly conducted in Western countries, particularly in Europe. However, the implementation of these criteria in different countries showed that they may be inappropriate for other regions (Bonow and Gheorghiade 2004; Bhardwaj et al. 2011). Current studies indicate variances not only in the criteria and their diagnosis range in different nations but also on the same ethnic groups in the different countries (Bonow and Gheorghiade 2004; Bhardwaj et al. 2011). These controversies cause more complexities for health care strategists particularly in countries receiving emigrants from different countries and ethnic groups. This evidence highlights a big gap that needs addressing.

Australia is an immigrant nation with a variety of ethnic groups and cultures that come together from five continents over the world. Given the limited comprehensive studies regarding to ethnicity and metabolic syndrome in Australia, this condition

made the best opportunity for this purpose. The current study was designed to evaluate overall health condition and metabolic syndrome risk factors amongst some ethnic groups as well as the effects of ethnicity on metabolic syndrome in Australia.

Given the importance of the personal and financial consequences of metabolic syndrome risk factors, the results of the study reveal important facts in regards to metabolic syndrome and also assist scientists and health strategists to define more accurate definitions, criteria and prevention program for metabolic syndrome.

1.2 Hypotheses

Ethnicity plays a significant role in developing metabolic syndrome components including general and central obesity, hypertension, dyslipidaemia, high blood glucose and insulin resistance.

1.3 Objective

The main objective of this study was to investigate the effects of ethnicity on metabolic syndrome risk factors in overweight and obese subjects. The aim was to clarify whether ethnicity may be a major factor responsible for the overall health situation of the participant.

Specific Objectives:

1. To compare metabolic syndrome criteria among a cross-section of immigrants from three ethnic groups in Western Australia using four common international definitions of metabolic syndrome
2. To describe the effects of ethnicity on the endothelial dysfunction in the ethnic groups under study,
3. To investigate the impact of diet on metabolic syndrome among the three ethnic groups,
4. To explore the correlation between adiponectin and different components of metabolic syndrome amongst ethnic groups.

This thesis consists of six chapters. After the introduction, the second chapter presents a literature review addressing different aspects involved in the metabolic syndrome. The chapter provides information on the results of previous studies investigating the impact of ethnicity on cardiovascular diseases and metabolic syndrome components. Chapter three provides an overview of the research methods used to test the hypothesis and address the objectives. The fourth chapter presents the results of this study. The findings of the study are discussed in chapter five. And, the final chapter presents an overall summary of the research, the significance of the study, the limitations as well as the final concluding comments.

Chapter 2

Literature Review

2.1 Chronic diseases

Chronic disease is irreversible, progressive and accrual illness leading to future functional impairment or disability. It is generally specified by a prolonged course of illness with complex and unknown aetiology and various risk factors; and a long latency period (Bull et al. 2004). Almost all international health organizations and institutes linked to public health such as World Health Organization use this term to encompass disease and disorders including:

- Cardiovascular diseases like heart disease, stroke and hypertension;
- Diabetes and its complications such as kidney diseases;
- Cancers;
- Chronic lung diseases;
- Chronic musculoskeletal disease eg Arthritis; and Chronic neurological disorders (Prevention 2009).

2.1.1 Worldwide prevalence of chronic disease

Chronic diseases make up a large proportion of non-communicable diseases (NCDs) and its prevalence has now reached to epidemic proportions worldwide causing more than 36 million deaths (63% of global deaths) in 2008 (WHO 2011c) and are projected to reach 52 million in 2030 (WHO 2013). Over 50% of NCDs deaths were caused by cardiovascular disease (17 million deaths) and diabetes (1.3 million deaths). More than 25% of these deaths occurred below 60 years which were mostly preventable. Premature death from non-communicable diseases were responsible for 22% and 35% of men and women mortality in low-income countries, comparing to the 8% and 10% among men and women in high-income courtiers respectively (WHO 2011c).

2.1.2 Prevalence of chronic diseases in Australia

According to a national survey carried in 2005, among the variety of chronic diseases, 30% of respondents had cardiovascular problems including uncomplicated hypertension and ischemic heart disease and 8.3% suffered from diabetes with a type 2 dominancy (Knox et al. 2008). In 2011, 21513 Australians died of coronary heart diseases representing more than one fifth of all deaths in Australia and it still remains the most important cause of death in this country (Australian Institute of Health and Welfare 2014). Reports released by the Australian Bureau Statistics (ABS) indicate that CVD had the most contribution to the burden of disease in Australia after cancer in 2007 (Australian Bureau of Statistics 2010).

2.2 Metabolic syndrome

Insulin resistance has been suggested as the most important aetiology of diabetes mellitus and cardiovascular diseases (Reaven 1988). It is established that the health consequences of insulin resistance are more dangerous when it is accompanied with a cluster of its associated metabolic disorders including obesity, hyperglycaemia, hyperlipidaemia, hypertension and proteinuria, now known as "metabolic syndrome". In the other words, the term of metabolic syndrome, described also with other names such as insulin resistance syndrome, cardiometabolic syndrome, dysmetabolic syndrome and syndrome X (Govindarajan et al. 2005; Onat et al. 2007; Gautier et al. 2010), refers to a collection of metabolic disorders associated with insulin resistance syndrome (Grundy 2004a).

2.2.1 Current definitions and position statement for metabolic syndrome

There are four global definitions for metabolic syndrome. In all definitions except one, providers have defined a core component as well as a collection of other minor variables. The American Association of Clinical Endocrinologist has also issued a position statement which modifies other definitions according to the clinical approach (Einhorn et al. 2003).

2.2.1.1 World Health Organization (WHO) Definition

According to the first definition provided by World Health Organization in 1998, Diabetes, impaired glucose tolerance or insulin resistance are mentioned as one of the fixed components marking metabolic syndrome for individuals (Table 1). Also, adiposity index with waist hip ratio >0.9 for male and 0.85 for female or obesity with Body Mass Index (BMI) more than 30 kg/m^2 has been defined as one of the variable criteria. Additionally, the measurement for dyslipidaemia, as the second variable criterion, followed by triglycerides (TG) ≥1.69 mmol/L and /or high-density lipoprotein cholesterol (HDL-C) <0.90 mmol/L for men and <1.01 mmol/L for women.

Hypertension, like diabetes, is both a disease and risk factor and is measured by Systolic Blood Pressure (SBP) ≥140 mmHg and Diastolic Blood Pressure (DBP) ≥90 mmHg indicating another criterion for metabolic syndrome. Excretion of albumin in urine (microalbuminuria) by ≥2.5mg/mmol creatinine for men and ≥3.5mg/mmol creatinine for women is the last variable component mentioned in WHO's definition. To be labelled metabolic syndrome, one of the fixed components and at least two variable criteria should be linked together (World Health Organization 1999).

Table 1: The clinical criteria for metabolic syndrome defined by WHO

Insulin resistance identified by one of the following

- Type 2 diabetes
- Impaired fasting glucose (IFG)
- Impaired glucose tolerance (IGT)

Or for those with normal fasting glucose levels (110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemia, euglycemic conditions

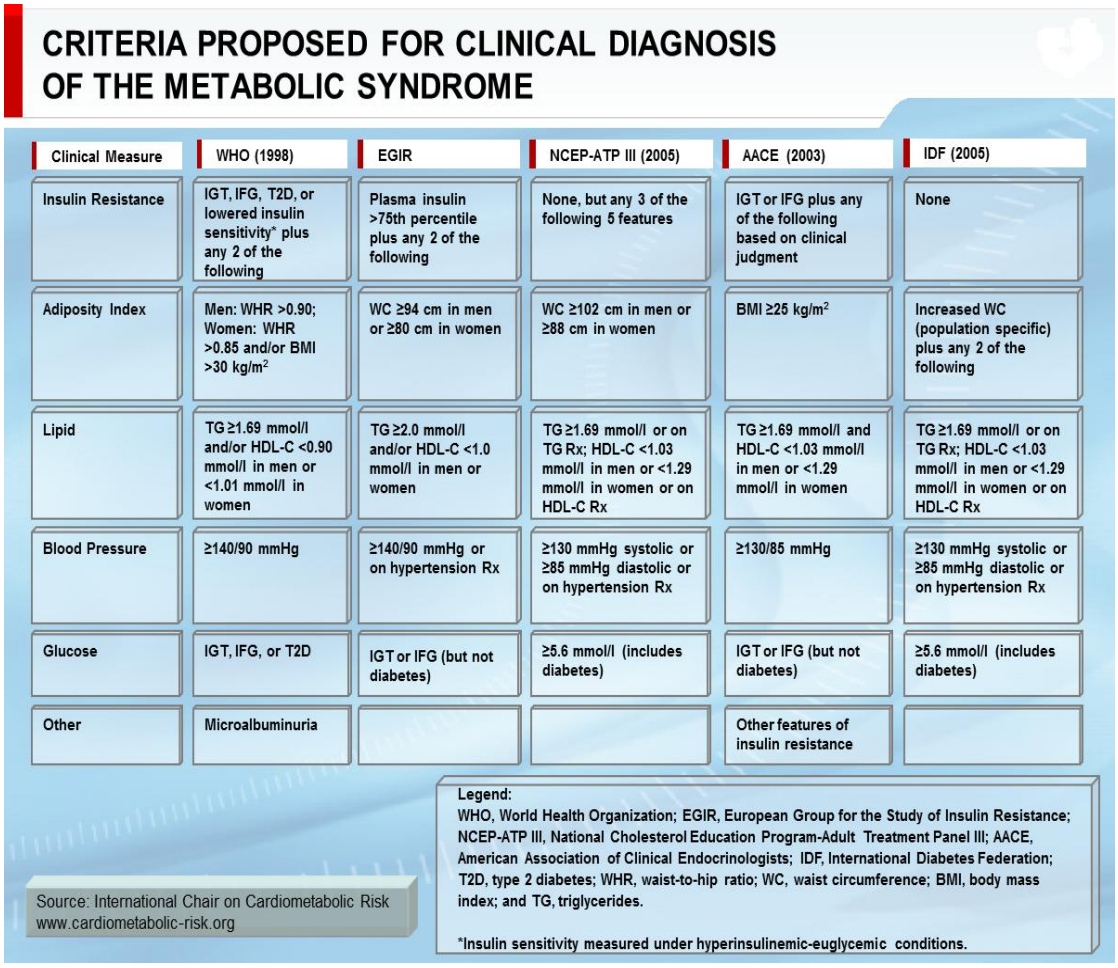
Plus any two of the following factors:

- BMI > 30kg/m2 and/or Waist: Hip ratio > 0.9 in males & >0.85 in females
- Antihypertensive medication and/or high blood pressure (≥140 mmHg systolic or ≥ 90mmHg diastolic)
- Triglycerides ≥ 150mg/dL
- HDL cholesterol < 35 mg/dL in males & < 39 mg/dL in females
- Urinary albumin excretion rate ≥ 20 µg/min or albumin: creatinine ratio ≥ 30mg/g

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

At the same time, the EGIR suggested a new definition of metabolic syndrome that cases need two or more criteria including central obesity, dyslipidaemia, hypertension and blood pressure as well as insulin resistance or hyperinsulinemia in only non-diabetic subjects. Central obesity has been determined by waist circumference ≥94cm for male and ≥80cm for female in current classification. Also dyslipidaemia is considered by TG>2mmlo/L or HDL-C<1mmol/L, and like WHO's definition, hypertension is defined by BP ≥140/90mmHg. Since, insulin resistance plays a key role in this definition; fasting blood glucose ≥ 6.1mmol/L is counted as another minor criterion. The same as WHO's definition, a combination of at least two changeable components is necessary for diagnosis of metabolic syndrome (Balkau et al. 2002).

Table 2: Definitions and statement for Metabolic Syndrome



2.2.1.3 National Cholesterol Education Program-Adult Treatment Panel III (ATP III) Definition

Scientists found that LDL plays a significant role in Coronary Heart Disease (CHD) compared to other components (Hulthe and Fagerberg 2002). Also, other clinical findings reveal significant co-relation between treatment of high levels of LDL and reducing CHD incidence (Austin et al. 1988). So, they modified the criteria for metabolic syndrome and have announced a third world-wide definition for it by reducing the diagnostic threshold of the WHO definition for certain criteria like HDL-C and hypertension. According to the new definition, central obesity has been defined by waist circumference >102 cm for male and >88cm for females.

Although, hyperinsulinemia and insulin resistance have been removed for the new classification, comparisons of both to previous definitions; and fasting plasma glucose level remained the same. With the strict strategy in reducing the diagnostic threshold of the WHO definition, triglyceride level ≥ 1.7 mmol/L for both gender; and low HDL-C <1.03 mmol/L and <1.29 mmol/L for male and female respectively have been agreed for dyslipidaemia criteria. In addition, metabolic syndrome is marked when three or more of five components that exist together in cases (Expert Panel on Detection and Treatment of High Blood Cholesterol in 2001).The following are the details of criteria suggested for clinical diagnosis of metabolic syndrome [Table 2].

2.2.1.4 American Association of Clinical Endocrinologist (AACE) Definition

Clinicians as first contact line to individuals and patients have been faced with unclear points and questions around diagnosis and treatment (Alberti, Zimmet, and Shaw 2006). Their most important questions are categorized in below:

- Is there any proof for treatment of the insulin resistance beyond treating individual components, e.g. dyslipidaemia and high blood pressure?
- Should the cut point for treatment of individual component be lesser while they are known as insulin resistance cases?
- Would treatment approaches for individual components be different when insulin resistance is present?

Therefore, the AACE to ensure consistency among endocrinologists, proposed solutions offering a means of understanding insulin resistance and feasible clinical attitude to recognize and deal with persons at risk by reviewing experts' experience and opinion. AACE eventually submitted definite differences to diagnose individuals with insulin resistance. Also, in parallel, they accepted the blood pressure and lipid criteria according to the ATP III guidelines. These summarized differences are as follows:

1. The Insulin Resistance Syndrome refers to a collection of metabolic disorders occurring mainly in individuals with hyperinsulinemia or insulin resistance.
2. Insulin resistance syndrome is different to diabetes.
3. While, BMI and WC are accepted as indices of obesity, they must be defined specifically in different ethnic groups.
4. Ethnicity is known as an important risk factor for insulin resistance and some non-Caucasian ancestries (e.g., Latino/ Hispanic American, African American, Native American, Asian American, Pacific Islander) are at higher risk of the Insulin Resistance Syndrome.
5. Other factors including hypertension, family history of diabetes type 2, CVD and a history of CVD, gestational diabetes, polycystic ovarian syndrome and acanthosis nigricans have been accepted that enhance the risk of developing the insulin resistance syndrome.
6. Individuals with diabetes type 2 usually are diagnosed by fasting blood glucose concentration; however the glucose level in plasma two hours after 75 gram oral glucose load is recognized as a more reliable test of risk for insulin resistance syndrome.

Given the mentioned process, unlike the three early definitions, the AACE intentionally provided a position statement instead of specific new definition for metabolic syndrome in order to rely on clinical judgment for diagnosis and treatment (Einhorn et al. 2003).

2.2.1.5 International Diabetes Federation (IDF) Definition

Experts in International Diabetes Federation (IDF) produced a new definition based on the essence of the ATP III definition. They defined waist circumference as an

index for adiposity according to ethnicity, instead of a general measurement for all populations [Table 3]; and changed fasting glucose by ≥5.6 mmol/L. Other criteria like abnormal high blood pressure and triglycerides have remained the same at ≥ 130/85 mmHg and ≥ 1.7 mmol/L, respectively. Also, high-density lipoprotein cholesterol (HDL-C) was determined by <1.03 mmol/L for men and < 1.29 mmol/L for women (Alberti, Zimmet, and Shaw 2006).

Table 3: Waist Circumference values according to Ethnicity/Country using in IDF definition for metabolic Syndrome

Ethnic / Country	Gender	Waist circumference
European	Male	≥94cm
	Female	≥80cm
South Asian	Male	≥90cm
	Female	≥80cm
Chinese	Male	≥90cm
	Female	≥80cm
Japanese	Male	≥85cm
	Female	≥90cm
South & Central Americans		Using South Asian data till specific data
Sub-Saharan Africans		Using European data till specific data
Middle East & East Mediterranean		Using European data till specific data

2.2.2 Prevalence of metabolic syndrome

2.2.2.1 Worldwide prevalence of metabolic syndrome

A large number of studies carried out across the five continents, tried to define prevalence of metabolic syndrome particularly during last decade. Some of them have been done by Cameron et al. (2007) in Australia, Balasubramanyam et al. (2008), Ford et al. (2002), Lin et al. (2007) and Karve et al. (2010) in United States, Hu et al. (2004) in Finland, Okafor (2012) in Africa and Gupta et al. (2004) in India.

The majority of early studies applied National Cholesterol Education Program (NCEP ATPIII) definition, mentioned in section 2.2.1.3, however later research focused mainly on IDF definition or a comparison to other current criteria. The prevalence of metabolic syndrome is high worldwide (International Diabetes Federation 2006); however its rates vary, because of different definitions and criteria being administrated (Cameron et al. 2007). In-addition, a rising trend in prevalence of metabolic syndrome is reported by several studies (James et al. 2004; Beltran-Sanchez et al. 2013). Likewise, studies indicate a parallel increase in prevalence of obesity confirming strong correlation between metabolic syndrome and obesity as its important driver(Alberti, Zimmet, and Shaw 2006).

In other words, while direct estimation for prevalence of metabolic syndrome is limited due to the necessary significant clinical work, obesity may, as a simpler criterion, be used as a reliable estimation for metabolic syndrome prevalence (Park et al. 2003; Daniels et al. 2005; Grundy et al. 2005; Bray and Bellanger 2006; Hossain, Kawar, and El Nahas 2007; Grundy 2008). According to a study undertaken in the US, one fourth of the population in the United States met the criteria for metabolic syndrome diagnosis. Also, the results show the prevalence of metabolic syndrome has been increased from 27.9% to 34.1% between 1994 and 2006 (Mozumdar and Liguori 2011). This trend has been confirmed with similar results presented by other studies carried out in other countries (Ford, Giles, and Mokdad 2004; Esteghamati et al. 2010)

2.2.2.2 Prevalence of metabolic syndrome in Australia

One of the first population based studies to determine the prevalence of metabolic syndrome in Australia revealed the prevalence of metabolic syndrome using IDF

definition was 30.7% (27.1-34.3). This rate was 21.7% (19.0-24.3), 22.1% (18.8-25.4), and 13.4% (11.8-14.9) when the data was adjusted to the WHO, ATPIII and EGIR criteria for metabolic syndrome, respectively (Cameron et al. 2007). Although, the prevalence rates are different due to specification of current definitions, the results indicate significant rise in the prevalence of metabolic syndrome in Australia as a more important point.

Based on IDF criteria, 30% of Australians aged 25 and over are known as metabolic syndrome cases (Cameron et al. 2007). Moreover, in the all definitions, the prevalence of metabolic syndrome increased with rising age in both genders, however it was clearly higher among men than women in the oldest age category. Namely, the prevalence of metabolic syndrome according to the WHO, ATPIII, EGIR and IDF among males and females were 25.4% versus 18.2%, 24.4% versus 19.9%, 15.6% versus 11.3% and 34.4% versus 27.2% (P<0.001) respectively. In addition, the study documented that participants had been diagnosed as Insulin resistant cases by 50.9%, 56.1%, 69.7% and 91.1% on the basis of IDF, ATPIII, WHO and EGIR definitions (Cameron et al. 2007).

2.2.3 Components of metabolic syndrome

2.2.3.1 Insulin resistance or hyperinsulinemia

According to definitions and guidelines for metabolic syndrome, insulin resistance is a condition in which insulin is produced more than normal, but it does not work properly in the body. Several studies indicate that insulin resistance develops into type 2 diabetes in individuals who have been involved with it for more than 10 years (Lillioja et al. 1988; Warram et al. 1990; Shulman 2000). Moreover, according to consistent findings it has been known as the best indicator to predict whether or not a person will become a diabetic in the future (DeFronzo 1988; Haffner et al. 1990; Bonora et al. 2004; Kumashiro et al. 2011).

2.2.3.1.1 Prevalence of insulin resistance

Despite useful research around insulin resistance, lack of comprehensive statistical data, probably due to diagnosis of insulin resistance which usually is secondary to other disorders like hypertension and hyperglycaemia, still remains (Bonora et al. 1998). According to several worldwide studies, presenting a powerful correlation

between insulin resistance and the numerous components of metabolic syndrome, prevalence of insulin resistance reportedly, ranges from 3-16% for white populations, while Japanese ethnicity received a rate of less 2% in comparison to the whites (Olatunbosun and Schade 2002).

2.2.3.1.2 Pathophysiology of insulin resistance

Insulin, as the fundamental anabolic hormone, is produced by the β cells in pancreas and plays an important role in growth, tissue developments as well as promotes glucose uptake into cells. Insulin is secreted when plasma glucose rises after a meal and maintains glucose homeostasis in numerous tissues (Shulman 2000; Sesti 2006). The severity of responses to insulin stimulation for glucose uptake along with the applied compensation methods for hyperglycaemia by individuals are two important factors playing a key role in insulin resistance's regulations and developing associated diseases in future.

Several studies suggest defects in pancreatic β cells results in inadequate compensatory secretion of insulin to combat the decreased tissue sensitivity, and thus leading to development of non-insulin dependent diabetes mellitus (NIDDM) among insulin–resistance subjects. However, evidences indicate that the combination of insulin resistance and hyperinsulinemia compensatory makes a vicious cycle which eventually predisposes conditions to develop some diseases and disorders like hypertension, several amounts of increase in glucose tolerance as well as increasing in triglycerides, a decrease in high density lipoprotein cholesterol (HDL-C), smaller denser low-density lipoprotein (LDL-C), and higher concentration of plasminogen activator inhibitor 1 (PAI-1) (Reaven 2011). Other than pancreatic β cells, there are also three major sites involved in maintenance of glucose homeostasis including muscles, adipose tissue and liver.

A. Pathophysiology of insulin resistance in muscles

Skeletal muscle is the major site of glucose disposal. After glucose is entered into the cells, it is transformed to glucose-6-phosphate by hexokinase II. Subsequently, about 20-25% of all glucose-6-phosphate is directed to the glycolysis pathway, while the remaining 75-80 % is converted to glycogen. The process of glycogen synthesis

which is regulated by the enzyme glycogen synthase occurs mainly in the skeletal muscles (DeFronzo and Tripathy 2009). In the pathogenesis of type 2 diabetes mellitus, impaired glycogen synthesis in muscle has been demonstrated as the main and initial detected defect accounting for insulin resistance (DeFronzo 2004). It is known that insulin plays key roles not only in the glucose transport system but also in different enzymatic steps involved in glucose disposal mechanisms. As a result, any defect in systems contributing to the entrance of glucose into the muscle cells, its phosphorylation, or glycogen synthesis may have a role in developing insulin resistance and the subsequent hyperglycaemia.

Although, exclusive mechanisms underlying these alternations have not been completely elucidated yet, evidence indicates that increased levels of plasma fatty acids has a key role in this regard (Roden 2004). Several specific mechnisms have been proposed to be involved in fatty acids-induced muscle insulin resistance, such as Randle cycle, inhibition of insulin signalling pathway, alternation in gene expression, increase in ROS, inflammation and mitochondrial dysfunction (Martins et al. 2012). Investigators employing nuclear magnetic resonance (NMR) spectroscopy technique suggested that saturated fatty acids may induce skeletal muscle insulin resistance through inhibiting glucose transportation or hexokinase II activity (Figure 1) (Kovacs and Stumvoll 2005; Sesti 2006).

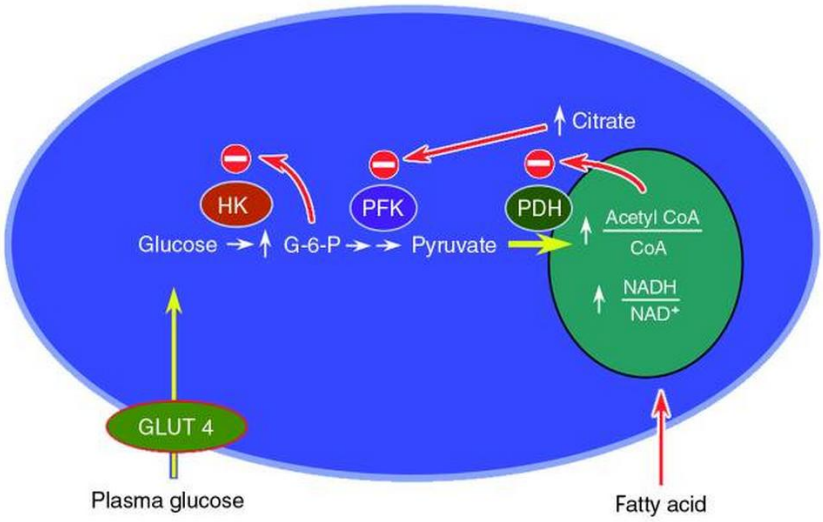


Figure 1: Mechanism of fatty acid–induced insulin resistance in skeletal muscle (Shulman 2000)

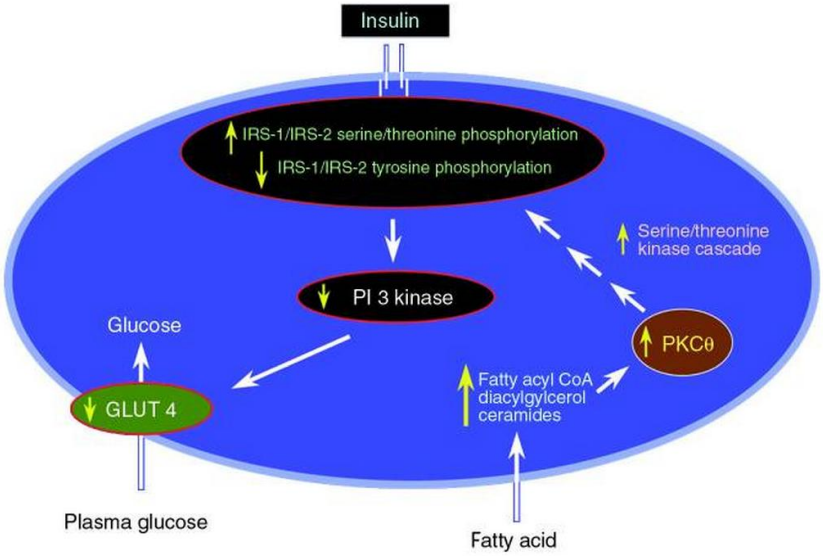


Figure 2: Proposed alternative mechanism for fatty acid–induced insulin resistance in human skeletal muscle (Shulman 2000)

Figure 2 shows another proposed mechanism for fatty acid-induced insulin resistance. In this process, intracellular fatty acid metabolites such as diacylglycerol, fatty acyl CoA and ceramides are increased due to increasing delivery of fatty acids to the muscles or a decreasing in intracellular fatty acid metabolism. Then, metabolites activate a cascade of seine/threonine kinase on insulin receptors 1 and 2 (IRS1 and IRS 2) which eventually reduces the capability of the insulin receptor substrates to active PI 3-kinase. Subsequently, it reduces glucose transport activity and inhibits insulin signalling (Shulman 2000; Sesti 2006; Martins et al. 2012).

Primarily, scientists suggested the failure in insulin-stimulating is limited to NIDDM cases, however later studies presented this defect involves both diabetics and normal individuals (Sesti 2006; Kumashiro et al. 2011).

B. Pathophysiology of insulin resistance in adipose tissue

As discussed above, increased levels of plasma FFA impairs action of insulin in the main insulin-target tissues. Given that adipose tissue is the primary source of plasma FFA, it has been considered as a major mediator of insulin resistance (Ruan and

Lodish 2003). Insulin is the main hormone in the body regulating systemic energy homeostasis by enhancing overall energy storage and suppressing energy mobilisation. Insulin plays its role in adipose tissue, through increasing glucose uptake, glycogen synthesis, fatty acid synthesis and de novo triglyceride synthesis, but reducing the release of FFA, in part by suppressing hormone- sensitive lipase activity (Belfrage et al. 1985; Chen et al. 1987; Stralfors and Honnor 1989; Ruan and Lodish 2003). In addition, insulin promotes lipoprotein lipase activity in adipose tissue, resulting in increasing the clearance of triglyceride-rich lipoproteins from plasma (Sadur and Eckel 1982). Accordingly, in the presence of adipose tissue insulin resistance, other tissues become exposed to increased levels of glucose and FFA.

Adipose tissue has been shown to secret a variety of factors, such as tumour necrosis factor-α (TNF- α), leptin, IL-6, adipocyte complement related protein of 30kDa (Acrp 30, adiponectin) and resistance contributing to the pathogenesis of obesity-associated insulin resistance. These adipose tissues-derived factors have been indicated to induce systemic insulin resistance in part by stimulating lipolysis in adipocytes resulting in increased FFA release (Ruan and Lodish 2003).

Independent of overall adiposity, abdominal or visceral adipose tissue (VAT) has a significant role to develop insulin resistance (Kelley et al. 2000b). Whereas, the thigh subcutaneous adipose tissue (TSAT) plays a different role compare to visceral adipose tissue as it has protective and more favourable inflammation profile in metabolic syndrome (Koster et al. 2010; Amati et al. 2012). As it shown in Figure 3, the subjects with high VAT have a negative correlation with insulin sensitivity compare to others with low amount of VAT (Koster et al. 2010).

Also, several experimental confirmed that the visceral adiposity is significant correlated with higher cytokines and inflammatory markers like IL-6, CRP and PAI-1 leads to a unhealthy metabolic condition in obese individuals (Karelis et al. 2005; Kintscher et al. 2008; Koster et al. 2010; Amati et al. 2012). In addition, infiltration of pro-inflammatory T-lymphocytes in visceral adiposity tissues after 5 days high fat diet highlighted that it may contributes in local inflammatory cell activation and subsequently develop insulin resistance (Kintscher et al. 2008).

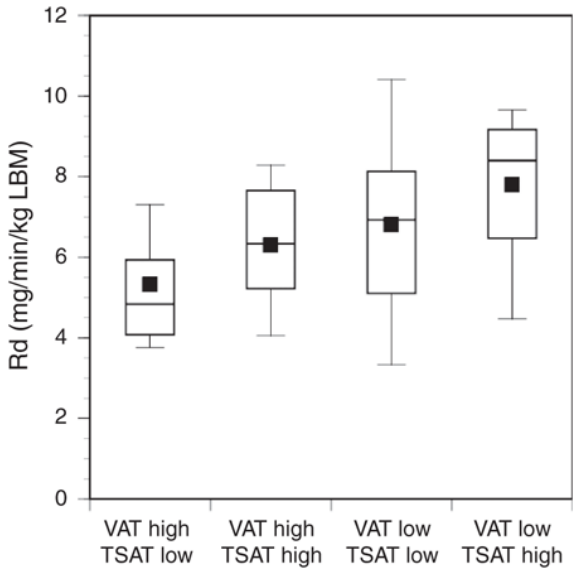


Figure 3: Insulin sensitivity (Rd) distribution by phenotype group**.** Box plots and means (Black Square). LBM, Lean Body Mass; Rd, Glucose Disposal; TSAT, Thigh Subcutaneous Adipose Tissue and VAT, Visceral Adipose Tissue (Koster et al. 2010)

C. Pathophysiology of insulin resistance in liver

Despite extensive evidence indicating the liver as a major organ involved in systemic insulin- resistance, underling mechanisms are less clear. As mentioned in previous section, insulin plays an essential role in regulating systemic energy homeostasis through promoting overall energy storage and reducing energy mobilisation. Insulin fulfils its role in the liver by inhibition of gluconeogenesis and glycogenolysis, as well as by stimulating glycogen synthesis, resulting in an overall decrease in hepatic glucose production (Ruan and Lodish 2003; Rui 2014). Accordingly, hyperglycaemia as the major consequence of insulin resistance can occurs mainly due to the failure of insulin to reduce hepatic glucose production.

According to several studies, FFAs have been also implicated as a significant contributing cause of hepatic insulin resistance. At early stage, Williamson and et al in 1966 presented promotion of gluconeogenesis due to increasing FFAs concentration in rat liver (Williamson, Kreisberg, and Felts 1966). It has been then shown that excess plasma FFA enhances substrate availability for hepatic triglyceride synthesis and gluconeogenesis, resulting in increased triglyceride-rich lipoproteins, such as VLDL, and hepatic glucose production (Staehr et al. 2003; Nagle, Klett, and Coleman 2009; Rui 2014).

2.2.3.2 Diabetes Mellitus

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by prolonged hyperglycaemia secondary to insulin resistance or failure in insulin secretion or both of the conditions. Diagnosis of diabetes usually is accompanied with high blood glucose concentration with or without symptoms experienced by individuals who have advanced diabetes like excessive thirst, polyuria, hunger, lethargy and weight loss (in type 1), particularly in early stages. However, the pathological and functional damages to various organs mostly are happened in the silent progress period of diabetes mellitus before its clinical diagnosis (Alberti and Zimmet 1998b; WHO 1999).

2.2.3.2.1 Prevalence of diabetes mellitus

Prevalence of diabetes is rising dramatically over the world. The early estimations projected that the prevalence of diabetes will increase from 4% to 5.4% between 1995 and 2025. This involves eventually 300 million people compare to 135 million at the start point of this period. The higher increase in the number of people with diabetes is predicted to be in developing countries by 170% (from 84 to 228 million), compare to a 42% increase (from 51 to 72 million) occurring in developed countries (King, Aubert, and Herman 1998).

The number of diabetic cases increased from 153 million in 1980 to 347 million in 2008 over the world (Danaei et al. 2011). In addition, WHO has estimated diabetes will be the 7th leading cause of death in 2030 (WHO 2011a). On the other hand, recent analysis considered 133 studies from 91 countries and revealed the increasing speed of prevalence of diabetes is much faster than early estimations. According to the analysis, the world prevalence of diabetes and the number of affected people aged more than 20 will increase from 6.4% by 285 million in 2010, to 7.7% and 439 million in 2030 respectively (Shaw, Sicree, and Zimmet 2010).

Australian Diabetes, Obesity and Lifestyle Study (AusDiab) as a population-based survey has been conducted on a national sample population of 11247 Australian adults including a range of normal, overweight and obese participants between 1999 and 2000. According to the AusDiab carried out by blood taking, the prevalence of diabetes has been estimated at 7.4% among adults aged more than 25 (Dunstan et al.

2001). Moreover, there was an accelerated trend in prevalence of diabetes between 1995 and 2008, with Australians self-reporting in a National Health Survey (NHS), which was conducted by the Australian Bureau Statistics (ABS) in 2006. Data indicate that the number of population diagnosed as diabetic, using clinical methods, significantly increased from 2.4% to 4.0% during 12 years(ABS 2006; Australian Institute of Health and Welfare 2011).

2.2.3.2.2 Pathophysiology of diabetes mellitus

Diabetes is classified into two major categories. The early classification divided diabetes to Insulin Dependent Diabetes Mellitus (IDDM) and Non-Insulin Dependent Diabetes Mellitus (NIDDM). However, latest grouping replaced this style to Type 1 and Type 2, which were closer to IDDM and NIDDM respectively, since the primary nomination was confusing and diabetes needs to be treated by external insulin in different stages(World Health Organization 1980, 1985).

A. Type 1

The term Type 1 diabetes mellitus is used to describe hyperglycaemia at diagnostic level which results from destruction of pancreatic islet beta-cell. In this type of diabetes, beta-cell destruction may be due to an autoimmune mediated process, identified by presence of anti-glutamic acid decarboxylase, islet cell or insulin antibodies, or an unknown aetiology. It does not include other forms of β cell destruction or failure arising from unknown specific causes, such as mitochondrial defects and cystic fibrosis. Type 1 diabetes, named juvenile-onset diabetes in primary classification, may present at any age, from childhood to the latest decades of life; however the peak of incidence is during childhood and adolescence (Molbak et al. 1994). Some individuals with type 1 diabetes are metabolically normal before presenting with a disease. However, as a result of the β cell destruction process, they eventually become dependent on insulin for survival and prevention of hyperglycaemia and its consequences like ketoacidosis, with a relatively different rate and level of destruction of the β cells in the pancreas.

This rate represents the rapid or slow progress and a range of narrow to extensive destruction signifies the level of damage of β cells. The rapidly progressive form

mainly occurs in children and adolescence with autoimmune diabetes mellitus (World Health Organization 1999). In these patients, ketoacidosis may the first sign of disease, however in others, particularly adults; remaining normal β cells are usually adequate to prevent ketoacidosis for many years (Zimmet 1995). Although, diabetic patients categorised in type 1 are not usually obese, obesity may be presented in this type as well.

B. Type 2

Type 2 is a multifactorial and multi-organ disorder characterised mainly by insulin resistance in the liver and peripheral tissues, β cell dysfunction; and accompanied with elevated concentration of free fatty acids and inflammatory mediators (Zinman 2011). It also is the most prevalent form of diabetes mellitus. In addition, the β cell dysfunction eventually also results in a relative lack of insulin. Patients in this category do not usually need to be treated by insulin, at least not in the initial phase; rather it is linked to defective insulin action or insulin resistance (Alberti and Zimmet 1998b). Accordingly, in some type 2 diabetic patients may have a normal or even elevated insulin circulatory level.

In contrast to type 1, type 2 diabetes mellitus has a more insidious onset, and the metabolic changes, (including hyperglycaemia) may not be sufficiently exaggerated level to cause the more obvious symptom and signs. Also, they usually do not experienced ketoacidosis other than under severe hyperglycaemia, or under the exacerbating influence of acute infection, trauma or similar stressful situation (Banerji et al. 1994; Umpierrez et al. 1995; Smiley, Chandra, and Umpierrez 2011). As a result, patients with type 2 diabetes may develop chronic consequences of hyperglycaemia silently for many years before identification (Harris 1993; Mooy et al. 1995). This type of diabetes is mainly linked to overweight and obesity, in particular central obesity. It has been suggested that central fat deposition is an important contributing or aggravating factor for insulin resistance (Kissebah et al. 1982; Bogardus et al. 1985; Campbell and Carlson 1993; Yang et al. 2010).

C. Gestational diabetes

Gestational diabetes is defined as severity of glucose intolerance first arising or diagnosed during (American Diabetes Association 2006). Women with diabetes mellitus onset before pregnancy are not categorised in this classification. Diabetic patients in this group should continue their treatment during pregnancy like before. Although, the worldwide prevalence of gestational diabetes is unclear, emerging evidence suggest an increased frequency affecting 1% to 14% of all pregnancies in United States depending on the particular population in question (Jovanovic and Pettitt 2001). A standard diagnostic tool, Oral Glucose Tolerance Test (OGTT) is used for diagnosis of gestational diabetes performed typically between weeks of 24 and 28 of pregnancy. However, they are advised to have additional follow-up by undertaking an OGTT six weeks after deliver (Alberti and Zimmet 1998b; Madarász et al. 2009).

D. Other specific types

Other specific types of diabetes mellitus mainly refer to some genetics and metabolic disorder with variety of aetiology. These diseases and disorders are classified in below briefly.

- Genetic defects of β cell function
- Genetic failure in insulin action
- Chemical induced diabetes due to cross-hormonal influence with some agents such as glucocorticoids
- Diabetes due to some infections such as mumps and congenital rubella
- Defects due to some endocrinopathies such as Pheochromocytoma and Cushing syndrome
- Diseases due to exocrine pancreas including infection and pancreatic carcinoma (Pak et al. 1988; Taylor 1992; Fabris et al. 1992; Assan et al. 1995; Byrne et al. 1996; Clement et al. 1996; Esposti, Ngo, and Myers 1996).

Although, all types of diabetes mellitus are considerable by themselves, this thesis is focusing on type 2 diabetes mellitus because of its prevalence and effect on metabolic syndrome.

2.2.3.2.3 Diagnosis of diabetes mellitus

Diagnosis of diabetes mellitus is commonly based on three different laboratory approaches; importantly and as indicated previously some individuals may have not any symptoms and signs during physical examination. These methods include fasting blood glucose, random blood glucose and oral glucose tolerance test (OGTT) to determine the extent of hyperglycaemia which mainly categorised to the milder forms of impaired fasting tolerance (IFG) or impaired glucose tolerance (IGT) and diabetes mellitus (Seino et al. 2010). Moreover, to measure blood glucose concentration, samples may be taken from venous plasma, venous whole blood or capillary whole blood. However, the extent of hyperglycaemia is defined by different level of glucose concentration in each laboratory method [Table 4].

Since, accurate and early diagnosis play a vital role in preventing life-long consequences of diabetes mellitus, it is very important to prevent mismeasurement and misdiagnosis which may happen in some provisional hyperglycaemias due to surgery, trauma, infection and other similar stressful condition. In this way, fasting plasma glucose (FPG) and 2-h OGTT are known as the more reliable diagnosis test compare to others and suggested for this purpose by WHO and IDF (World Health Organization 2006).

Table 4: Values for diagnosis of diabetes mellitus and other specific classification of hyperglycaemia (Alberti and Zimmet 1998b)

	Glucose concentration, mmol/l (mg/dl)		
	Whole blood		Plasma
	Venous	Capillary	Venous
Diabetes Mellitus:			
Fasting	≥6.1 (≥110)	≥6.1 (≥110)	≥7.0 (≥126)
or			
2-h post glucose load	≥10.0 (≥180)	≥11.1 (≥200)	≥11.1 (≥200)
or both			
Impaired Glucose Tolerance (IGT):			
Fasting (if measured)	<6.1 (<110)	<6.1 (<110)	<7.0 (<126)
and			
2-h post glucose load	≥6.7 (≥120) and <10.0 (<180)	≥7.8 (≥140) and <11.1 (<200)	≥7.8 (≥140) and <11.1 (<200)
Impaired Fasting Glycaemia(IFG):			
Fasting	≥5.6 (≥100) and <6.1 (<110)	≥5.6 (≥100) and <6.1 (<110)	≥6.1 (≥110) and <7.0 (<126)
and (if measured)			
2-h post glucose load	<6.7 (<120)	<7.8 (<140)	<7.8 (<140)

The Australian diabetes society recommended venous plasma glucose as standard laboratory method to determine hyperglycaemic conditions. In addition, consensus findings insist samples should be analysed by accredited laboratories and the glucose meter is unreliable for conclusive diagnosis, since generally its imprecision remains high.(Poirier et al. 1998; National Health and Medical Research Council 2001; Diabetes Australia Western Australia 2005).

Standard glucose concentration for the diagnosis of diabetes mellitus is based on values mentioned in Table 4; however the diagnosis process is different according to magnitude of glucose concentration in different individuals. So that, single fasting plasma glucose value of 7mmol/l and above or a 2-h post-challenging value of 11.1mmol/l and greater is sufficient to diagnosis diabetes in symptomatic individuals. However, asymptomatic patients' need to at least two higher than normal results performed in different days to be marked as diabetic case (Alberti and

Zimmet 1998a; Reaven 2004; Diabetes Australia Western Australia 2005; World Health Organization 2006). Additionally, people with unverified hyperglycaemia are advised to repeat related tests periodically (Diabetes Australia Western Australia 2005).

The International Diabetes Federation (IDF) has established a clear protocol, consistent with the WHO framework (International Diabetes Federation 1999). Subsequently, a practical diagnostic algorithm has been produced by Lamb and Day based on that guideline (Figure 4) (Lamb and Day 2000).

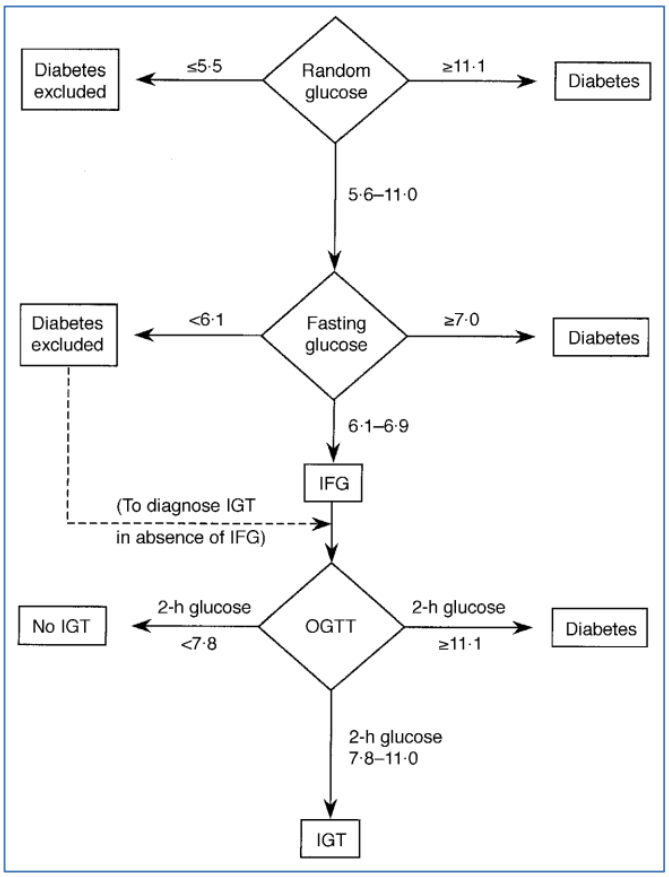


Figure 4: Diagnostic algorithm for diabetes mellitus (Lamb and Day 2000)

2.2.3.3 Impaired glucose regulation

Impaired glucose regulation is referred to an intermediate stage of abnormal glucose metabolism resulting in blood glucose levels, between that for the normal range and diabetes (Alberti and Zimmet 1998a). This glucose metabolism disorder may be represented in the fasting state or in the post-prandial condition.

Impaired glucose tolerance (IGT) is distinguished form impaired fasting glucose (IFG) by post glucose load. Prevalence of IGT is in wide-ranging between <3% and 20% among populations over the world. Early studies used raw WHO data for more than 150,000 persons from 75 countries and classified it in low (<3%), moderate (3-10%) and high (11-20%) prevalence group which was observed in many population globally. However, recent estimation pronounced an average worldwide prevalence of 6.4% and predicted to arise to 7.1% by 2030 (King and Rewers 1993; International Diabetes Federation 2011). The AusDiab study revealed 16.4% of adult Australian aged 25 and over had impaired glucose regulation. This rate includes prevalence of IGT and IFG by 10.6% and 5.8% respectively, and varies by gender, being 9.2% and 11.2% for male and female respectively (Dunstan et al. 2001).

The OGTT is based upon measurement the glucose concentration after 2-h loading of 75g oral glucose. Subjects with glucose concentration more than normal (7.8mmol/L), but lower the diabetic range (11.1mmol/L) are classified as IGT(Alberti and Zimmet 1998a). However, IDF recommended the mean of two OGTT is necessary to makes reliable criterion to diagnosis of IGT, since values of glucose circulatory may be different day to day (Dunstan et al. 2001). In addition, diagnosed IGT cases are at greater risk than metabolic syndrome individuals without increased fasting glucose. Because many with IGT are undiagnosed, they are not taking part in prevention programs such as lifestyle modification or pharmacological intervention (Karve and Hayward 2010). Although, many people with diagnosed diabetes do develop cardiovascular, on a population level, IGT may play a stronger role because of its higher prevalence and long silent period before diagnosis (DECODE Study Group 1999). The risk factors for IGT are similar to diabetes and rises due to age, stressful condition, overweight and obesity, family history of hypertension, dyslipidaemia and diabetes; and physical inactivity (Banerji et al. 1994; Lim et al. 2000).

2.2.3.4 Obesity

Obesity is one of the most important and critical factors that play a key role in metabolic syndrome. The significant role of obesity mainly refers to its powerful effect in predisposing to hyperglycaemia, diabetes and cardiovascular diseases (CVD) as well as wide range of their complications, morbidities and mortality, as discussed below (Kip et al. 2004). The rapid increase in prevalence worldwide results in significant population burdens in morbidity and premature mortality (Kelly et al. 2008; Reilly and Kelly 2010).

2.2.3.4.1 Definition of obesity, measurement and weight classification

Obesity is an atypical increase of body fat in proportion to body size. Although, obesity principally is considered in proportion of whole body fat, evidence shows a stronger correlation between fat accumulation in abdomen and trunk (central obesity); and associated complication compared to general obesity (i.e. affecting subcutaneous fat). Obesity usually depends on age, sex, and ethnic group. It substantially increases morbidity and mortality due to a wide range of diseases including: diabetes, CVD, stroke, respiratory disorders and gallbladder diseases as well as a variety of cancers like oesophagus, breast (postmenopausal), endometrium, colon and rectum, and kidney (Expert panel on the identification evaluation and treatment of overweight in adults 1998; Ogden et al. 2010; Purnell 2011).

Despite difficulties to measure body fat, accurate measurement to evaluate the risk of obesity is necessary. Body mass index (BMI) traditionally is used to evaluate obesity by anthropometric measurement of weight (kg)/ height (m^2). The WHO classification has been developed among individuals with European ethnicities that were at higher risk of diabetes, CVD and hypertension. Then, persons with BMI=19-24.9; 25-29.9; and $\geq$30 kg/m^2 are categorised in normal, overweight and obese range respectively [Table 5] (Expert panel on the identification evaluation and treatment of overweight in adults 1998; Pi-Sunyer 2000). Other measurement tools like magnetic resonance imaging, computer-assist tomography scanning and underwater weighing are accurate, but using these applications is expensive and or impractical for routine use. However, Dual Energy X-ray Absorptiometry (DEXA) as another accurate instrument has been considered for investigational purposes (Nagy and Clair 2000).

2.2.3.4.2 Prevalence

Obesity has the highest and fastest growing prevalence of the risk factors of metabolic syndrome. Its incidence has made it a global pandemic causing major problems for health systems. Although, it seems the increasing prevalence rate emerged first in high income countries, this trend is now also apparent in most middle and many low income countries particularly in their urban regions (Kimokoti and Millen 2011; Swinburn et al. 2011; Raban, Dandona, and Dandona 2012). The world health organization estimates 1.5 billion adults aged 20 and over were overweight and obese in 2008 by using classification mentioned in table 5 (WHO 2011d).

Table 5: Classification of Overweight and Obesity by BMI

BMI (kg/m^2)	Obesity Class	Defined as
<18.5		Underweight
18.5-24.9		Normal
25-29.9		Overweight
30-34.9	I	Obesity
35-39.9	II	
40	III	Extreme Obesity

Source: (Expert panel on the identification evaluation and treatment of overweight in adults 1998)

According to the WHO statistics, more than 200 million men and approximately 300 million women were placed in the obese range. In addition, in 2010, about 35 and 8 million children were obese in developing and developed countries respectively (Pereira et al. 2002; Azadbakht, Mirmiran, Esmaillzadeh, and Azizi 2005; WHO 2011d; Swinburn et al. 2011). The prevalence of obesity can however vary substantially by country, ranging between 0.46% in Vietnam and 78.5% in Nauru which apparently is due to differences in socioeconomic features and specific living conditions related to each country, region or ethnic group (WHO 2012).

A population-based national survey in Australia (AusDiab) showed that in 1999-2000, 19.3% of men and 22.2% of women were classified in the obese group. The AudDiab study indicated this rate was 2.5 folds higher than in 1980 and the peak of

this prevalence was particularly high (17.4%) in young adult males aged between 25 and 34 (Cameron et al. 2003; Seidell 2010). Another Australian study undertaken in 2004-2005, illustrated that 62% of men and 45% of women were classified as overweight or obese and this classification peaked in the age group of 55-64 years with 72% of men and 58% of women affected respectively. Moreover, these proportions have significantly increased during the last ten years from 52% to 62% for men and from 37% to 45% for women (Snijder et al. 2007). Recent epidemiologic study projected using the results of AusDiab survey and estimated the future prevalence in Australia. According to their analysis, an estimate 64.9% of the normal weight 25-29-year-olds in 2000 will be overweight or obese at age 60-64 years. The study's finding also estimates prevalence of obesity will increase to 70% in the coming decade among Australian adults unless effective prevention programs change this pattern (Walls et al. 2011).

A meta-analysis used the standard BMI criteria and studied on relevant publication performed between 1990 and 2008 in European countries. The results indicated the range from 4% to 28% of men and from 6.2% to 36.5% of women were obese by direct measurement (Berghofer et al. 2008). Despite some discrepancies, there was no considerable difference between direct measurement and self-reported methods when the results were compared to each other. Another study indicates the overall prevalence of obesity in India is 50.1% (Bhardwaj et al. 2011). However, this study used different criteria to the WHO's international classification and considered obesity range to be BMI$\geq$25kg/m^2. The current research also indicated a prevalence of 68.9% for obesity where waist circumference is assessed instead of BMI.

In addition, similar to many countries, the prevalence of obesity among Iranians aged 25 to 64 years with a 2.5 times growth, significantly increased from 13.6% to 22.3% between 1999 and 2007. This pattern was statistically significant among urban and rural area, in both genders and all age groups. Also, the increasing trend in BMI was significant (P<0.001) from 25.03±0.05 in 1999 to 26.14±0.05 and 26.47±0.015 in 2005 and 2007 respectively (Esteghamati et al. 2010). The major underlying cause of obesity is an imbalance between energy intake and metabolism. This is explained by an excess intake of highly available and inexpensive energy-dense, high-calorie foods on the one hand, and a low level of physical activity, resulting from propensity

to sedentary lifestyle, on the other (Grundy 2004b; Hossain, Kawar, and El Nahas 2007; WHO 2009; Esteghamati et al. 2010).

2.2.3.4.3 Central obesity

A number of investigations (Shiwaku et al. 2005; Eckel, Grundy, and Zimmet 2005; Enkhmaa et al. 2005) found WHO definition (Section 2.2.1.1) inappropriate to be considered for all regions and ethnic groups. Some of them suggested the cut-off for BMI should be different among of ethnic groups whereas other studies concluded central obesity is a more reliable criterion than BMI for diagnosis of metabolic syndrome (Expert Panel on Detection and Treatment of High Blood Cholesterol in 2001; Balkau et al. 2002; Cameron et al. 2003). Sufficient evidence has emerged during the last decade showing a direct correlation between central obesity and the consequences of metabolic syndrome particularly insulin resistance and diabetes (Brunner et al. 1997; Isomaa et al. 2001; Ritchie and Connell 2007; Yang et al. 2010).

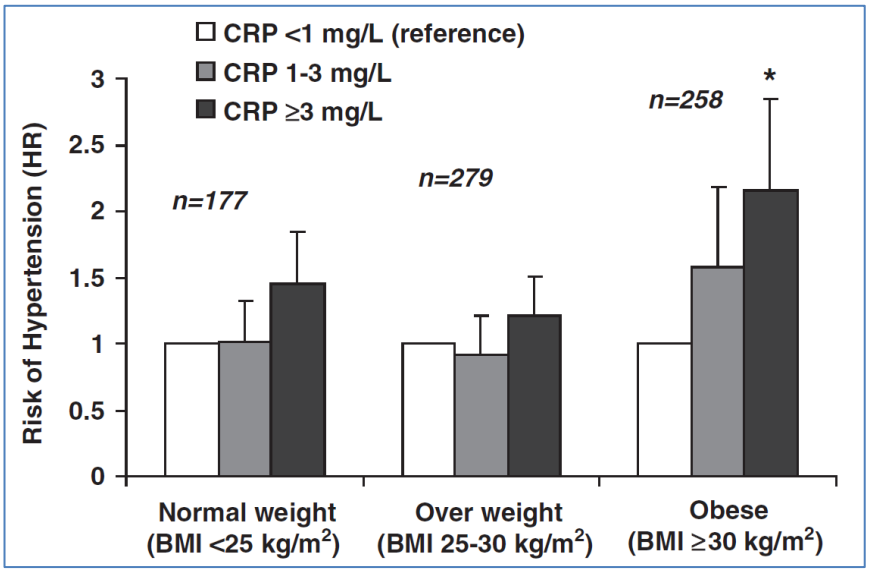
It has been shown that total and regional fat mass are extensively under influence of genetic factors (Malis et al. 2005). Many studies confirmed a strong association between BMI and the percentage of body fat (PBF) (Goh et al. 2004; Mehdad et al. 2012), however it was shown that this relationship is completely ethnic-specific (Deurenberg-Yap et al. 2000; Deurenberg, Deurenberg-Yap, and Guricci 2002). Similarly, the findings of Hughes et al. in Singapore showed that the BMI and WHR were significantly different in their correlations with obesity among diverse ethnic groups. For instance, both genders in Indians were predominantly prone to develop central obesity (measured by WHR), while Malays mainly tend to develop general obesity (measured by BMI) (Hughes et al. 1997). Accordingly, a principal research investigating the relations between BMI, total body fat and PBF as main indices of general obesity or between those reflecting central adiposity (e.g. truncal fat mass, WC, WHR) in different ethnic groups may help to elucidate unclear points in this regard.

2.2.3.4.4 Relationship between obesity and other cardiovascular risk factors

Obesity influences on other components of the metabolic syndrome causing substantial aggravation on related consequences. Significant association between increased body fat and insulin resistance has been demonstrated in many studies (Kahn, Hull, and Utzschneider 2006; Qatanani and Lazar 2007). It is now known that in individuals with obesity, adipose tissue releases increased amount of various factors, such as non-esterified fatty acids (NEFAs), glycerol, hormones and pro-inflammatory cytokines which all contribute to the development of insulin resistance (Kahn, Hull, and Utzschneider 2006).

It was shown that obesity is also associated with increased risks for hypertension and hyperlipidaemia (Kotsis et al. 2010; Repas 2011). While the exact mechanisms by which obesity can directly cause hypertension have not been fully understood, activation of sympathetic nervous system, activation of the renin-angiotensin system and sodium retention have been proposed as the main alternations (Engeli, Negrel, and Sharma 2000; Re 2009). Additionally, it has been suggested that obesity-induced inflammation may also have an important role in promoting vascular dysfunction and subsequent hypertension (Kotsis et al. 2010). This was supported with the findings of a multi ethnic study on atherosclerosis, showing that obese individuals with CRP≥3mg/L were at higher risk for developing hypertension (twofold) compared to those with CRP<1mg/L. Meanwhile, a moderate effect of inflammation alone has been detected with hypertension risk (Figure 4) (Lakoski et al. 2010).

Figure 5: CRP Category among normal, overweight and obese individuals and risk for HTN



Abbreviations: HTN, hypertension; BMI, body mass index; CRP, C-reactive protein.(Lakoski et al. 2010)

2.2.3.5 Hypertension

High blood pressure as a major component of metabolic syndrome is defined as the prolonged elevation of the systemic arterial pressure. Hypertension is a strong contributor in development of metabolic syndrome and its consequences, such as chronic heart disease (CHD), stroke and renal failure (Chobanian et al. 2003; Grundy 2004b). Clinically, a systolic blood pressure (SBP) equal or higher than 140 mmHg or diastolic blood pressure (DBP) equal or higher than 90 mmHg or being under antihypertensive medication is defined as hypertension.

Currently, and on the global scale, one billion people over the world suffer from high blood pressure; and statistics predict 1.56 billion adults will be affected by hypertension in 2025 (Kearney et al. 2005). Nearly, two-third of hypertensive cases are in developing countries and this trend apparently will be continued in the future without effective prevention programs. In addition, hypertension as “silent killer” claims almost 7.5 million or 13% of all deaths every year globally (van Vark et al.

2012), because particularly in pre-hypertension or early stages, individuals are often unaware of its presence. As mentioned, high blood pressure is highly associated with cardiovascular diseases and approximately 60% of diabetic patients suffer from hypertension as well (WHO 2011b). Table 6 shows the diagnostic classification of blood pressure in adults according to the National Cholesterol Education Program Expert Panel(NCEP 2002).

Table 6: Categorical calcification of blood pressure in adults

Categories	***Systolic blood pressure***	***Diastolic blood pressure***
Normal	<120	and <80
Pre-hypertension	120-139	or 80-89
Hypertension Stage 1	140-159	or 90-99
Hypertension Stage 2	≥160	or ≥100

2.2.3.5.1 Pathophysiology of hypertension

Particularly during last decade, studies on CVD have increasingly explored the interplay between hypertension, inflammation and cardiovascular events (Bautista 2003; Boos and Lip 2005). It is proposed hypertension causes a sequence initiating secretion of different mediators like IL-6 and C-reactive protein (CRP). Then this process is followed by failure to produce vasodilating endothelial factors especially nitric oxide (NO) and prostacyclin (PGI2), resulting endothelial dysfunction and eventually hypertension (Bautista 2003; Lakoski et al. 2010). On the other hand, increasing blood pressure consequently harms the arterial walls and this round develops a vicious cycle aggravating the primary inflammation. The experimental evidence shows the degree of endothelial dysfunction is associated with severity of blood pressure directly (Brasier, Recinos, and Eledrisi 2002).

2.2.3.5.2 Hypertension, mediators and markers

C-reactive protein, as one of the general acute phase reactants, is produced in response to the inflammation. Although, it was traditionally revealed it is mainly produced by liver, latter studies show it can be produced by epithelial cells of the

respiratory tract and kidney epithelium under certain conditions (Gould and Weiser 2001; Jabs et al. 2003; Jialal, Devaraj, and Venugopal 2004). In addition, Calabro et al showed that human coronary artery smooth muscles cell as well as adipocytes can synthesize CRP following stimulation by inflammatory cytokines (Calabró, Willerson, and Yeh 2003; Calabro et al. 2005; Yeh 2005). Likewise, the RAS has long recognized as another contributing factor leading to hypertension(Lakoski et al. 2010). Angiotensin II (Ang II) produced via the RAS, can increase blood pressure directly since it plays not only in increase renal sodium and water retention, but it also has a vasoconstrictor role. Additionally, it has confirmed Ang II induces the expression of endothelial pro-inflammatory cytokines like IL-6 and vascular cell adhesion molecules type 1 (VCAM-1). Moreover, Ang II can promote the intracellular production of H_2O_2 in endothelial cells and smooth muscle cells. This, in turn, increases inflammatory cytokines production and subsequently the risk of atherosclerosis via pro-inflammatory effects (Hernandez-Presa et al. 1997; Kranzhofer et al. 1999; Tummala et al. 1999; Pueyo et al. 2000).

2.2.3.6 Dyslipidaemia

Dyslipidaemia is diagnosed by increased LDL-cholesterol and triglycerides, and low concentration of HDL-cholesterol, which occur commonly in combination to each other. However, isolate low HDL-cholesterol may be found in some cases occasionally (Grundy et al. 2004; Wyszynski et al. 2005). Dyslipidaemia is a main contributor in developing atherosclerosis and CVD.

2.2.3.6.1 Lipoproteins and atherogenicity

Lipoproteins predominantly are constituted by two main components: lipids including triglyceride, cholesterol and phospholipids; and protein or apoproteins. The function of lipoproteins is to transport lipids in plasma. Low density lipoprotein (LDL) for example transports cholesterol and individuals cholesterol esters to peripheral tissues (Murtola et al. 2011). Lipoproteins are traditionally classified into five main groups according to their densities, and a sixth and more recently described member, lipoprotein (a) is often also now included. These groups are lipoprotein (a), high density lipoproteins (HDL), low density lipoproteins (LDL), intermediate density lipoproteins (IDL), very low density lipoproteins (VLDL) and chylomicrons (CM) [Table 7]. The higher density lipoproteins have higher percentage of protein

relative to lipid as well as an inverse association to the size (Garrett and Grisham 1995; Gennest and Libby 2011).

Another classification categorises lipoproteins according to their surface proteins called apolipoproteins. Apolipoprotein A (apo A) and apolipoprotein (apo B) with two subclasses including apoB100 and apoB48 are two important features in this classification (Chahil and Ginsberg 2006). All apo B-lipoproteins are able to harm the endothelial layer and activate the inflammatory atherogenic process through the injured blood vessels. However, HDL as the major apo A – containing lipoprotein has anti-atherogenic activity, which is mainly due to its principal role in reverse cholesterol transport (RCT). During RCT process, apo A lipoprotein accepts the cholesterol accumulated in peripheral cells (e.g. macrophages present in atherosclerosis lesions) are return them to the liver to be subsequently excreted into the bile (Chahil and Ginsberg 2006; Cavigiolio et al. 2008; Rader et al. 2009; Rothblat and Phillips 2010).

Table 7: Plasma Lipoproteins composition in fasting state (Gennest and Libby 2011)

	Origin	**Density (g/ml)**	**Size (nm)**	**% Protein**	**Cholesterol (mmol/L)†**	**Triglyceride (mmol/L)‡**	**Major apo**
CM	Intestine	<0.95	100-1000	1-2	0.0	0	B48
VLDL	Liver	<1.006	40-50	10	0.1-0.4	0.2-1.2	B100
IDL	VLDL	1.006-1.019	25-30	18	0.1-0.3	0.1-0.3	B100, E
LDL	IDL	1.019-1.063	20-25	25	1.5-3.5	0.2-0.4	B100
HDL	Liver, intestine	1.063-1.210	6-10	40-55	0.9-1.6	0.1-0.2	AI AI
LP (a)	Liver	1.051-1.082	25	30-50			B100, (a)

Apo: apolipoproteins; CM: Chylomicrons ; HDL: high-density lipoprotein; IDL: intermediate-density lipoprotein; LDL: low-density lipoprotein; LP : lipoprotein ; VLDL: very-low-density lipoprotein.
†In mmol/L; for mg/dl, multiply by 38.67.‡In mmol/L; for mg/dl, multiply by 88.5.

2.3 Atherosclerosis

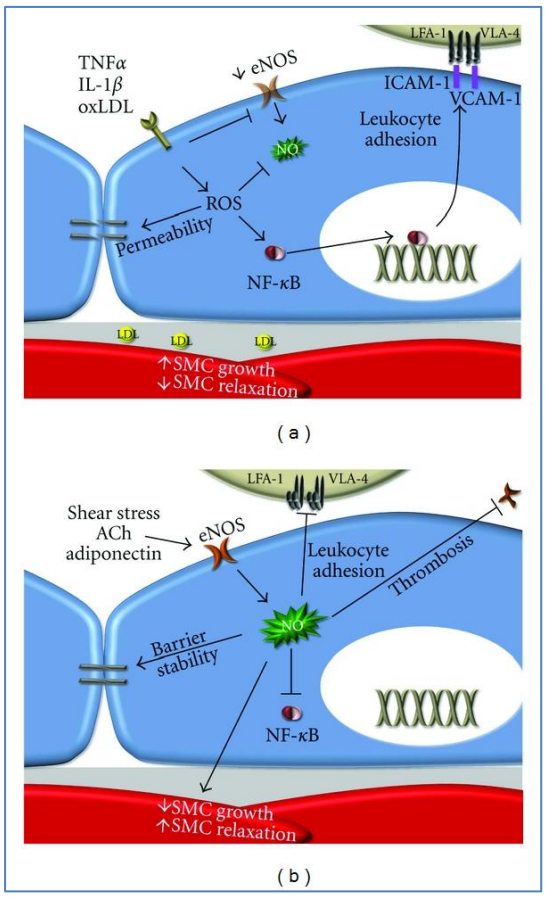
Atherosclerosis is a chronic and progressive inflammatory disease involving blood vessels almost in all sizes (Gornik and Beckman 2005). It usually starts from the early years of life and the clinical signs manifest in middle to late adulthood. This disorder takes place through three main processes. These stages and processes are:

1. proliferation of endothelial smooth muscles cells (SMC) by the mutual action with inflammatory cellular elements;
2. formation by the accumulated smooth muscle cells in a layer of collagen-rich matrix and elastin fibres;
3. and uptake and accumulation of lipids, predominantly as cholesterol esters and free cholesterol formats.

Among several hypotheses explaining the factors that trigger atherosclerosis, two theories predominate: these include "oxidation" and "response to injury", with the latter widely accepted at this time (Ross 1993). According to the "response to injury" theory, atherosclerosis process starts with the injury to the arterial wall which triggers inflammatory reactions, participating in atherosclerotic plaque formation.

In normal conditions, arterial endothelium plays a considerable role in controlling homeostasis of the cardiovascular system by releasing vasodilator nitric oxide (NO) as well as antithrombotic and fibrinolytic factors. However, in response to injury, NO and acetylcholine present an inverted effect causing vasoconstriction in damaged endothelium by releasing agents such as thromboxane A_2 and prostaglandins. In parallel, abnormal intracellular signalling increases the intracellular Ca^{2+} which leads to extra vasoconstriction (Mallika, Goswami, and Rajappa 2007; Sherwood 2009). In addition, pro-inflammatory cytokines such as tumour necrosis factor (TNF-α) or interleukin-1β (IL-1β) stimulate the endothelial cells to express vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1) causing an aggression and adhesion of platelets and monocytes on the site of damage (Li et al. 1993; Maziere and Maziere 2009).

Figure 6: Interplay between endothelial cell dysfunction and endothelial cell activation



(a)
Cytokines and oxidized LDL stimulate endothelial cell permeability and NF-κB-dependent inflammatory gene expression. ROS appear to play a central role mediating both responses.

(b)
In addition to its vasodilatory properties, NO promotes barrier stability, limits inflammation, inhibits platelet aggregation, and limits SMC proliferation. Loss of these protective properties in endothelial cell dysfunction therefore perpetuates endothelial cell activation(Funk, Yurdagul, and Orr 2012).

As a consequence of inflammation, monocytes enter into the intima which, in turn, increases endothelial permeability (Figure 6). Subsequently, plasma atherogenic lipoproteins, particularly LDL, are able to move through the endothelial layer and mediate or contribute to form a visible “fatty steak”, a hallmark of atherosclerosis in early stage. The lipoprotein accumulation causes that the layer of vessels to bulge into arterial lumen gradually. By continued inflammation and monocyte invasion as well as increased herniation, the lumens of blood vessel are reduced. Both biochemical and mechanical changes exacerbate oxidative stress and cause arterial damage in a vicious cycle (Figure 7) (Woywodt et al. 2002; Boon NA 2002; Hayashi et al. 2007; Mallika, Goswami, and Rajappa 2007).

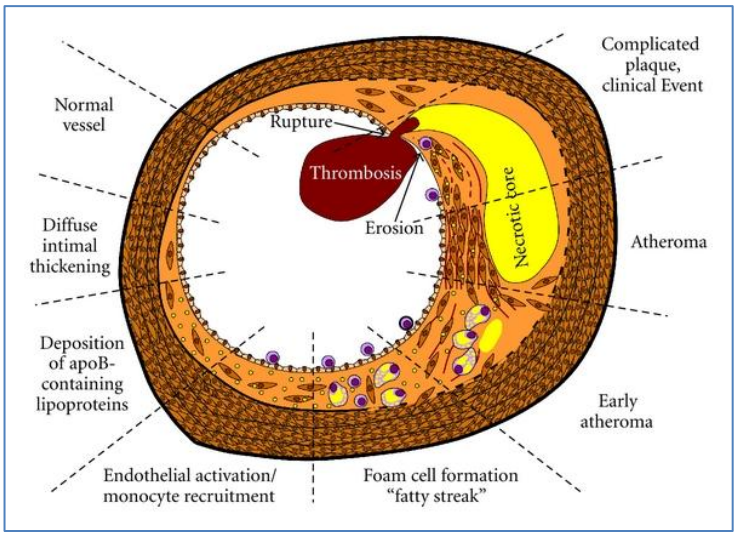


Figure 7: Stages of atherosclerotic plaque formation. Early apoB-containing lipoprotein accumulation and monocyte binding drive the early stages of plaque development forming fatty streaks in the vessel wall. While these processes continue in advanced atherosclerosis, monocyte cell death, smooth muscle recruitment, and matrix deposition are hallmarks of atheroma formation.(Funk, Yurdagul, and Orr 2012)

The "fatty streak" lesion can occur in infants and young children, while it develops into a "fibrous plaque" with age as an advanced lesion is formed (Figure 7) (Mallika, Goswami, and Rajappa 2007; Maziere and Maziere 2009).

2.3.1 Atherosclerosis risk factors

Risk factors of atherosclerosis encompass a collection of variety of factors which can be categorised in three main groups.

The first modifiable group can be controlled by changing in lifestyle and include obesity, physical inactivity and smoking. Risk factors such as hypertension, diabetes mellitus, insulin resistance and dyslipidaemia can be modified by both lifestyle modification or through medication. In contrast, risk factors including age, gender and ethnic or familiar specification are classified under unmodifiable group (Fleming 1999; Fauci, Braunwald, and Isselbacher 2003).

Metabolic syndrome and its components can accelerate the atherosclerosis process through pro-inflammatory and inflammatory stages. Adipose tissue can continue to increased production of cytokines which consequently causes reductions in insulin sensitivity and establishes a systemic pro-inflammatory state. The influence of

dyslipidaemia, particularly increased level of LDL, is well known in both lesion commencement and progression in atherosclerosis as is the role of various forms/modifications of LDL. For example, LDL oxidation synergises atherogenisity of lipoproteins, and dense and small LDL particles play more significant atherogenic role than buoyant and large LDL particles(Lamarche et al. 2001; Blake et al. 2002; Hulthe and Fagerberg 2002; Vakkilainen et al. 2003). The triglyceride-rich particles and their remnants are, like LDL, also considered to contribute to plaque development.

Chylomicron remnants, which are present particularly in the postprandial state, are considered to be particular atherogenic. Triglyceride-rich particles can accumulate due to increased production or impaired clearance, for example due to lack or inhibition of lipoprotein lipase. Similarly, chronic hyperglycaemia in diabetic patients speeds up the production of advanced glycation end products (AGEs) which in turn activate extra parallel processes for arterial inflammation (Schmidt et al. 1999). Other features involved in metabolic syndrome such as increased PAI-1 and hyper-fibrinogenemia contribute in inflammatory phenomenon as well (Sorrentino 2005).

Endothelial dysfunction subsequent to imbalance between vasodilator and vasoconstrictor's action, such as NO and angiotensin II, presents its role as risk factor in atherosclerosis via increasing circumferential wall tension (CWT). Endothelial damage initiates and intensifies atherosclerosis due to defect in production and dysfunction of nitric oxide (Davignon and Ganz 2004; Funk, Yurdagul, and Orr 2012).

2.3.2 Atherosclerosis and inflammatory biomarkers

Many studies over last decade have attempted to find a variety of biomarkers in relation to atherosclerosis as well as to determine how their modulation influences its development or prevention. Most experimental studies on metabolic syndrome have focused more on acute phase reactants, e.g. C- reactive protein (CRP), plasminogen activator inhibitor-1 (PAI-1) and cellular adhesion molecules (CAMs) such as VCAM-1 than other biomarkers.

CRP is known as the strongest non lipid biomarker to predict the risk of cardiovascular events compared to other predictors (Ridker et al. 2013). It is a marker of inflammation synthetized primarily by the liver following microbial infection, autoimmune reactions and tissue injury. Additionally, it was shown that CRP can be produced by renal cortical tubular epithelial cells in response to inflammatory stimuli (Jabs et al. 2003). It has also been detected in atherosclerotic lesions of human arterial wall (Yasojima et al. 2001), which could be the result of its participation in vascular inflammation. Several studies confirm its role in myocardial infarction, cardiac sudden death, stroke, diabetes mellitus and peripheral artery diseases (Ridker et al. 2000; Albert et al. 2002; Ridker et al. 2002; Linnemann et al. 2006; Ridker et al. 2008). Also, increased levels of CRP are associated positively with body weight in both men and women (Linnemann et al. 2006; Zuliani et al. 2009). Moreover, a number of studies reveal that some medications (e.g statins/aspirin) which reduce the risk of atherosclerosis have been shown to modify CRP circulatory levels in parallel of their treatment effects (Fisher et al. 2008; Ridker et al. 2008)

In addition to the above mentioned clinical roles, serum CRP is an important marker predicting metabolic syndrome (Anand et al. 2004). Compared to other biomarker predictors for cardiovascular events and metabolic syndrome, CRP has a long life and a lower diurnal and seasonal variation in circulatory systems (Packard and Libby 2008). Furthermore, CRP is a well validated screening test for conventional risk factors and other inflammatory markers; and it is simply analysed by standardized high sensitive immunoassay method which is relatively inexpensive and widely available (Pearson et al. 2003; Anand et al. 2004; Packard and Libby 2008). Additionally, detectability of CRP in early stages of atherosclerosis is another advantage compare to the other biomarkers predicting the risk of cardiovascular diseases (Figure 8).

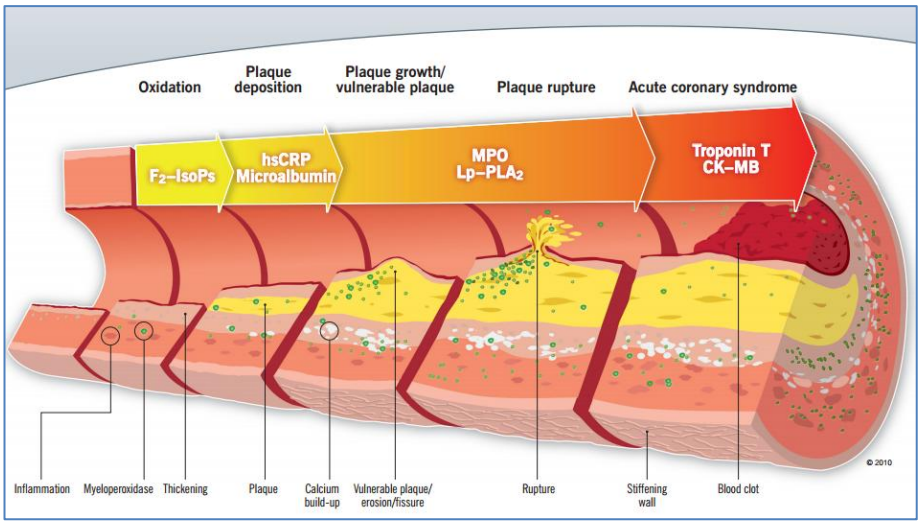


Figure 8: Inflammatory Biomarkers and the progression of atherosclerosis. The progression of atherosclerosis involves various inflammatory biomarkers that can be easily measured to determine an individual's risk for heart disease and cardiac events (ClevelandHeartLab 2010)

The American Heart Association has identified a highly sensitive technique used for the measurement of CRP (hs-CRP) as an independent inflammatory marker predicting the risk of coronary diseases (Pearson et al. 2003). Serum CRP concentration usually rise up to 100 – 200 mg/L during an acute phase reaction. However, just a small elevation in CRP levels is thought to be useful for predicting CVD risk. The current guideline for cardiovascular risk assessment categorized the variety of risks according to the different levels of hs-CRP. Accordingly, the classified groups of low, intermediate and high risk are defined by the levels of 0 to <1mg/L, 1-3mg/L, >3-10 mg/L respectively, however the CRP levels > 10mg/L is recognized as unspecific elevation. In individuals with CRP concentration more than 10 mg/L, the test should be repeated at a late time to rule out infection, malignancy or autoimmune diseases (Yeh and Willerson 2003). In contrast, there are few controversies around the role of CRP to develop cardiovascular events and metabolic syndrome. Without denying this overall role, they commonly emphasize that the occurrence of CVD is multifactorial and CRP plays a role along with other risk factors including genetics (Lin et al. 2012).

PAI-1, along with other inflammatory cytokines including TNF and IL-6, can be released by adipose tissue. The production of these inflammatory agents depends on the number of adipocytes; however insulin reduces their production through the

suppression of lipolysis (Grundy 2006). PAI-1 as anti-fibrinolytic factor contributes to the shift of balance from antithrombotic to pro-thrombotic statues (Landmesser, Hornig, and Drexler 2004). An early study exploring a population with high prevalence of coronary heart disease showed an increased PAI-1 production during the first acute myocardial infarction (AMI) in both men and women (Thogersen et al. 1998). Evidence suggested elevated PAI-1 concentration may be influenced by cardiovascular risk factors such as genetic susceptibility, insulin resistance and obesity (Brown et al. 1998; Grundy et al. 2004). Also, the resulting thrombosis subsequent to rupture or erosion in the arterial wall, even in a small plaque, can be larger in person who is under a pro-thrombotic status. This pro-thrombotic condition causes the person to be at risk of major life-threatening cardiovascular events. Although, the exact mechanism is not yet understood, it is known that anti-platelet therapy or anti-coagulant therapy reduces the risk of cardiovascular events (Pearson et al. 2002; Grundy 2006).

2.4 Diet and metabolic syndrome

Although the metabolic syndrome is associated to dietary intake, the mechanism of how metabolic syndrome develops is not yet well understood (Esposito et al. 2004; Azadbakht, Mirmiran, Esmaillzadeh, Azizi, et al. 2005; Kimokoti and Millen 2011). Industrialization and technological advances cause a universal transition of nutritional behaviour with a shift from plant-based foods to high energy dense regime. There are many studies exploring the relationship between different nutritional patterns and incidence of metabolic syndrome, its components and cardiovascular disease (Sonnenberg et al. 2005; Esmaillzadeh et al. 2007; Azadbakht et al. 2007; Panagiotakos et al. 2007; Fogli-Cawley et al. 2007; Lutsey, Steffen, and Stevens 2008; Babio et al. 2009; Denova-Gutierrez et al. 2010; Kim and Jo 2011).

Existing studies mainly attempt to classify food items into healthy, or prudent, patterns and fast energy or Western patterns, and the data analysed based on appropriate classification. Evidence from some of the studies, reveal a strong association between ten year incidence and death rates from coronary heart diseases and average intake dietary energy from saturated fatty acids. In addition, there was

no indication of association to death rates either from proteins or polyunsaturated fats in the diet (Keys et al. 1986). In 9 years observation, Lutsey et al. (2008) examined the association between the incidences of metabolic syndrome and two different dietary patterns.

Fruits, cruciferous and carotenoid vegetables, poultry and fish were typified as prudent dietary whereas high consumption of processed meat, refined grains, fried foods and red meat were placed in western pattern in this study. Their results showed an association between a Western dietary pattern and an 18% higher risk of metabolic syndrome incidence which confirm previous similar correlation in other studies (Sonnenberg et al. 2005; Esmaillzadeh et al. 2007; Lutsey, Steffen, and Stevens 2008).

Since the 1980s, the Mediterranean diet has been recognized as cardio-protective (Keys et al. 1986). This dietary pattern is characterised by high intake of monounsaturated fatty acids (mostly from olives), vegetables, nuts, whole grain cereals, legumes and white meat (poultry and fish) along with low/ moderate red meat and alcohol consumption. Evidence derived from a meta-analysis of 50 countries including more than half million individuals confirmed a significant association between Mediterranean diet and low cardiovascular risk (Babio et al. 2009). Also, other randomized controlled trials showed that consumption of healthy diets like Mediterranean patterns can improve metabolic syndrome components and subsequently reduce the incidence of metabolic syndrome among those who are diagnosed as metabolic syndrome cases (Esposito et al. 2004; Esmaillzadeh et al. 2007).

Additionally, a number of experimental trials show that whole grain and cereal fibre consumption is correlated to low incidence of metabolic syndrome risk factors (McKeown et al. 2004; Esmaillzadeh, Mirmiran, and Azizi 2005a; Sahyoun et al. 2006). Furthermore, the risk of the hypertriglyceridemic waist (HW) phenotype (i.e., central obesity in combination with hypertriglyceridemia) was inversely correlated with high intake of whole grain; however the consumption of refined grains was significantly associated to the risk of HW phenotype (Esmaillzadeh, Mirmiran, and Azizi 2005b).

The role of dietary fibres in reduction of risk of chronic diseases like diabetes mellitus and CVD has been shown in many studies, however the biological mechanism resulting in these effects is not completely understood yet (Barclay et al. 2008; Ventura et al. 2009; He et al. 2010). Among all dietary fibres, legumes have characteristically low energy density whereas vegetable proteins have high dietary fibre and oligosaccharides. The results of dietary intervention studies indicate that consumption of legumes helps to improve glycaemic control. The legume intake is associated with lower incidence of type 2 diabetes (Villegas et al. 2008), better maintenance of blood glucose concentration (Venn and Mann 2004; Rotimi et al. 2010), improvement in weight control and weight loss (Papanikolaou and Fulgoni 2008; Hermsdorff et al. 2011), preventing inflammation and endothelial dysfunction, improvement in antioxidant status (Rotimi et al. 2010), reduced risk of coronary heart diseases and mortality rate due to cardiovascular cause (Bazzano et al. 2001; Nothlings et al. 2008).

Evidence shows a significant reduction in total and LDL cholesterol concentration subsequent to a 14 day legume (kidney beans) intake, although there was no significant increase in the levels of HDL levels (Kolonel et al. 2000; Venn and Mann 2004; Villegas et al. 2008; Trinidad et al. 2010). Similarly, the results from another research study undertaken among Iranian women show the consumption of legume is inversely correlated to serum concentration of CAMs and inflammatory biomarkers such as CRP, TNFα and IL-6 (Esmaillzadeh and Azadbakht 2012).

2.5 Physical activity and metabolic syndrome

Physical activity is one of the most effective components for regulating energy balance. Unlike the basal metabolic rate, physical activity is under voluntary control. Acknowledgment of the significance of physical activity has increased due to the epidemics of the westernised lifestyle and other related risk factors leading to metabolic syndrome such as obesity, and chronic disease. Physical inactivity causes greater risk of metabolic syndrome's components and consequences like CVD and diabetes mellitus (Wannamethee et al. 1998; Helmrich et al. 1991; Dunstan et al. 2005). Physical inactivity commonly develops metabolic syndrome through increase in the risk of obesity and prepare the conditions for insulin resistance and

dyslipidaemia (Jakes et al. 2003; Boparai, Davila, and Chandalia 2011; Cameron and Shaw 2011).

Several studies carried out in different countries evaluated the relationship between physical activity or inactivity and metabolic syndrome. One of those findings show the odds ratio (OR) of having metabolic syndrome is directly related to leisure time activities including watching TV or video or using computer outside of work. Namely, OR with 95% confidence interval (CI) were 1.41, 1.37, 1.70 and 2.10 for one, two, three and four hours per day watching TV and using computer respectively when those compared with participants who were involved less than one hour of these behaviours. In contrast, individuals who were not involved in moderate or vigorous physical activity had higher ORs by two times compare to who had ≥150 minutes per week of similar activity (Ford et al. 2005)

As mentioned already (section 2.2.3.1), insulin resistance is one of the fundamental mechanisms that plays a key role in developing metabolic syndrome. Attempts to determine the relationship between insulin resistance and physical activity among Iranian society revealed that decreasing physical activity in different levels is associated with increasing BMI, systolic blood pressure, waist circumference, fasting blood glucose and HOMA (homeostatic model assessment) score significantly. The results of this study also indicated the lower total physical activity score (TPA) and commuting have invert correlation with higher HOMA after adjustment for age, sex, BMI, smoking and residential region ($P<0.01$). This independent pattern was observed similarly when the duration of vigorous or moderate-intensity physical activity has been examined. Additionally, in association with all variety of physical activities and HOMA, work-time physical activity presented higher contribution compare to the moderate and recreation time physical activity. However, the prolonged sedentary behaviour significantly correlated to higher HOMA values (Esteghamati et al. 2009).

Published results from another study accomplished in Australia showed lengthier TV watching more than 14 hours per week is positively associated with a greater risk of insulin resistance, dyslipidaemia and obesity in both sexes (Dunstan et al. 2005). Also, TV watching presented stronger association with metabolic syndrome in

women compared to men and this relationship was independent of all other factors. These findings were similar for the association with TV viewing when alternative metabolic syndrome criteria include NCEP and IDF were applied. Furthermore, the prevalence of metabolic syndrome was associated with each 1 hour increase in TV watching in men and women by 12% and 26% respectively.

Other findings showed that the prevalence of insulin resistance and dyslipidaemia in both genders, and prevalence of obesity and hypertension in women are correlated to a total physical activity time of ≥2.5 hours per week. Woman who did not undertake the public health physical activity goal of ≥2.5 hours per week through walking and moderate physical activity were significantly more likely to have the metabolic syndrome compare to those who did not do any vigorous physical activity but still achieved the public health target. However, this level of moderate physical activity had no protective effect against metabolic syndrome in men. There was significant inverse correlation with metabolic syndrome in both sexes for between those who undertake ≥1 hour vigorous physical activity (see section 3.4.4) per week and those who participated in only <1 hour per week of the similar activity. The prevalence of metabolic syndrome reduction in man and women by 11% and 28% respectively has been associated with each 30 min increase in physical activity per day (Dunstan et al. 2005).

Several studies assessing physical activity behaviour among different ethnic groups revealed that Asian Indians are more inactive compare to white Caucasians (Zimmet 1992; Jernigan et al. 2010; Misra et al. 2012). Also, the prevalence of metabolic syndrome is higher than most of other ethnic groups which were compared to Indians in several countries including United States, UK and Fiji. Similar to other studies, the prevalence of metabolic syndrome increased by age and it was more common among Indian women than men (Taylor et al. 1984; Ramachandran et al. 2003; Boparai, Davila, and Chandalia 2011; Brian et al. 2011; Williams et al. 2011).

Moreover, it has been shown that the prevalence of impaired glucose tolerance and diabetes mellitus were significantly higher at the lower quartile of physical activity among sedentary, moderate heavy and heavy South Indian workers by 16.8%,13.2% and 11% respectively (Ramachandran et al. 2003; Misra et al. 2012). Evidence

confirms that prevention programmes encouraging decrease in amount of times spent for watching TV or using a computer, particularly along with increased physical activity decrease the prevalence of MS (Dunstan et al. 2005; Ford et al. 2005).

2.6 Ethnicity and metabolic syndrome

2.6.1 Genetic factors and metabolic syndrome

It is now established that genetic factors have a powerful influence on the incidence of obesity and other components of metabolic syndrome (Reaven et al. 1967; Tobey et al. 1981; Nakamura et al. 1994; Bonora et al. 1998; Nesto 2003; Kristiansson et al. 2012). During last decade, studies in different countries like Belgium, French and US have shown variations in the prevalence of metabolic syndrome risk factors. In addition, metabolic syndrome risk factor rates were different among various ethnic groups even in a society; and in this regard, other than environmental factors, genetic factors play a key role (Ferrannini et al. 1987; Shen et al. 1988; Bouchard and Perusse 1988; Korkeila et al. 1991).

For example, evidence suggests that the accelerated rate of premature diabetes and CVD in South Asians immigrants is due to inherent insulin resistance as well as an increased susceptibility to the development of the metabolic syndrome in the framework of a Western lifestyle. It is suggested that a thrifty genotype involves insulin resistance and selective partitioning of excess calories into visceral stores in this ethnic group (Fabsitz, Carmelli, and Hewitt 1992; Cleland and Sattar 2005). However, Black male immigrants of African descent tend to display a different fat distribution phenotype, also resulting obesity and insulin resistance but with a paradoxically healthy lipid profile (hyperinsulinemia, low serum triglycerides and high HDL-cholesterol). The anti-atherogenic lipid profile found in African black males seems to have potentially a protective role against cardiac events, and is expected to modify the substantial effects of environmental factors increasing the risk of CVD in this ethnic group (Glueck et al. 1984; Herd et al. 2001; Kumar et al. 2006; Veghari GR 2007).

It is undoubtedly true that obesity is not simply a direct result of overeating, but it mainly results from a complex interaction of the environment and genetic factors. In

a small number of people, obesity may be developed because of a single-gene disorder, mainly defects in genes encoding leptin (*Ob* gene) or the leptin receptor (Zhang et al. 1994; Clement et al. 1998). Leptin is a hormone secreted primarily by adipose tissue, regulating fat mass in the body through profound effects on appetite and energy expenditure. Leptin deficiency is an autosomal recessive trait causing massive obesity in *ob/ob* mice and humans (Montague et al. 1997).

In most cases, genetic factors contributing to obesity are not limited to a single-gene defect, but it results from a combination of various genes disorders. Recent studies have identified more than 300 genes and gene makers with potential influence (promoting or protective) on obesity (Chagnon et al. 2003). Involvement of this number of genes may cause many different types of obesity.

2.6.2 Impact of ethnicity on metabolic syndrome components

Over the last two decades, studies have investigated the impact of ethnicity on cardiovascular diseases and metabolic syndrome components among different ethnic groups particularly African and South Asian immigrants. The results of the studies among immigrants showed that ethnic groups with African ancestry had higher rates of obesity, insulin resistant, hypertension and diabetes type 2, but a lower rate of the metabolic syndrome when compared to Caucasians. The studies suggest that African diabetic individuals have not demonstrated the typical dyslipidaemia of the metabolic syndrome (Ferrannini et al. 1987; Herd et al. 2001; Kumar et al. 2006; Veghari GR 2007).

This pattern has been different from what has been found in South Asian immigrants. The finding of a large study conducted on Indians and Pakistanis living in London (the Southall study) indicated that after matching for age and BMI, South Asian men had higher waist: hip ratio, SBP, insulin levels after glucose load and serum triglyceride as well as lower HDL-C than Caucasians (McKeigue et al. 1993). Also, high prevalence of insulin resistance syndrome along with a tendency to central obesity among this ethnic group is suggested (Church, Gilbert, and Khokhar 2006).

In addition, the prevalence of type 2 diabetes was 20% compared with 5% in the Caucasian subjects (McKeigue, Shah, and Marmot 1991). Consistent with the Southall study, in the another study, anthropometric measures of 73 South Asian and 1287 Caucasian children aged 8–11 years were compared with their fasting and post-glucose insulin concentrations (Sorensen and Stunkard 1994). Although, South Asian children had a lower ponderal index (weight/body surface area), there was no difference in waist circumference or waist: hip ratio, suggesting a predisposition to preferential accumulation of central adiposity. Also, although both their fasting and post-glucose-load glucose levels were similar, insulin levels were around 50% higher in South Asians than Caucasian. Moreover, fasting triglyceride levels were 12% higher in this ethnic minority (Sorensen and Stunkard 1994).

It is not completely elucidated which key pathways in metabolism are involved in ethnic differences in metabolic and vascular functions. However some existing findings such as different concentrations of leptin (Glenday et al. 2006; Wu et al. 2007), anti-inflammatory markers such as CRP (Dhawan et al. 1994; Deurenberg-Yap et al. 2001; Chambers et al. 2001; Whincup et al. 2002; Misra and Vikram 2004; Anand et al. 2004; Kelley-Hedgepeth et al. 2008; Cushman et al. 2009), adipocytokinase like adiponectin and Plasminogen Activator Inhibitor-1 (Cappuccio 1997; Misra and Vikram 2004; Kuller 2004), in some ethnic groups, particularly in South Asian population have been highlighted in this regard.

There has been convincing evidence to indicate a higher prevalence of metabolic syndrome risk factors and diabetes among Asians compared with Caucasians, suggesting the use of lower anthropometric cut-points to indicate overweight among Asians (Meis et al. 2006). As mentioned above, the results of the Southall study as well as other studies in this field has accepted this fact among South Asian immigrants; and some of them suggest that familial factors apply a stronger impact than environmental factors causing a more powerful influence on developing obesity and its consequences (Korkeila et al. 1991; Guillaume et al. 1995).

There are few studies comparing cardiovascular risk factors among Asian immigrants with different nationalities (Kuller 2004; Tillin et al. 2005). Similarly, limited studies exploring metabolic syndrome risk factors among immigrants in

Australia have been mainly focused on Caucasians (Ball et al. 2003). Accordingly, a multiethnic study investigating the impact of ethnicity on metabolic syndrome risk factors among Asian immigrants compared to those with European ancestry would provide interesting and new data. With this background in-depth review presented in chapter 2, the next chapter presents the methods used in the study.

Chapter 3

Methodology

As already mentioned (in sections 2.1.1, 2.2.2.1 and 2.2.2.2) the risk factors of metabolic syndrome may be influenced by different factors such as genetics, socioeconomics and cultural issues. Although many studies have been undertaken globally and offer various definitions for metabolic syndrome, there is still no general consensus about accurate definitions and their diagnostic criteria, in particular among different ethnic groups.

Australians from a variety of ethnic groups and cultures come together from five continents over the world. Given the limited comprehensive studies on ethnicity and metabolic syndrome in Australia, this condition provided the best opportunity to explore some of the controversies around this issue. This current study was designed to evaluate overall health condition and metabolic syndrome risk factors amongst some ethnic groups as well as to study the effects of ethnicity on metabolic syndrome in Australia. It was hypothesized that ethnicity may play an important role in the development of the metabolic syndrome.

3.1 Study design

This was a cross-sectional, pilot study describing the possible impacts and fundamental relationship between ethnicity and metabolic syndrome components among West Australian immigrants. Also, this method was appropriate to examine the impact of ethnicity on the endothelial dysfunction and dietary configuration in metabolic syndrome.

3.2 Participants

Given the main hypothesis, it was rational that the current study would focus on some ethnic groups which may have the most impact on health in respect to the

metabolic syndrome. So, the chosen ethnic groups for this study needed to meet at least one criterion below:

- That they were a major ethnic group in Australia which can thus have a significant impact on health nationally
- That existing similar studies about migrants from those ethnic groups have been undertaken in the origin or other countries

According to the released information of census carried out in 2013 by the Australian Bureau of Statistics (ABS), migrants from Europe, China and India made most population in Australia. According to the Australian census in 2011, European, Indian and Iranian ancestry have made proportions of 51.2%, 1.8% and 0.2% of Australians respectively. India was the main source of permanent additions in 2012-13 with an increase of 28.4% compare to previous year. In addition, Indians and Iranians ancestry showed an increased by 66.5% and 53.4% in census 2011 compared to census 2006, respectively (Australian Bureau of Statistics 2013). On the other hand, there were similar studies about European, Indian and Iranian in their home countries as well as the destination countries for migrants, over the world. Given the above facts, participants were chosen through three targeted ethnic groups in Western Australia that included Australians from European countries, Indians and Iranian.

With respect the key role of body fat in relation to different components of MS, sample size was calculated based on an predicted 10% reduction in body fat percentage in Indian group relative to two other groups, assuming a standard deviation of 8.3% (Vasudev et al. 2004). Using a clinical trial formula (Jeyaseelan and Rao 1989), a sample of eighty four subjects (twenty eight subjects in each groups) could provide sufficient power (80%) to detect predicted difference at the 5% significance level.

3.2.1 Recruitment phase

After receiving the ethics approval for the study from Curtin University (approval number HR 179/2008) and in order to recruit participants from the targeted ethnic groups, a wide range of methods was applied to recruit necessary participants for the study. The recruitment phase commenced through general and ethnic specific advertising in The West Australian, community newspapers, Curtin University radio and website, and multicultural broadcasting as well as direct contact to the ethnic associations and communities in Perth.

In the first step, the following major government departments were contacted to source appropriate participants for the study:

- Department of Immigration and Citizenship, DIAC
- Australian Bureau of Statistics, ABS
- Department of Health (data linkage system)
- Department of Communities, WA
- Office of Multicultural Interests, OMI

However, the DIAC's data was not accessible because of individuals' privacy, as protected by government legislation. In addition, upon further consideration, the data from these departments were not considered optimal for this purpose as they could introduce considerable biases. For example, the data from department of health belonged only to those who have been admitted in hospitals as inpatients.

In the next step, contact with some communities and advertising in the popular edition of The West Australian newspaper were undertaken twice. Although, we received a good response from European groups via these methods, the recruitment was not satisfactory in other ethnic groups.

3.2.2 The second method of recruitment

To find required participants particularly from ethnic groups other than European, a new method was established. In this method, the latest census information carried out by the Australian Bureau of Statistics (ABS) in 2006 was analysed. The online ABS data base was used to determine the number of resident for each ethnic group in different suburbs. Then, 28 of 78 suburbs with the highest targeted ethnic populations were chosen for recruitment.

To recognize the targeted suburbs with the most concentration of the targeted ethnic groups, an influence index was defined for all 28 suburbs using the formula below:

$$Influence\ index\ (\%) = \frac{Total\ population\ of\ all\ needed\ ethnic\ groups}{Total\ population\ of\ suburb}$$

The influence indexes were different and ranged from 15.3% to 79.8%. The 14 suburbs in Perth were selected as final targeted areas according to the higher population and influence index. In the next step, the flyers [Appendix 1] were distributed in the selected suburbs.

Inclusion criteria

Volunteers were recruited according to the inclusion and exclusion criteria which was necessary to define as this study has focused on the metabolic syndrome criteria among three ethnic groups. The inclusion and exclusion criteria as well as the reason why those are selected are listed below:

- Age 18 years and more
- Parents of the volunteers must be from one of the European countries, India and Iran, since the study was aimed to evaluate the ethnicity effect on the metabolic syndrome
- Participants have lived in Australia for at least 5 years, as the study's goals need to reduce biases from the effects of environment as much as possible
- Have working knowledge of written and spoken English in order to prevent any mistake or misunderstanding during their participation

Plus one or more criteria mentioned below:

- Are overweight: Body Mass Index (Weight/Height^2) of 25 or more
- Waist circumference: 94 cm for Male and 80 cm for Female or more
- Blood pressure 130/85 and higher or taking medication
- Hypertriglyceridemia or hypercholesterolemia or taking medication
- Diabetes

The above inclusion criteria were selected as they are the basic conditions for metabolic syndrome diagnosis according to variety of its definitions and usually are detectable by individuals. Pregnant and breastfeeding women were excluded from the study, as participants need to be evaluated for body composition by Dual Energy X-Ray Absorptiometry (DEXA) test as well.

A screening questionnaire

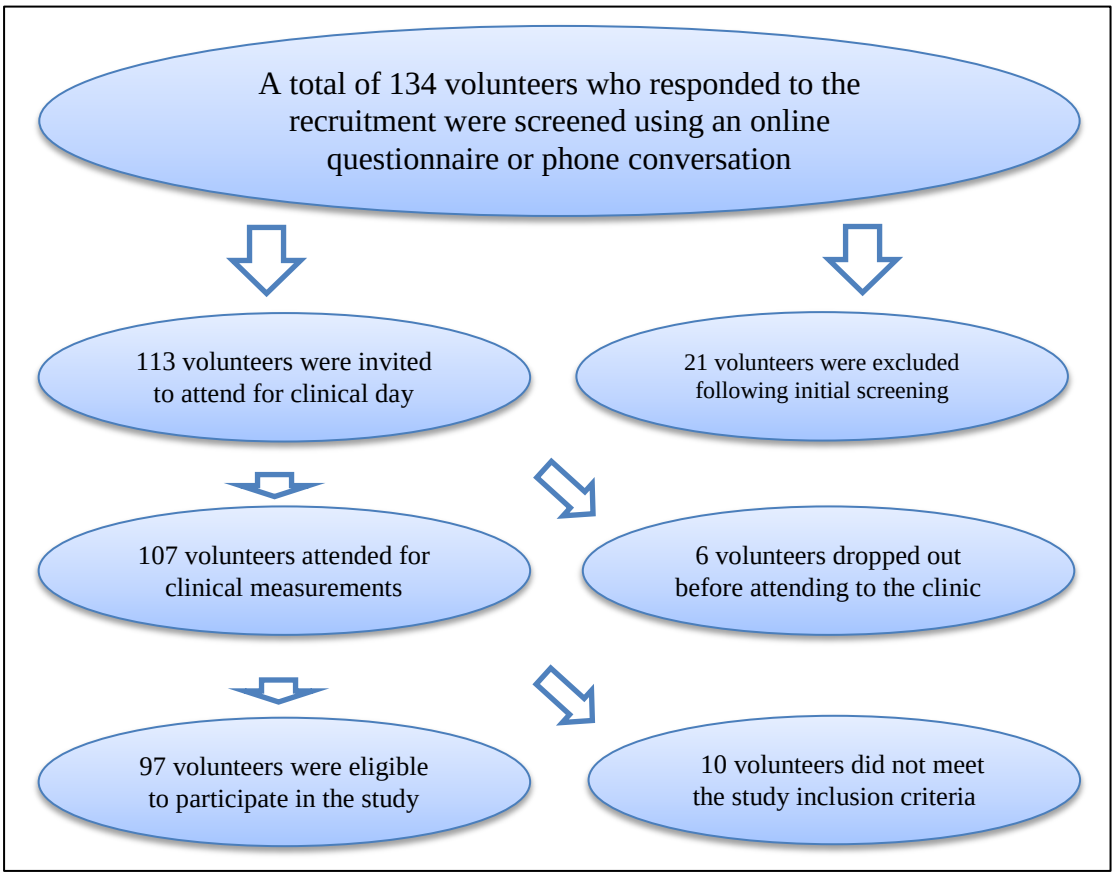
Following recruitment, prospective volunteers were invited to fill out an online screening questionnaire uploaded on the Curtin University website. The information of potential volunteers who were not familiar with the online method or had no access to the internet was taken via telephone. Both online and telephone screening questionnaires included some questions related to the volunteers' general demographic information such as age, sex, height, weight, background and medical history as well as the questions relating to the study's inclusion criteria [Appendix 2].

Table 8: Characteristics of the study subjects

	European	Indian	Iranian	Total
Male	11 (31.4%)	16 (55.2%)	22 (66.7%)	49 (50.5%)
Female	24 (68.6%)	13 (44.8%)	11 (33.3%)	48 (49.5%)
Total	35 (100%)	29 (100%)	33 (100%)	97 (100%)

A total of 97 volunteers were eligible to participate in the study (49 males and 48 females). In all, 35 participants (11 males and 24 females) were from European countries, 29 participants (16 males and 13 females) from India and 33 participants (22 males and 11 females) from Iran [Table 8]. The subject recruitment and withdrawal is summarised in Diagram 1.

Diagram 1: The subject recruitment and withdrawal



3.3 Materials used for data collection

- Blood Collection Set 21G: (BD Vacutainer®, NJ, USA)
- Body composition monitor: (Model BC 541, Tanita corporation, China)
- Citrate blood collection tube 4.5ml: (BD Vacutainer®, NJ, USA)
- Dietary questionnaire: (Cancer Council, Victoria , Australia)
- Examination gloves: (Labserv, Victoria, Australia)
- Food frequency questionnaire: (Cancer Council of Victoria, Australia)
- Human Adiponectin ELISA kit: (Life Research Pty Ltd, Victoria, Australia)
- Human ELISA kit for Plasminogen Activator Inhibitor 1 (PAI1), Life Research Pty Ltd, Victoria, Australia
- Human ELISA kit for Vascular Cell Adhesion Molecule 1 (VCAM1), Life Research Pty Ltd, Victoria, Australia
- Human E-Selectin ELISA kit, Life Research Pty Ltd, Victoria, Australia
- International physical activity questionnaire (IPAQ)
- Laboratory centrifuge: Hettich zentrifugen, Germany
- Lunar Prodigy Pro: General Electric Company, USA
- Microcentrifuge tube 1.5 ml: Labserv, Victoria, Australia
- Multiple sample luer adapter: BD Vacutainer®, NJ,USA
- One Use Holder: BD Vacutainer®, New South Wales, NJ, USA
- Plain plastic vial 5 ml: Lomb Scientific Pty. Ltd., WA, Australia
- Plastic transfer pipettes 1ml: Livingstone international Pty. Ltd. NSW, Australia
- Portable stadiometer: Mentone Education Centre, design number 1013522, Victoria, Australia
- Skin cleaning swabs saturated with 70% v/v Isopropyl Alcohol BP: BSN medical (Aust) Pty.Ltd., Victoria, Australia
- Sphygmomanometer: empire® N - Stand model, Riester, Germany
- SST™ II Advance blood collection tube 10ml: BD Vacutainer®, NJ, USA
- Washable patient Gown

3.4 Methods of data collection

A summary of different steps of data collection and the clinical assessment protocol used in this study is presented in Table 9.

Table 9: Summary table describing different steps of data collection and clinical assessment protocols

A. Introductory Phase

1. Recruitment via different methods described in Section 3.2.1
2. Screening of respondents via online screening questionnaire/ telephone
3. Contact with eligible volunteers to arrange an appointment for clinical examination date, and to send food frequently questionnaire.

B. Clinical assessment protocols

1. On the morning of clinical examination date, participants attended at the Health Service Centre, Curtin University, following an overnight fast of 10-14 hours
2. Upon arrival, volunteers received the participant information sheet explaining the study's procedures and protocols in details. The written consent form was then obtained.
3. Participants were then asked to empty their bladder and collect a midstream urine sample.
4. Anthropometric measurements were taken with volunteers dressed in light indoor clothing, without shoes and an empty bladder.
5. Volunteers were then asked to take a rest of 15 minutes prior to blood pressure assessment and blood sampling.
6. Systolic and diastolic blood pressures were taken using the blood pressure manometer with the appropriate adult cuff size.
7. Blood samples were then taken through venepuncture. The separated plasma and serum were stored at -80º C.
8. The Food frequency questionnaire and physical activity questionnaire completed by participants were then checked by investigators.
9. Lastly, body composition assessment was done using the method of whole body dual energy x-ray absorptiometry (DEXA) available in the school of physiotherapy at Curtin University.

3.4.1 Introductory phone conversation

After a primary screening, volunteers who met the inclusion criteria received overall information about the study via phone conversation and email. They also received answers to questions they had. Their questions were usually about the eligibility conditions, the time that they needed to allocate for their contribution in the study, their medical history as well as their appointment. Participants were also instructed to fast overnight between 10-14 hours before attending in out-patient clinic at Curtin University for clinical assessment explained in below.

3.4.2 Clinical assessment protocols

Clinical assessments including anthropometrical, biomedical, biophysical variables were conducted in outpatient clinic at the Health Service Centre; and the research room at Health Sciences Building, Curtin University, Bentley Campus, Western Australia. On presentation to the clinic, volunteers received the participant information sheet [Appendix 3] explaining the study's procedures and protocols in details. Then, they completed a written consent form and signed it before clinical examination and phlebotomy [Appendix 4].

3.4.2.1 Anthropometrical measurement

Anthropometric measurements were taken with volunteers dressed in light indoor clothing, without shoes and an empty bladder. Participants were weighed on a calibrated portable electronic scale to the nearest 0.1 kg. Height was measured with a portable stadiometer (Mentone Education Centre) to the nearest 0.5 cm with participants in stocked feet, standing straight against a wall. Body Mass Index (BMI) was calculated as weight/height^2 (kg/m^2) and classified into normal weight (BMI<25), overweight (25≤BMI<30) and obesity (BMI ≥30).

Waist circumference was measured twice in the standing position, halfway between the lateral lower margin of ribs and the iliac crest on hip bone, with abdomen relaxed, arms relaxed at the sides and feet collected together. Hip circumference was measured at the widest horizontal point over the buttocks. The average of two measurements to the nearest 0.1 cm, using a plastic measuring-tape, was taken the final record. Waist circumference was measured according to the WHO recommendation and classification for different ethnic groups (Gibson 2005; WHO

2005). Waist hip ratio (WHR) was calculated as the ratio between waist and hip circumferences.

3.4.2.2 Blood pressure measurement

After the anthropometrical measurements, participants were asked to take a rest of about 15 minutes prior to blood pressure assessment to establish their systolic and diastolic pressures. Systolic (SBP) and diastolic (DBP) blood pressure were taken using the blood pressure manometer (Riester, Germany) with the appropriate adult cuff size. The average of three times measurements on the left arm with 5 minutes interval; and the subjects in supine position was recorded.

3.4.2.3 Biomedical assessment

Blood samples were taken through venepuncture into plasma and serum vacutainer tubes by qualified nurse in the Health Service Centre at Curtin University. Blood samples were centrifuged in the Laboratory centrifuge, [Hettich zentrifugen, Germany], at RCF 2000 g for 10 minutes for both plasma and serum tubes. However, serum tubes were left at the normal room temperature (18 - 25º C) for 15 to 30 minutes in vertical position to be clotted prior to centrifugation. The separated plasma and serum were stored in 1.5 mL microcentrifuge tubes at -80º C.

The fasting samples were analysed for glucose, insulin, hs-CRP, triglyceride, total cholesterol, LDL and HDL cholesterol, VCAM-1, Adiponectin and E-selectin.

For urine samples, participants were asked to empty their bladder and take a midstream urine sample. Ten mL of each urine sample was stored in two separate 5 mL plain vials at -80º C, until analysis for albumin and creatinine.

Enzymatic colorimetric assays on a general chemistry analyser were used to determine the levels of serum glucose, triglyceride and total cholesterol levels. The concentration of serum HDL cholesterol was measured using an appropriate direct method (Ultra HDL assay). All of these analysis were performed using Abbott diagnostic kits (Abbott laboratories, IL, USA) with a between- and within-run coefficient of variation <4.3%. LDL cholesterol was calculated using a modified

version of the Friedewald equation (Friedewald, Levy, and Fredrickson 1972) with quantities in mmol/L.

Insulin concentrations were measured by the Abbott Architect insulin assay. The derived concentration of fasting glucose and insulin were used to calculate the homeostatic model assessment (HOMA) score through the related equation below (Bonora et al. 2000). This method was defined and used for first time by Matthews and et al. in 1985 (Matthews et al. 1985).

$$HOMA = \frac{fasting\ insulin\ \left(\frac{mIU}{L}\right) \times fasting\ glucose\ \left(\frac{mmol}{L}\right)}{22.5}$$

A score > 2.5 signifies low insulin sensitivity in adults (Keskin et al. 2005).

Serum hs-CRP was assessed by nephelometry using a BNII analyser (Siemens Healthcare Diagnostic Inc. Newark, DE, USA) with between and within-run coefficient of variation of 8.4% and 5.7% respectively.

The albumin and creatinine levels were assessed to determine albumin/creatinine ratio in the fasting spot urinary samples. An albumin excretion ≥ 30 and < 300 mg/g creatinine was classified as microalbuminuria. Clinical albuminuria was detected in the present of an albumin creatinine ratio ≥300 mg/g (Molitch et al. 2004). The level of albumin in urine samples were assessed by the Abbott Micro-albumin assay, with between and within-run coefficient variation of 12.9% and 7.4% (Wako Pure Chemical Industries, Ltd. Osaka, Japan).

ELISA assays were used to analyse VCAM-1 (USCN Life Science Inc., Houston, USA), Adiponectin (Assaypro Inc., Missouri, USA) and E-selectin (Cusabio, Hubei, China) respectively. All ELISA assays were done at Curtin University and the remainder were undertaken by the biochemistry department at Royal Perth Hospital laboratory.

3.4.3 Dietary intake assessment

Usual dietary habits over the 12 past months were assessed using the validated food frequency questionnaire developed by the Cancer Council of Victoria, Australia [Appendix 5] (Giles and Ireland 1996; Hodge et al. 2000). This semi-quantitative dietary questionnaire is established specifically for use in Australian adults; and includes 74 food items with 10 frequency response options extending from 'Never' to '3 or more times per day'.

It also included 3 photographs of scaled portions for four foods (used to calculate a serving size calibrator), questions about the overall frequency of fruits and vegetables intake (used to calibrate the overestimation of these items in the food list), and questions on some food intakes like bread that do not fit into the frequency format simply.

In addition, the 74 food items were categorized into four different groups:
A) Cereal foods; sweets and snacks;
B) Dairy products, meats and fish;
C) Fruit and
D) Vegetables.

Moreover, the assessment of alcoholic beverages intake was covered by a set of separate questions. The output of the questionnaire comprised 35 nutrients such as total carbohydrate and fat, protein; and total saturated monounsaturated and polyunsaturated fatty acids (Cancer Council Victoria 2009).

Participants received the dietary questionnaire and were instructed on how to complete it at home prior to attending the clinic on the clinical examination date (the day on which patient samples and anthropometric measurements were taken) in order to fill out it at a more convenient time. However, they given additional guidance during clinical examination, if they have had any questions or concerns. Then, the filled questionnaires were checked by the researcher to ensure they were completed satisfactorily; and any probable errors were edited in-situ.

Dietary questionnaires were analysed by the Cancer Council Victoria, Australia using the related software. The software calculates the weight of each food item according to the serving size recorded respond by individuals and multiplies with the frequency of consume. The frequency scale used for the analysis of above 74 food items is shown in Table 10.

Table 10: The frequency scale uses the food items

Recorded respond	Frequency	Daily equivalent frequency
1	Never	0
2	Less than once per month	0.02
3	1-3 times per month	0.07
4	Once per week	0.14
5	Twice per week	0.28
6	3-4 per week	0.5
7	5-6 per week	0.78
8	Once per day	1
9	Twice per day	2
10	3 or more per day	3

Cancer Council Victoria (Giles and Ireland 1996)

The final outcomes are classified in different formats including:

1. Raw data
2. Nutrients computed from food without alcoholic beverages (including carotenoids and fatty acids, glycaemic index and glycaemic load),
3. Nutrients from alcoholic beverages,
4. Nutrients from food intakes, and
5. An error report

All derived information classified in above categories show the total energy received from carbohydrate, protein and fat including total saturated fatty acids, monounsaturated fatty acids and polyunsaturated acids and other nutrients in every individual. The analysis outcomes also demonstrate the amount of the main minerals, vitamins and dietary fibres consumed by participants.

3.4.4 Physical activity

Participants' physical activity level was assessed using the short version of the self-administrated international physical activity questionnaire (IPAQ). The validity and reliability of this questionnaire has been tested in over 12 countries, including Australia (Craig et al. 2003). The questionnaire assesses three specific types of activities including walking, moderate-intensity and vigorous-intensity activities (described through the questionnaire along with some examples [Appendix 6]) during a period of one week.

They cover the activities undertaken through four comprehensive domains including:

1) leisure time physical activity,
2) domestic and yard activities,
3) work-related physical activity,
4) Transport-related physical activities.

Data collected from the questionnaires were analysed in a continuous scoring format. Based on the level of intensity, each group of activities was assigned a metabolic equivalent score (METs) derived from the reliability study undertaken in 2000-2001. The Met score for walking, moderate-intensity and sever-intensity activities are 3.3, 4.0 and 8.0, respectively (Craig et al. 2003). The score for each group of activities was calculated by multiplying the time spent on those activities (in minutes) by the assigned MET value. The total value for one week was the sum of the scores (MET-minutes/week) calculated for each activity:

Total physical activity MET-minutes/week = sum of Walking [1]+ Moderate [2]+ Vigorous [3] MET minutes/week scores:

1. Walking MET-minutes/week = 3.3 * walking minutes * walking days/week
2. Moderate MET-minutes/week = 4.0 * mod.-intensity activity min * moderate days/week
3. Vigorous MET-minutes/week = 8.0 * vig.-intensity activity min * vig.-intensity days/week

3.4.5 Body composition

Body composition assessment was the last clinical parameter which was measured, done through body scanning in the school of physiotherapy at Curtin University. For this purpose, the method of whole body dual energy x-ray absorptiometry (DEXA) was used [Lunar Prodigy (GE Corporation, USA)]. It is reliable, economical and safe method compared to other methods such as CT scan as it uses low dose x-ray of two different energy levels (Van Loan and Mayclin 1992). Female participants were rechecked to ensure they are not pregnant or breastfeeding. Then, they were informed about the scanning procedure in detail. Participants also were requested to change into a laboratory gown and remove all personal metal items like jewellery or watches prior to the scan.

3.5 Statistical analysis

SPSS statistics package for windows, version 21 (IBM Corporation, USA) was used for all statistical analysis. The analysis started with descriptive statistics. Cross-tabulation analysis was used to obtain a frequency distribution of categorical variables, and to compare different definitions of metabolic syndrome. For continuous variables, including anthropometric, biomedical, dietary and physical activity measurements, data are presented as mean ± standard deviation (SD) (in the text and tables), and mean ± standard error of mean (SEM) (in charts). All continuous variables were also assessed for normality. Transformation or a nonparametric test, like Shapiro-Wilk, was used if the variable was not normally distributed.

To assess variance equality, the Leven test was used between categorical and continuous variables.

The level of agreement between different definitions of metabolic syndrome was assessed using the kappa coefficient. Kappa values lower than 0.40 were considered as a “poor” agreement beyond chance, values between 0.40 and 0.75 indicated as “fair” to “good” agreement beyond chance, and coefficients 0.75 and greater were

considered as “agreement” beyond chance (Landis and Koch 1977; Fleiss 1981), Independent t tests were used to compare anthropometrics with metabolic variables among genders.

One way ANOVA with Tukey’s HSD adjustment was used to compare the categorical and all normal continuous variables which met other parametric conditions for this purpose. In addition, the association between continuous variables were evaluated using Pearson Correlation using SPSS software. Some variables, such as fasting blood glucose, which did not meet the parametric conditions were assessed by related non-parametric tests such as the Kruskal Wallis test.

3.6 Ethical Considerations

The study was conducted according to the guidelines laid down in the Helsinki declaration and the National Health and Medical Research Council Guidelines (NHMRC, 2007) and all protocols involving human subjects were approved by the Curtin University Human Research Ethics Committee (HR 179/2008). All participants participated voluntarily, provided informed consent and were made aware that they could withdraw at any time from the study. The results were also shared with the participants.

Chapter 3 has provided an overview of the research methods used to test the hypothesis and address the objectives. The next chapter presents the results of the study.

Chapter 4

Results

Introduction

This chapter provides the results in six sections including the overall characteristics of the study groups, comparison of the different definitions of metabolic syndrome, dietary configuration and physical activity levels, assessment the components of metabolic syndrome, the effects of ethnicity on endothelial dysfunction and assessment of adiponectin in three ethnic groups. Firstly, an overview of basic measures is given and then these are evaluated in relation to other derived indices and to features such as diet and physical activity.

4.1 Overall characteristics

One hundred and thirty-four individuals responded to the advertisements and invitation to participate in the study. Initially, the potential volunteers were screened for the inclusion and exclusion criteria via telephone and email. Of 106 volunteers who seemed suitable, 97 were considered eligible during final screening at the clinic by the investigator. All ninety-seven participants (49 males and 48 females) from three ethnic groups in Western Australia completed the assessments planned for this study.

The participants ranged in age from 19 to 74 years (46.2±13.7). As shown in the Table 11, participants with a background from European countries had higher mean age than Indians (55.6±11.7 vs. 38.2±11.5 y; $P<0.001$) and Iranians (55.6±11.7 vs. 43.2±12.5; $P<0.001$). Participants also had a mean weight of 84.8±13.9 kg. There was no significant difference in the mean weight of participants in three ethnic groups (Europeans: 86.6 ±14.2 kg, Indians: 80.1±12.7 kg, Iranians: 86.9±15.9 kg; All P values > 0.05).

The overall mean BMI was 29.95 (kg/m^2), ranging from 25.0 to 41.1, with a higher, but not significant difference, in women than men, 30.1 (±4.2) and 29.8 (±3.4) respectively; (P=0.67). In all, 56.7% of the 97 participants were overweight, whereas 43.3% of them were classified as obese cases.

The mean WC, HC and WHR found were 99.4 ±11.0 cm, 106.1 ±9.3 cm and 0.09 ±0.1 respectively. Participants had mean total body fat percentage of 37.3 (±7.9), truncal body fat percentage 55.2 (±7.1) and total fat mass (g) / total lean mass (g) percentage 65.9 (±22.7). Also, they had mean SBP of 121.3 ±13.97 mmHg, DBP of 79.44 ±1.13 mmHg, fasting plasma glucose of 5.23±0.11 mmol/L, serum triglyceride of 1.45±0.08 mmol/L, total cholesterol of 5.20±0.10 mmol/L, HDL-cholesterol of 1.22±0.03 mmol/L and LDL-cholesterol of 3.31±0.08 mmol/L.

Table 11: Anthropometric and metabolic characteristics of participants in each ethnic group, unadjusted for age or sex

Participants' characteristics	European		Indian		Iranian		P-value 1[a]	P-value 2[a]	P-value 3[a]	Between-groups P-value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range				
Age (y)	55.6 (11.07)	21-74	38.2 (11.49)	24-64	43.2 (12.45)	18.5-70	<0.001	<0.001	0.220	<0.001
Weight (kg)	86.6 (14.2)	58-112	80.14 (12.71)	55.5-96.9	86.92 (15.1)	57-134	0.149	0.995	0.130	0.10
Body mass index (kg/m^2) [b]	30.78 (3.9)	25.0-41.1	29.02 (3.7)	25.2-41.0	29.88 (3.8)	25.1-40.5	0.137	0.572	0.618	0.16
Waist circumference (cm)	102.3 (11.1)	84.0-132.0	96.1 (10.0)	72.0-121.0	99.2 (11.0)	78.0-129.0	0.062	0.460	0.502	0.08
Hip circumference (cm)[b]	108.7 (10.7)	91.0-141.0	102.52 (8.1)	92.0-124.0	106.4 (8.0)	90.0-128.0	0.019	0.592	0.182	0.03
Waist/Hip ratio	0.942(0.08)	0.77-1.08	0.937(0.07)	0.79-1.04	0.932(0.08)	0.76-1.07	0.957	0.831	0.959	0.84
Systolic blood pressure (mmHg)[b]	125.4 (15.2)	104-160	120.6 (14.2)	95-160	117.6 (11.5)	98-142	0.346	0.059	0.690	0.07
Diastolic blood pressure (mmHg)	83.0 (10.2)	64-103	80.2 (10.4)	50-105	75.06 (11.4)	56-94	0.554	0.008	0.152	0.01
Fasting glucose (mmol/L)	5.6 (1.10)	4.7-9.8	5.22 (1.00)	4.3-8.7	4.85 (0.99)	3.8-9.7	0.017	<0.001	0.073	<0.001
Fasting insulin (µIU/mL)	10.6 (5.65)	3.6-23.9	9.76 (4.22)	3.6-20.8	8.35 (5.98)	1.3-28.7	0.963	0.061	0.135	0.06
hs-CRP (mg/L) [b]	4.37 (5.34)	0.4-24.6	3.54 (3.66)	0.3-14.2	2.75 (3.09)	0.2-15.2	0.949	0.659	0.858	0.68
Total cholesterol (mmol/L)	5.64 (0.81)	4.0-7.2	5.21 (1.04)	3.4-7.3	4.72 (0.81)	2.5-6.2	0.14	<0.001	0.08	<0.001
LDL-chol (mmol/L)	3.55 (0.72)	1.6-5.0	3.38 (0.89)	1.2-5.4	3.00 (0.75)	1.4-4.2	0.661	0.014	0.150	0.02
HDL-chol (mmol/L)	1.38 (0.32)	0.7-2.4	1.13 (0.24)	0.8-1.7	1.12 (0.29)	0.7-1.9	0.003	0.001	0.983	<0.001
Triglycerides (mmol/L) [b]	1.54 (0.84)	0.6-3.8	1.53 (0.67)	0.6-3.3	1.30 (0.74)	0.3-3.5	0.956	0.294	0.205	0.18
HOMA score [c]	2.78 (1.97)	0.83-9.45	2.30 (1.13)	0.7- 4.68	1.80 (1.27)	0.22-5.74	0.785	0.011	0.082	0.03
Physical activity (MET/min)	3003.5 (3036.17)	219.00-15564.00	5090.65 (7019.39)	318.00-27888.00	5433.83 (6380.59)	930.00-25992	0.535	0.063	0.494	0.20

a. P1, P2 and P3 demonstrate P values between European and Indian, European and Iranian; and Indian and Iranian groups respectively; b. P-values were determined after the variable was log transformed; c. All P-values were determined using a one-way ANOVA with Tukey's HSD test, except for fasting glucose, fasting Insulin, HOMA and physical activity which were determined using a nonparametric test (Kruskal Wallis);hs-CRP, high sensitive C - reactive protein; LDL-chol, low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; HOMA, homeostatic model of assessment.

Table 12: Anthropometric and metabolic characteristics of participants in each ethnic group, after adjusting for age and gender

Participants' characteristics	European		Indian		Iranian		P-value 1[a]	P-value 2[a]	P-value 3[a]	Between-groups P-value
	Mean (SEM)	95% CI	Mean (SEM)	95% CI	Mean (SEM)	95% CI				
Weight (kg)	90.17(2.47)	85.26-95.09	78.56(2.42)	73.75-83.37	84.91(2.27)	80.41-89.41	0.002	0.131	0.053	0.009
BMI (kg/m^2)[b]	30.72(0.787)	29.16-32.28	29.11(0.77)	27.58-30.64	29.92(0.721)	28.49-31.36	0.145	0.443	0.387	0.34
WC (cm)	100.69(2.08)	96.55-104.83	97.75(2.04)	93.70-101.81	99.137(1.90)	95.34-102.93	0.352	0.595	0.614	0.65
HC (cm)[b]	107.74(1.82)	104.12-111.37	102.59(1.78)	99.04-106.14	107.10(1.67)	103.78-110.42	0.061	0.856	0.051	0.09
W/H	0.937(0.012)	0.914-0.960	0.952(0.011)	0.930-0.975	0.926(0.011)	0.905-0.947	0.399	0.490	0.090	0.24
SBP (mmHg)[b]	120.53(2.62)	115.31-125.74	123.82(2.56)	118.71-128.92	117.92(2.40)	113.14-122.69	0.422	0.473	0.094	0.24
DBP (mmHg)	80.75(2.09)	76.59-84.91	82.00(2.05)	77.93-86.07	75.17(1.91)	71.36(78.98)	0.692	0.059	0.014	0.03
hs-CRP (mg/L)[b]	4.64(0.832)	2.99-6.29	3.50(0.814)	1.88-5.11	2.80(0.76)	1.28-4.31	0.825	0.645	0.812	0.90
Total cholesterol (mmol/L)	5.40(0.17)	5.06-5.74	5.24(0.168)	4.90-5.57	4.68(0.157)	4.37-4.99	0.525	0.003	0.015	0.005
LDL-chol (mmol/L)	3.38(0.154)	3.07-3.68	3.37(0.15)	3.07-3.67	2.96(0.141)	2.68-3.24	0.980	0.055	0.044	0.06
HDL-chol (mmol/L)	1.28(0.05)	1.18-1.38	1.16(0.049)	1.06-1.26	1.16(0.046)	1.07-1.25)	0.125	0.102	0.987	0.21
Triglycerides (mmol/L)[b]	1.61(0.153)	1.31-1.91	1.52(0.15)	1.22-1.82	1.20(0.14)	0.92-1.48	0.98	0.037	0.028	0.04

a. P1, P2 and P3 demonstrate within - groups P values between European and Indian, European and Iranian; and Indian and Iranian groups respectively
b. P-values were determined after the variable was log transformed. All P-values were determined using a one-way ANOVA with Tukey's HSD test. BMI, body mass index; WC, waist circumference; HC, hip circumference; W/C, Waist/Hip ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure, hs-CRP, high sensitive C - reactive protein; LDL-chol, low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol

4.2 Comparison between the different definitions of metabolic syndrome

According to the WHO classification [see Section 2.2.1.1, Table 1 & Table 4], 28.6% of participants in the European group, 27.6% of those in the Indian group and 18.2% of those in the Iranian group were identified as having metabolic syndrome. These percentages changed to 22.9%, 37.9% and 27.3% respectively, when ATPIII criteria [see Section 2.2.1.3] were used as the basis of classification [Table 13].

Furthermore, there was an increased discrepancy when participants were classified with regard to EGIR and IDF criteria [see sections 2.2.1.2 & 2.2.1.5], namely 17.1% of European participants, 27.6% of Indians and 21.2% of Iranians according to EGIR definition, compared to 28.6%, 41.4% and 27.3%, respectively based on IDF definition.

Table 13: Percentages of participants classified as having metabolic syndrome based on four commonly used definitions

Ethnicity / Definition		WHO% (n)	EGIR% (n)	ATPIII% (n)	IDF% (n)
Europeans (n=35)	Overall	28.6(10)	17.1(6)	22.9(8)	28.6(10)
	Male(11)	27.3(3)	9.1 (1)	27.3(3)	36.4 (4)
	Female(24)	29.2(7)	20.8 (5)	20.8(5)	25.0 (6)
Indians (n=29)	Overall	27.6(8)	27.6 (8)	37.9 (11)	41.4 (12)
	Male (16)	25(4)	25 (4)	31.3(5)	37.5 (6)
	Female (13)	30.8(4)	30.8 (4)	46.2(6)	46.2(6)
Iranians (n=33)	Overall	18.2(6)	21.2 (7)	27.3 (9)	27.3 (9)
	Male (22)	9.1(2)	18.2 (4)	22.7(5)	22.7(5)
	Female (11)	36.4(4)	27.3 (3)	36.4(4)	36.4(4)
Total (n=97)	Overall	24.7(24)	21.6 (21)	28.9 (28)	32 (31)
	Male (49)	18.4(9)	18.4(9)	26.5 (13)	30.6 (15)
	Female(48)	31.3(15)	25 (12)	31.3(15)	33.3(16)

The total percentage of participants meeting metabolic syndrome criteria was the highest for the IDF (32%) followed by ATPIII (28.9%), WHO (24.7%) and EGIR (21.6%), Also, metabolic syndrome was more prevalent among female participants relative to males, using four definitions [Table 13].

Table 15 presents the level of agreement between metabolic syndrome defined by WHO, EGIR, ATPIII and IDF in three ethnic groups. Four definition of metabolic syndrome showed different levels of agreement in Europeans, Indians and Iranians. Overall, there was an excellent agreement (see Section 3.5) between IDF and ATPIII definitions (κ=0.83). IDF and ATPIII also showed the highest agreement in European (κ =0.851) and Iranian (κ =0.847) groups. However, in Indians the highest concordance was observed between WHO and EGIR (κ =0.827). WHO definition also showed a good agreement (see Section 3.5) with metabolic syndrome defined by ATPIII and IDF.

Insulin resistance (based on the calculated HOMA score > 2.5) was identified in 91.7%, 90.5%, 67.9% and 67.7% of participants classified as having metabolic syndrome based on WHO, EGIR, ATPIII and IDF criteria, respectively. Also, the highest percentage of participants with insulin resistance was discovered by WHO definition (66.7%), followed by IDF (63.6%). However, ATPIII and EGIR failed to detect 42.4% of insulin resistant participants [Table 14].

Table 14: Number of participants with hyperglycaemia and insulin resistance classified as having metabolic syndrome based on four commonly used definitions

	WHO (n = 24)	**EGIR (n = 21)**	**ATPIII (n = 28)**	**IDF (n = 31)**
IR based on HOMA > 2.5 (n=33)	22 (66.7%)	19 (57.6%)	19 (57.6%)	21(63.6%)
Diabetes mellitus (n= 6)	5 (83.3%)	5 (83.3%)	5 (83.3%)	5 (83.3%)
IFG (n= 5)	3 (60%)	4 (80%)	4 (80%)	4 (80%)

Table 15: The level of agreement between metabolic syndrome defined by WHO, EGIR, ATPIII and IDF in three ethnic groups

Ethnicity / Definition		WHO	EGIR	ATPIII	IDF
European	WHO κ	1	0.682	0.553	0.580
	Sig.		<0.001	0.001	0.001
	EGIR κ	0.682	1	0.822	0.682
	Sig.	<0.001		<0.001	<0.001
	ATPIII κ	0.553	0.822	1	0.851
	Sig.	0.001	<0.001		<0.001
	IDF κ	0.580	0.682	0.851	1
	Sig.	0.001	<0.001	<0.001	
Indian	WHO κ	1	0.827	0.613	0.70
	Sig.		<0.001	0.001	<0.001
	EGIR κ	0.827	1	0.613	0.701
	Sig.	<0.001		0.001	<0.001
	ATPIII κ	0.613	0.613	1	0.784
	Sig.	0.001	0.001		<0.001
	IDF κ	0.70	0.701	0.784	1
	Sig.	<0.001	<0.001	<0.001	
Iranian	WHO κ	1	0.713	0.403	0.57
	Sig.		<0.001	0.017	0.001
	EGIR κ	0.827	1	0.343	0.507
	Sig.	<0.001		0.046	0.003
	ATPIII κ	0.403	0.343	1	0.847
	Sig.	0.017	0.046		<0.001
	IDF κ	0.57	0.507	0.847	1
	Sig.	0.001	0.003	<0.001	
Total	WHO κ	1	0.740	0.528	0.622
	Sig.		<0.001	<0.001	<0.001
	EGIR κ	0.740	1	0.593	0.637
	Sig.	<0.001		<0.001	<0.001
	ATPIII κ	0.528	0.593	1	0.830
	Sig.	<0.001	<0.001		<0.001
	IDF κ	0.622	0.637	0.830	1
	Sig.	<0.001	<0.001	<0.001	

The level of agreement was assessed using the kappa coefficient. WHO, world health organization; EGIR, European Group for the Study of Insulin Resistance; ATP III, Adult Treatment Panel III; IDF, International Diabetes Federation

4.3 Dietary characteristics and physical activity levels in three ethnic groups

Increased risks of metabolic syndrome in different populations can be due to the factors related to health behaviours. Accordingly, individuals participating in this study were also evaluated for dietary habits, nutrients intake and levels of physical activity. Different components of metabolic syndrome were then assessed among the ethnic groups after controlling for these factors, as potential confounders.

Overall, participants of this study had a mean (±SD) daily energy intake of 6708.08± 2941.18 kJ/day, carbohydrate intake of 175.93±8.13, protein intake of 79.17± 4.23 g/day and total fat intake of 62.39±3.15 g/day.

Using ANOVA analysis, ethnicity was significantly associated with the intakes of bread & cereal foods (P= 0.03), meat & fish (P<0.001), vegetable & legumes (P<0.001), and fruit (P=0.001) as well as nutrients of protein (P<0.001), cholesterol (P=0.01), potassium (P= 0.007), sodium (P=0.01) and magnesium (P=0.04).

Although, there was no significant difference between the amounts of carbohydrate taken by the three ethnic groups, they showed differences in regard to the intake of other nutrients [Table 16]. Namely, participants in Indian group had significantly lower intakes of protein (Indians: 55.2±37.6, Europeans: 83.5±31.4, Iranians: 95.7±46.0 g/day), magnesium (Indians: 219.1± 97.8, Europeans: 276.2±99.4, Iranians: 289.1±132.2 mg/day) and sodium (Indians: 1505.3±853.6, Europeans: 2103±851.0, Iranians: 2160.2±1037.3 mg/day) compared to Europeans and Iranians (all P-values between Indians vs. Europeans & Iranians <0.05).

Indian participants also had significantly lower intake of total daily energy intake (Indians: 5732.2±2772.3, Iranians: 7527.3±3239.1 KJ/day, P=0.02) and dietary fat (Indians: 52.7±31.5, Iranians: 67.7±31.6 g/day, P=0.04) compared to Iranians [Table 16].

As to be expected, the lower intake of protein in Indians was associated with the lower consumptions of meat & fish, (Europeans: 156.1±96.0, Indians: 60.5±140.3, Iranians: 192.8±135.8 g/day), as the main source of this nutrient [Table 17]. The highest and lowest consumption of vegetables & legumes per day were consumed by Europeans and Indians, respectively (Europeans: 162.8±87.1, Indians: 58.5±35.1, Iranians: 79.2±39.6 g/day), while participants in Iranian group consumed the highest amounts of fruits (Europeans: 225.4±162.5, Indians: 243.0±170.2, Iranians: 383.9±188.0 g/day) and breads & cereal foods (Europeans: 195.8±108.9, Indians: 174.9±100.1, Iranians: 254.9±155.5 g/day) in comparison with Europeans and Indians.

Correlation analysis showed a significant association between BMI and total fat intake (ρ=0.21, P= 0.04). We found no significant correlations between different energy/nutrients intakes and blood glucose and insulin, HOMA, SBP, DBP, serum total cholesterol and LDL-cholesterol. However, the levels of serum TG and HDL-cholesterol were significantly correlated with dietary intakes of total energy (TG: ρ=0.22 , P=0.03 ; HDL-C: ρ= - 0.25, P= 0.01), carbohydrate (TG: ρ= 0.21, P= 0.04; HDL-C: ρ= - 0.32 , P= 0.002), total fat (TG: ρ= 0.22, P=0.03 ; HDL-C: ρ= - 0.21, P= 0.04) and saturated fat(TG: ρ= 0.23 , P=0.02 ; HDL-C: ρ= -0.24, P=0.02).

As shown in Table 11, Iranian participants had non- significant trends to a higher mean physical activity levels relative to Europeans (P=0.06) and Indians (P=0.49). Meanwhile, there was a significant difference between mean physical activities levels determined in male and in female participants (M: 5667.3± 6241.3; F: 3216.1 ±4832.2, P = 0.01).

In partial correlation analysis, we found no significant association between the levels of physical activity and blood glucose, insulin, insulin resistance (indicated by HOMA), serum lipid profile, or indices of obesity (BMI, WC, W/H), after controlling for age and gender.

Table 16: Characteristics of the dietary intake by three ethnic groups

Ethnicity/ Nutrient	Europeans		Indians		Iranians		P-value 1[a]	P-value 2[a]	P- value 3[a]	Between-groups P-value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range				
Energy [b] (KJ/d)	6744.2 (2599.3)	2675.6-12789.2	5732.2 (2772.3)	2591-15594.4	7527.3 (3239.1)	3192.4-19228.0	0.174	0.555	0.019	0.02
Carbohydrate (g/d)	160.75 (72.44)	46.6-342.6	164.8(76.3)	70.7-332.4	201.8 (86.6)	88.3- 446.6	0.978	0.085	0.158	0.07
Protein [b] (g/d)	83.46 (31.41)	33.4-163.1	55.2(37.6)	16.5-223.0	95.7(46.0)	31.05-279.5	<0.001	0.554	<0.001	<0.001
Total Fat [b] (g/d)	65.36 (4.92)	26.0-130.3	52.7 (31.5)	19.5-169.7	67.7(31.6)	31.5-189.2	0.085	0.915	0.037	0.03
Sat. Fat [b] (g/d)	26.21(11.39)	10.7-47.2	23.8 (14.0)	9.54-75.46	27.4 (13.5)	7.40-72.09	0.530	0.967	0.400	0.39
Poly. Fat [b] (g/d)	9.49 (5.77)	2.65-26.69	6.69 (4.51)	1.52-19.42	8.83 (4.86)	3.59-28.28	0.024	0.992	0.035	0.01
Mono. Fat [b] (g/d)	23.76 (11.09)	8.91-53.57	17.42(11.57)	5.58-61.04	24.57(11.79)	11.11-71.45	0.008	0.907	0.003	0.002
Cholesterol [b] (mg/d)	280.6(120.0)	123.4-605.0	201.7(177.3)	44.9-898.1	310.8(144.9)	76.2-730.8	0.001	0.819	<0.001	<0.001
Fibre (g/day)	19.45(8.59)	2.72-35.50	15.80(8.67)	3.67-35.84	20.88(9.33)	7.23-49.71	0.235	0.784	0.068	0.08
Calcium (mg/d)	848.53(280.5)	379.5-1397.6	743.79(320.2)	187.0-1321.2	878.54(311.3)	357.8-1895.8	0.358	0.912	0.194	0.20
Magnesium [b] (mg/d)	276.19 (99.36)	110.0-532.6	219.1(97.8)	73.5-478.2	289.1(132.2)	112.6-819.6	0.033	0.944	0.016	0.01
Sodium [b] (mg/d)	2103.7(851.0)	660.30-4199.7	1505.3(853.6)	504.3-4423.0	2160.2(1037.3)	687.4-5867.1	0.004	0.999	0.004	0.001
Potassium [b] (mg/d)	2564.0 (810.1)	1186.4-4124.1	1946.0(879.8)	809.7-4971.0	2585.9 (929.2)	984.7-5901.3	0.003	0.999	0.003	0.001

a. P1, P2 and P3 demonstrate within- groups P- values between European and Indian, European and Iranian; and Indian and Iranian groups respectively
b. P-values were determined after the variable was log transformed. All P-values were determined using a one-way ANOVA with Tukey's HSD test; Sat. Fat, saturated fat; Mono. Fat, mono unsaturated fat; Poly. Fat, poly unsaturated fat.

Table 17: The main source of dietary intake along with the amount of dietary consumption by three ethnic groups

Ethnicity/ Food intake	Europeans		Indians		Iranians		P- value 1[a]	P- value 2[a]	P- value 3[a]	Between-groups P-value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range				
Breads& Cereal foods [b] (g/day)	195.84 (108.85)	24.30-494.70	174.87 (100.12)	29.80-422.70	254.85 (155.48)	65.70-663.50	0.783	0.156	0.044	0.04
Meat& Fish [b] (g/day)	156.06 (96.02)	34.10-466.20	60.47 (140.29)	0.00-754.40	192.81 (135.80)	30.0-706.50	<0.001	<0.001	0.534	<0.001
Dairy [c] (g/day)	367.35 (206.52)	35.60-950.00	406.06 (219.07)	6.90-906.00	337.74 (156.78)	80.40-932.80	0.964	0.955	0.858	0.87
Fruits [c] (g/day)	225.40 (162.50)	19.40-864.20	242.98 (170.18)	40.0-718.50	383.85 (188.01)	61.90-1019.10	0.916	<0.001	0.003	<0.001
Vegetables& Legumes [c] (g/day)	162.82 (87.13)	17.00-448.60	58.47 (35.15)	9.70-138.70	79.19 (39.56)	12.90-170.30	<0.001	<0.001	0.079	<0.001
Edible fat [d] (g/day)	7.40 (9.25)	0.00-42.00	8.81 (11.52)	0.00-42.00	6.33 (8.98)	0.00-28.00	0.886	0.218	0.241	0.39

a. P1, P2 and P3 demonstrate P- values between European and Indian, European and Iranian; and Indian and Iranian groups respectively
b. P-values were determined after the variable was square-root transformed.
c. P-values were determined after the variable was log transformed.
d. P-values were determined using non-parametric test.
All P-values were determined using a one-way ANOVA with Tukey's HSD test, except for edible fat which was determined using a nonparametric test (Kruskal Wallis).

4.4 Assessment of metabolic syndrome criteria

4.4.1 Anthropometric measurements

European, Indian and Iranian study participants had mean BMI (±SD) of 30.8 (±3.9), 29.0 (±3.7) and 29.9 (±3.8) kg/m^2, respectively. The higher BMI in European participants was accompanied with a higher body fat percentage (derived from DEXA analysis) when they were compared with Indians (39.6±8.2% vs. 37.2±7.6 %, P=0.45) and Iranians (39.6±8.2% vs. 35.1±7.3%, P<0.05) [Table 18& Figure 9].

Using multiple regression analysis, a model including ethnicity, sex, BMI, physical activity, and total energy intake could predict 79.5% and 78.7 % of variability in total body fat percentage and total fat-to-lean mass ratio in the participants, respectively. Interestingly, after adjustment for age and gender Indians had a significantly higher total body fat percentage when they were compared with Europeans (38.68±0.75% vs. 36.13±0.76%, P<0.05) and Iranians (38.68±0.75% vs. 36.67±0.70%, P<0.05) with the same BMI [Figure 10].

The effect of ethnicity on the body fat distribution was assessed by evaluating the participants' truncal body fat percentages. Participants in Indian group had a higher mean (±SD) truncal body fat percentage (56.4±5.3) relative to European (54.8±6.7) and Iranian (54.5±8.6) groups, although the differences were not statistically significant (P values >0.05) [Figure 9].

Using stepwise backward multiple regression, truncal body fat percentage was significantly related to ethnicity (P=0.002; for Europeans: β= - 0.007; for Indians: β=2.5; Iranians: β=0, as the reference group), age (β= 0.1, P=0.002), sex (P<0.001; for female: β= - 10.2; for male: β= 0, as the reference gender) and waist circumference (β= 0.2, P<0.001).

Neither participants' energy& nutrient intakes nor their physical activity levels had significant effect on the body fat distribution. There was no change in the trend, but the differences between the Indians' truncal body fat percentages (estimated mean±SEM) and those determined in Europeans and Iranians increased after

adjustment for age, sex and WC (European: 54.4±1.0%, Indian: 57.8±0.9%, Iranians: 53.3±0.9%) [Figure 10].

Table 18: Body composition characteristics derived from DEXA

Participants' characteristics	Europeans		Indians		Iranians		P-value 1[a]	P-value 2[a]	P-value 3[a]	Between-groups P-value
	Mean (SD)	Range	Mean (SD)	Range	Mean (SD)	Range				
Total body mass (kg)	85.80(14.26)	56.44-109.84	79.19(12.58)	55.06-96.48	86.16(13.34)	63.86-129.59	0.129	0.993	0.110	0.08
Total fat mass (kg)	33.88(9.34)	19.95-62.31	29.21(6.78)	21.78-45.57	30.40(8.52)	12.74-53.21	0.072	0.204	0.842	0.07
Total lean mass (kg)	49.16(11.50)	32.71-76.35	47.25(10.80)	29.58-64.20	52.76(9.18)	35.84-80.07	0.751	0.343	0.106	0.12
Total bone mass (kg)	2.76(0.52)	1.96-4.03	2.74(0.56)	1.75-4.02	30.08(0.47)	2.07-3.91	0.984	0.122	0.104	0.07
Total body fat (%) [c]	39.60(8.21)	23.32-57.02	37.24(7.58)	24.29-53.08	35.07(7.31)	18.91-51.08	0.445	<0.05	0.516	0.06
Total body lean mass (%) [d]	57.16(7.95)	40.58-73.49	59.30(7.27)	43.62-71.22	61.40(7.03)	45.86-76.68	0.489	0.054	0.511	0.07
Total body Fat/Lean mass ratio	0.73(0.24)	0.32-1.41	0.65(0.22)	0.34-1.22	0.59(0.20)	0.24-0.77	0.413	0.042	0.53	0.05
Truncal fat mass (kg)	18.48(5.38)	9.58-35.80	16.45(3.96)	11.41-24.61	16.68(5.59)	6.77-28.99	0.252	0.313	0.982	0.21
Total trunk mass (kg)	43.50(8.85)	26.12-63.58	39.73(7.16)	26.20-51.72	42.49(1.55)	25.45-72.97	0.181	0.873	0.407	0.20
Truncal body fat percentage (%)[e]	54.81(6.74)	43.72-70.24	56.37(5.31)	47.78-63.87	54.55(8.62)	32.72-67.47	0.657	0.987	0.571	0.56
Truncal fat percentage (%)[f]	42.40(7.14)	27.46-59.08	41.42(6.17)	27.98-57.43	38.57(7.65)	22.25-53.70	0.846	0.07	0.256	0.07
Truncal fat/ lean ratio	0.79(0.23)	0.39-1.50	0.75(0.21)	0.41-1.42	0.68(0.22)	0.29-1.23	0.811	0.105	0.371	0.12
Z-Score	1.26(0.95)	-0.57-4.23	2.20(1.09)	0.00-4.21	2.04(1.30)	-0.46-4.33	0.003	0.014	0.836	0.002

a. P1, P2 and P3 demonstrate P- values between European and Indian, European and Iranian; and Indian and Iranian groups respectively; b. P-values were determined after the variable was log transformed; c. Total body fat percentage was calculated using following equation: Total fat mass (kg)/Total body mass (kg) ×100; d. Total body lean mass percentage was calculated using following equation: Total lean mass (kg)/Total body mass (kg) ×100; e. Truncal body fat percentage was calculated using following equation: Truncal fat mass (kg)/Total fat mass (kg) ×100; f. Trunk fat percentage was calculated using following equation: Truncal fat mass (kg)/Total trunk mass (kg) ×100. All P-values were determined using a one-way ANOVA with Tukey's HSD test.

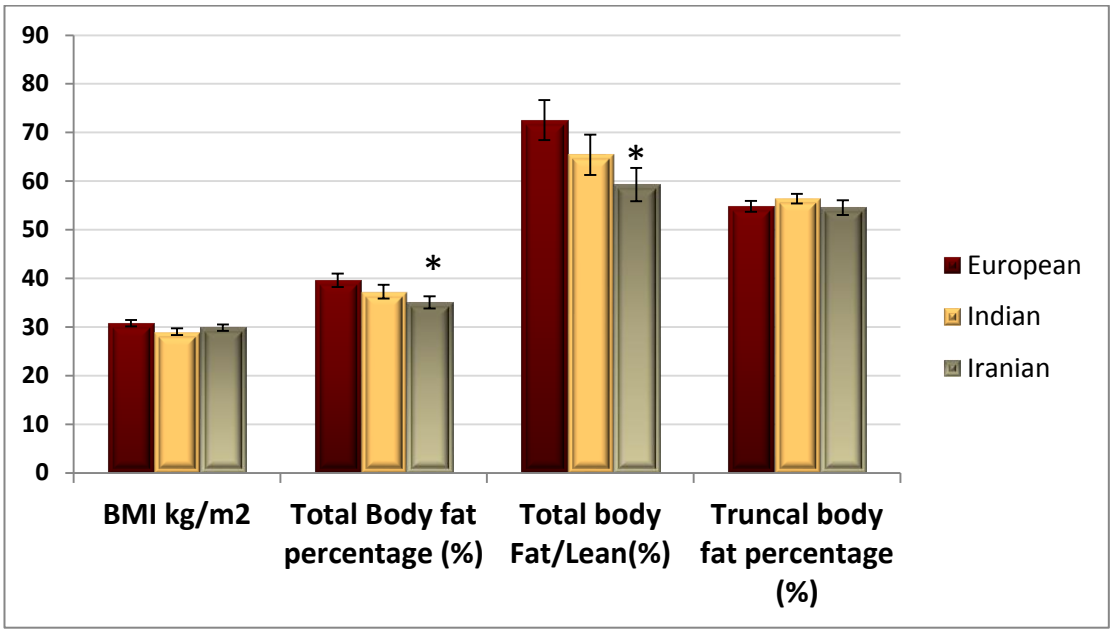


Figure 9: Comparison between BMI, total body fat percentage and fat distribution in three ethnic groups. *Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with European group; Truncal body fat percentage, Truncal fat mass /Total body fat ×100; Total body fat percentage, Total fat mass/Total body mass×100.*

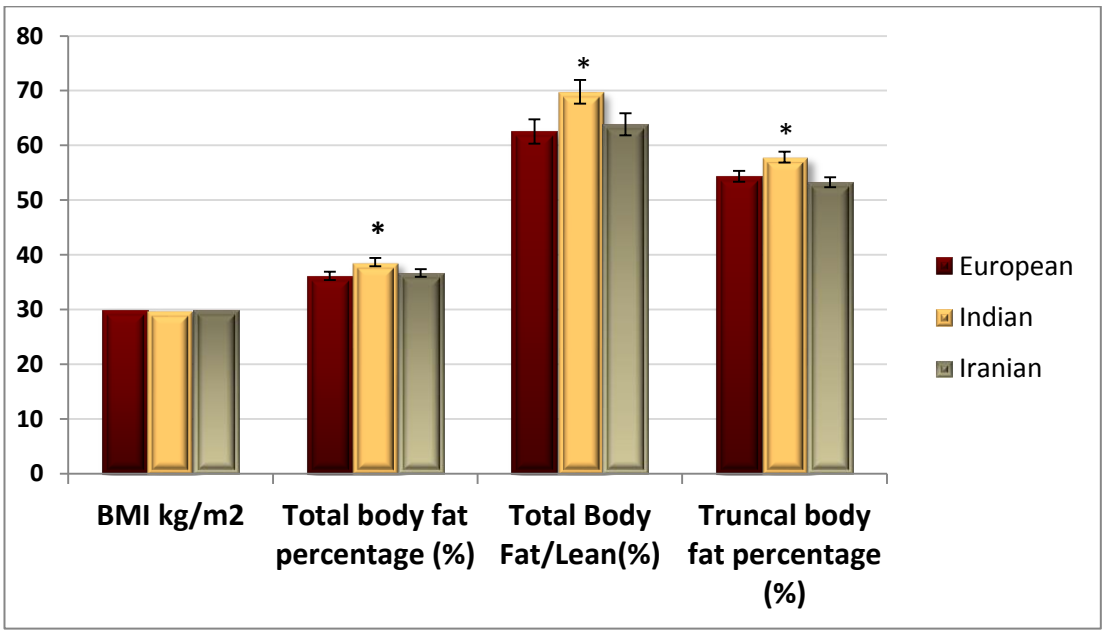


Figure 10: Comparison between the estimated mean values of BMI, total body fat percentage and fat distribution in three ethnic groups, after adjustment for potential confounders (age, sex and BMI). *Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with European and Iranian groups.*

A pattern similar to that observed for BMI and total body fat percentage was also found when the three ethnic groups were compared for WC, truncal fat percentage and truncal fat/lean ratio, as indices of central obesity [Table 18]. Indian and European participants had the lowest and the highest mean (±SD) values of WC [Table 11], respectively. Higher WC in European group was accompanied with tendencies toward higher truncal fat percentage and truncal fat-to-lean mass ratio. However, Indians had higher percentages of fat and fat-to-lean mass ratio in the abdominal region in comparison with Iranians, although the difference was not statistically significant [Table 18 & Figure 11].

This trend changed after adjustment for age, sex and WC. Namely, for a given age (47.16 y) and WC (99.36 cm), the Indian group had the highest estimated mean percentage of truncal fat (mean±SEM) (European: 39.5±1.0 %, Indian: 42.7±1.0 %, Iranian: 39.5±0.9 %; P values between Europeans & Indians and Iranians & Indians<0.05) and truncal fat-to-lean mass ratio (European: 0.39±0.01, Indian: 0.43±0.01, Iranian: 0.39±0.009; P values between Europeans & Indians and Iranians & Indians <0.05) among three ethnic groups [Figure 12]. In the other word, truncal mass in Indian participants contained higher amount of fat mass relative to Europeans and Iranians with the same WC.

In correlation analysis, there was a strong relationship between BMI and WC measured in the three ethnic groups after controlling for age and sex (European: r = 0.90, P <0.001; Indian: r = 0.88, P <0.001; Iranian r = 0.81, P<0.001). Also, BMI and WC were significantly correlated with different measures of total and truncal adiposity whether expressed in absolute or relative terms, except for truncal body fat percentage [Table 19]. There was a significant correlation between WC and the truncal body fat percentage in European (r=0.41, P=0.017) and Iranian (r=0.59, p<0.001) groups, but not in Indians (r=0.14, P=0.489).

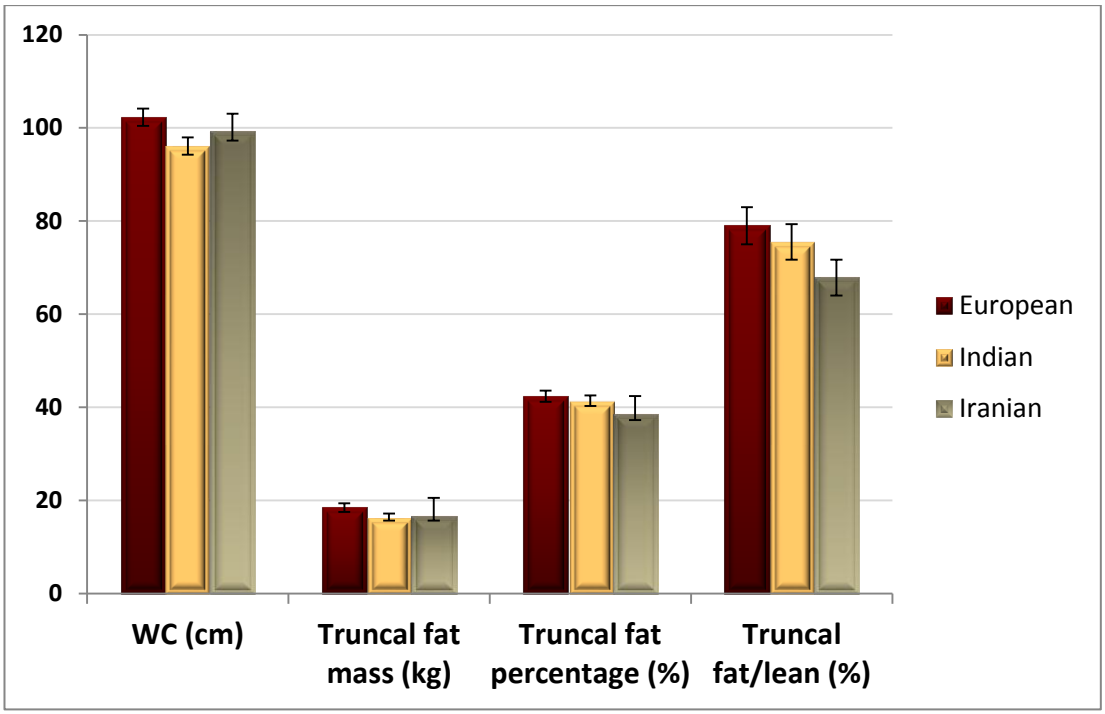


Figure 11: Comparison between WC, truncal fat mass, and percentages of truncal fat and fat/lean mass in three ethnic groups. *Data are presented as mean ±SEM; Truncal fat percentage, Truncal fat/Total trunk mass%.*

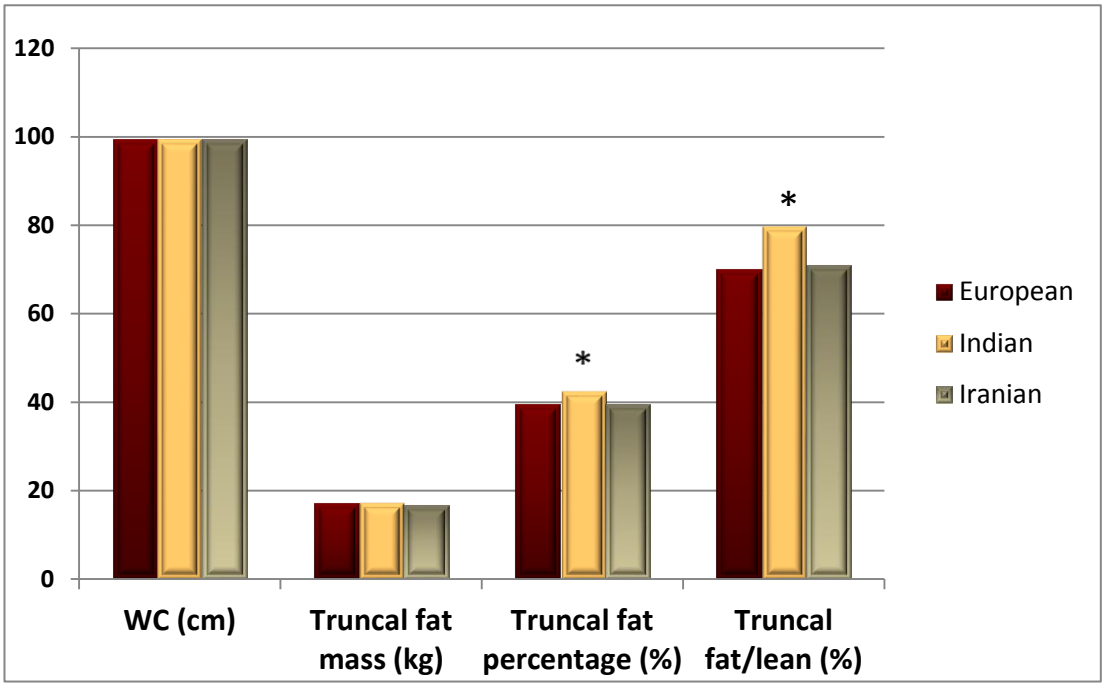


Figure 12: Comparison between the estimated means of truncal fat and fat/lean percentages and truncal fat mass in three ethnic groups after adjustment for age, sex and WC. *Data are presented as mean ±SEM; Truncal fat percentage, Truncal fat/Total trunk mass%.*, Significant difference (P<0.05) in comparison with European and Iranian groups.*

Table 19: Correlation between anthropometric measurements and different measures of total and truncal adiposity in three ethnic groups after controlling for age and sex

Ethnicity / variables			WC	HC	Total body fat mass	Total body fat%	Total fat/lean	Truncal body fat%	Truncal fat mass	Truncal fat /truncal mass	Truncal fat/lean
Overall	BMI	Correlation	0.861	0.834	0.886	0.657	0.679	0.250	0.854	0.579	0.602
		Sig.	<0.001	<0.001	<0.001	<0.001	<0.001	0.015	<0.001	<0.001	<0.001
	WC	Correlation	1.000	0.783	0.841	0.614	0.624	0.351	0.857	0.582	0.596
		Sig.		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	HC	Correlation	0.834	1.000	0.853	0.666	0.702	0.150	0.794	0.572	0.610
		Sig.	<0.001		<0.001	<0.001	<0.001	0.147	<0.001	<0.001	<0.001
European	BMI	Correlation	0.899	0.852	0.914	0.716	0.749	0.268	0.887	0.644	0.692
		Sig.	<0.001	<0.001	<0.001	<0.001	<0.001	0.131	<0.001	<0.001	0.001
	WC	Correlation	1.000	0.823	0.864	0.685	0.700	0.414	0.898	0.664	0.699
		Sig.		<0.001	<0.001	<0.001	<0.001	0.017	<0.001	<0.001	<0.001
	HC	Correlation	0.823	1.000	0.805	0.850	0.746	0.192	0.806	0.645	0.701
		Sig.	<0.001		<0.001	<0.001	<0.001	0.285	<0.001	<0.001	<0.001
Indian	BMI	Correlation	0.885	0.815	0.899	0.689	0.716	0.227	0.875	0.608	0.602
		Sig.	<0.001	<0.001	<0.001	<0.001	<0.001	0.254	<0.001	0.001	0.001
	WC	Correlation	1.000	0.773	0.864	0.582	0.589	0.139	0.823	0.497	0.472
		Sig.		<0.001	<0.001	0.001	0.001	0.489	<0.001	0.008	0.013
	HC	Correlation	0.773	1.000	0.806	0.655	0.703	0.248	0.813	0.635	0.665
		Sig.	<0.001		<0.001	<0.001	<0.001	0.213	<0.001	<0.001	<0.001
Iranian	BMI	Correlation	0.810	0.864	0.866	0.674	0.657	0.429	0.849	0.645	0.626
		Sig.	<0.001	<0.001	<0.001	<0.001	<0.001	0.016	<0.001	<0.001	0.001
	WC	Correlation	1.000	0.768	0.808	0.634	0.623	0.590	0.853	0.656	0.647
		Sig.		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	HC	Correlation	0.768	1.000	0.918	0.776	0.752	0.424	0.879	0.720	0.687
		Sig.	<0.001		<0.001	<0.001	<0.001	0.018	<0.001	<0.001	<0.001

BMI, body mass index; WC, waist circumference; HC, hip circumference

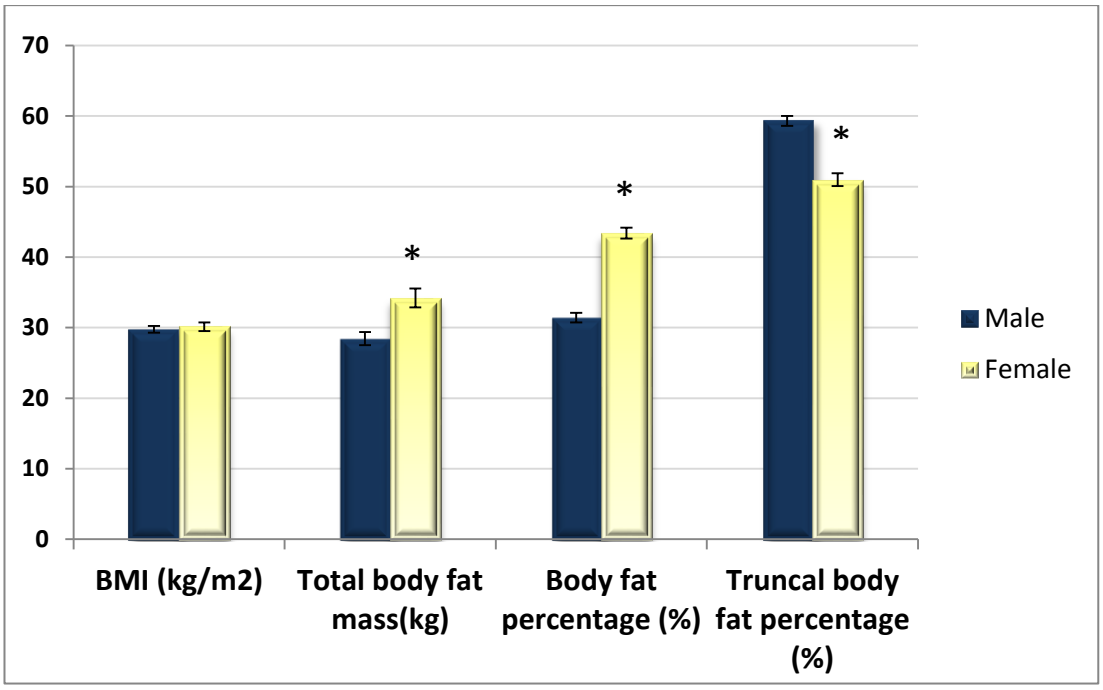


Figure 13: Comparison between BMI, total body fat and fat distribution in male and female participants**.** *Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with males; Truncal body fat percentage, Truncal fat mass /Total body fat %; Body fat percentage, Total fat mass/Total body mass %.*

There was no significant difference between the mean BMI of men and women (M: 29.8± 3.4 vs. W: 30.1±4.2 kg/m^2, P=0.67) [Figure 13]. However, women had significantly higher total body fat (34.2± 9.5 vs. 28.4± 6.5 kg, P= 0.001), body fat percentage (43.4±5.3 vs. 31.4 ±4.8%, p<0.001) and total body fat/total lean mass ratio (0.83±0.2 vs. 0.49±0.1, p<0.001) as well as a lower truncal fat percentage (51.0±6.3 vs. 59.3±5.0, p<0.001) relative to men. This pattern was also observed for men and women in all three ethnic groups. For all ethnicities, men had a lower total body fat compared to women; however they were more likely to accumulate fat in the abdominal or visceral area (indicated by truncal body fat percentage)[Table 20].

By bivariate correlation analysis, BMI was positively associated with different cardiovascular risk factors, including SBP (r = 0.26, P=0.01), HOMA (r = 0.49, P<0.001), hs- CRP (r = 0.40, P=0.001), TG (r = 0.29, P=0.004), insulin (r = 0.49, P<0.001) and glucose (r = 0.25, P=0.01) levels.

Table 20: Comparison between different measures of total and truncal adiposity in males and females of each ethnic group, estimated after adjusting for age and related anthropometric variables (BMI/WC).

Variables/ Ethnicity		Total fat mass (kg)		Total body fat%		Truncal body fat%		Truncal fat mass (kg)		Truncal fat/lean	
		Mean(SE)	95% CI	Mean(SE)	95% CI	Mean(SE)	95% CI	Mean(SE)	95% CI	Mean(SE)	95% CI
Europeans	Overall	32.91(0.86) a†	31.2-34.6	38.92 (1.31) a†	36.3-41.5	52.71 (1.25) a††	50.2-55.2	17.88(0.54)e	16.7-18.9	0.77(0.04)e	0.70-0.85
	Female	36.45(0.74) b*	34.9-38.0	44.18 (0.68) b*	42.8-45.5	52.07(0.91) b*	50.2-53.9	19.63(0.51) f*	18.6-20.7	0.91(0.03) f*	0.85-0.97
	Male	28.27(1.11) b	26.0-30.5	29.62 (0.01) b	27.5-31.7	60.80(1.35) b	58.0-63.5	15.00(0.76) f	14.4-17.5	0.52(0.04) f	0.44-0.61
Indians	Overall	30.44(0.91) a	28.6-32.2	38.02 (1.40) a	35.2-40.7	58.23 (1.32) a	55.6-60.9	17.29(0.57) e	16.1-18.4	0.77(0.04) e	0.69-0.85
	Female	31.15(0.84) c*	29.4-32.9	43.76(0.96) c*	41.8-45.7	52.51(1.16)c*	50.2-54.9	17.96(0.69) g*	16.5-19.4	0.92(0.04)g*	0.83-1.01
	Male	27.63(0.756) c	26.1-29.2	31.94(0.87) c	30.2-33.7	59.48(1.05)	57.3-61.6	15.22(0.62) g	13.9-16.5	0.62(0.04) g	0.53-0.70
Iranians	Overall	30.34(0.80) a	28.7-31.9	35.11 (1.23) a	32.7-37.6	55.13 (1.17) a	52.8-57.5	16.58(0.50) e	15.6-17.6	0.68(0.04) e	0.60-0.75
	Female	32.93(1.30) d*	30.3-35.6	41.19(1.35) d*	38.4-44.0	47.04 (1.69)d*	43.6-50.5	17.43(0.93) h	15.5-19.3	0.82(0.05) h*	0.71-0.92
	Male	29.13(0.922) d	27.2-31.0	32.01(0.96) d	30.1-33.9	58.29 (1.95)	55.9-60.7	16.30(0.65) h	15.0-17.6	0.61(0.04) h	0.54-0.68

a. The mean values are estimated at the following values: Age= 46.16, BMI= 29.95, b. The mean values are estimated at the following values: Age= 55.56, BMI= 30.78;
c. The mean values are estimated at the following values: Age= 38.21, BMI=29.02; d. The mean values are estimated at the following values: Age 43.19. BMI=29.88;
e. The mean values are estimated at the following values: Age= 46.16, WC= 99.36, f. The mean values are estimated at the following values: Age= 55.56, WC= 102.27;
g. The mean values are estimated at the following values: Age= 38.21, WC=96.07; h. The mean values are estimated at the following values: Age 43.19. WC=99.15,
*Estimated means were determined using a multiple linear regression analysis; *. Significant difference at the 0.05 levels compared with males in the same ethnic group, † and ††. Significant difference at the 0.05 levels compared with Iranians and Indians, respectively.*

Table 21: Comparison between different adiposity measurements of European, Indian and Iranian participants in each gender group, estimated after adjusting for age and related anthropometric variables.

Variables/ Ethnicity		Total fat mass (kg)		Total body fat%		Truncal body fat%		Truncal fat mass (kg)		Truncal fat/lean (%)	
		Mean(SE)	95% CI	Mean(SE)	95% CI	Mean(SE)	95% CI	Mean(SE)	Mean(SE)	Mean(SE)	95% CI
Female	**Overall**	33.98(0.55) ^{a*}	32.8-35.1	43.34 (0.56) ^{a*}	42.2-44.4	50.63 (0.74) ^{a*}	49.1-52.1	18.57(0.39) ^{d*}	17.8-19.34	0.89(0.02) ^{d*}	0.84-0.93
	Europeans	35.17 (0.80) ^{b}	33.5-36.7	43.34 (0.83) ^{b}	41.7-45.0	50.76 (1.31) ^{b}	48.1-53.4	17.92 (0.69) ^{e}	16.5-19.3	0.84(0.04) ^{e}	0.77-0.93
	Indians	33.19 (1.08) ^{b}	31.0-35.4	45.09 (1.12) ^{b†}	42.8-47.3	53.10 (1.76) ^{b†}	50.4-57.5	18.09 (0.93) ^{e}	16.2-19.9	0.95 (0.05) ^{e†}	0.84-1.06
	Iranians	33.35 (1.10) ^{b}	31.1-35.6	41.63 (1.14) ^{b}	39.3-43.9	47.86 (1.81) ^{b}	44.2-51.5	16.38 (0.95) ^{e}	14.5-18.3	0.80 (0.05) ^{e}	0.69-0.91
Male	**Overall**	28.67(0.54) ^{a}	27.6-29.7	31.50 (0.56) ^{a}	30.4-32.6	59.65 (0.74) ^{a}	58.2-61.1	15.97(0.38) ^{d}	15.2-16.7	0.59 (0.02) ^{d}	0.55-0.64
	Europeans	27.65 (1.28) ^{c}	25.1-30.2	29.10 (1.30) ^{c}	26.5-31.7	57.70 (1.28) ^{c††}	55.1-60.3	16.50 (0.73) ^{f}	15.0-18.0	0.56 (0.04) ^{f}	0.48-0.63
	Indians	28.38 (0.99) ^{c}	16.4-30.4	32.38 (1.00) ^{c}	30.4-34.4	61.54 (0.99) ^{c†}	59.5-63.5	16.89 (0.56) ^{f}	15.7-18.0	0.65 (0.03) ^{f}	0.59-0.71
	Iranians	28.88 (0.79) ^{c}	27.3-30.5	31.86 (0.81) ^{c}	30.2-33.5	58.50 (0.79) ^{c}	56.9-60.1	17.14 (0.45) ^{f}	16.2-18.1	0.63 (0.02) ^{f}	0.58-0.68

*a. The mean values are estimated at the following values: Age= 46.16, BMI= 29.95, b. The mean values are estimated at the following values: Age= 48.05, BMI= 30.12; c. The mean values are estimated at the following values: Age= 44.31, BMI=29.78; d. The mean values are estimated at the following values: Age= 46.16, WC= 99.36, e. The mean values are estimated at the following values: Age= 48.05, WC= 97.43; f. The mean values are estimated at the following values: Age= 44.31, WC=101.24; Estimated means were determined using a multiple linear regression analysis *. Significant difference at the 0.05 levels compared with males in overall, † and ††. Significant difference at the 0.05 levels compared with Iranians and Indians in the same gender group, respectively.*

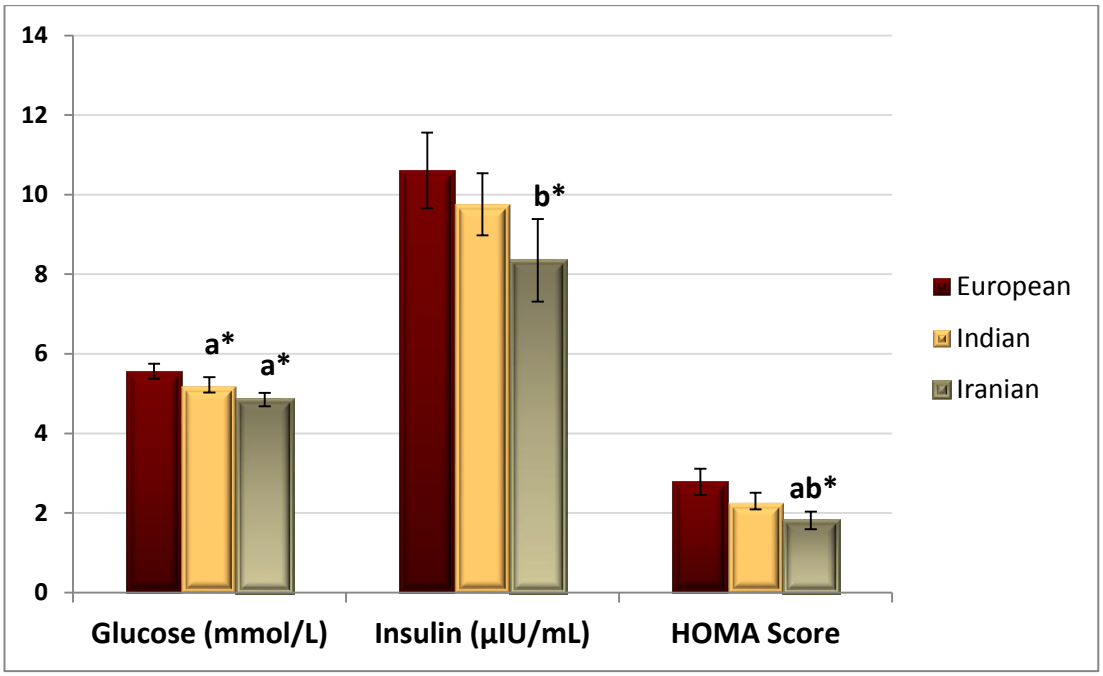


Figure 14: Glucose, insulin and HOMA Score in three ethnic groups. *Data are presented as mean ± SEM; a*, b* and ab*, Significant difference (P<0.05) in comparison with Europeans, Indians, and both European and Indian groups, respectively.*

4.4.2 Glucose, insulin and HOMA score

As shown in Table 11, European participants had a significantly higher mean value of fasting glucose relative to Indians (5.6±1.1 vs. 5.2±1.0 mmol/L, P=.0.017) and Iranians (5.6±1.1 vs. 4.8±1.0 mmol/L, P<0.001) in non-parametric tests. There was no significant difference between mean fasting glucose measured in Indian group compared to those in Iranians. Also, a tendency toward an increased mean value was detected when European participants were compared with Iranian group (10.6 ±5.6 vs. 8.35±5.98 µIU/mL, P=0.052) for insulin.

This was accompanied with a significant difference between Europeans' HOMA score and those determined in Iranians (P=0.019). Furthermore, in spite of having a lower BMI [Table 11], Indian participants had higher mean values of glucose (P=0.073); insulin (P=0.034) and HOMA score (P=0.037) in comparison with Iranians [Figure 14].

Interestingly, the results of HOMA mentioned above changed after adjusting for age, gender and WC. Namely, in the same age (46.2 y) and WC (99.4 cm), Indians had the highest estimated mean (±SE) HOMA compared to Europeans (0.85 ± 0.1 vs.

0.70 ± 0.1, P = 0.35) and Iranians (0.85 ± 0.1 vs. 0.37± 0.1, P = 0.001). There was a significant difference between the mean value estimated in Europeans and Iranians (P= 0.03), after adjustment for these variables. Also, this pattern remained with no change after additional adjustment for the level of physical activity and total carbohydrate intake; it just resulted in a slight change in the estimated mean (± SE) in Europeans (0.69 ± 0.1) and Iranians (0.38±0.1).

Partial correlation analysis showed that, in overall, the measures of general and truncal adiposity were more closely correlated with insulin and HOMA score than glucose after controlling for age and gender [Table 22]. This was also true across ethnicities. No significant association was detected between glucose and body composition assessments in the three ethnic groups (all P values > 0.05), except for glucose levels in European participants which were correlated with WC (r=0.35, P=0.046) and BMI (r=0.46, P=0.007).

The strongest correlations between insulin (HOMA score) and BMI, WC and different body fat measurements were found among Iranians. In the Indian group, insulin and HOMA score were more correlated with total body fat mass (insulin: r=0.43, P=0.025; HOMA: r=0.46, P=0.015) and total body fat percentage (insulin: r=0.38, P=0.051; HOMA: r=0.39, P=0.043) than BMI (insulin: r=0.35, P=0.073; HOMA: r=0.36, P=0.069).

Multiple regression analysis highlighted that HOMA (Ln) was related to ethnicity (P= 0.01) as well as WC (P= 0.01), truncal fat mass (P=0.04), truncal body fat percentage (P=0.006) and total fat mass (P=0.02), but BMI and total body fat percentage had no significant role (P>0.05).

Table 22: Correlation between glucose, insulin and HOMA score determined in three ethnic groups and different body composition measurements after controlling for age and sex

Ethnicity / variables			BMI	WC	Total body fat mass	Total body fat%	Total fat/lean	Truncal body fat%	Truncal fat mass	Truncal fat /truncal mass	Truncal fat/lean
Overall	Glucose	Correlation	0.220	0.197	0.163	0.145	0.127	0.244	0.214	0.168	0.146
		Sig.	0.038	0.053	0.115	0.162	0.221	0.017	0.038	0.103	0.157
	Insulin	Correlation	0.478	0.556	0.415	0.278	0.264	0.345	0.460	0.291	0.265
		Sig.	<0.001	<0.001	<0.001	0.006	0.010	0.001	<0.001	0.004	0.010
	HOMA score	Correlation	0.482	0.526	0.392	0.254	0.242	0.340	0.442	0.259	0.237
		Sig.	<0.001	<0.001	<0.001	0.013	0.018	0.001	<0.001	0.011	0.021
European	Glucose	Correlation	0.458	0.346	0.323	0.274	0.248	0.220	0.341	0.237	0.215
		Sig.	0.007	0.046	0.067	0.123	0.165	0.218	0.052	0.183	0.229
	Insulin	Correlation	0.527	0.540	0.345	0.143	0.152	0.363	0.392	0.117	0.126
		Sig.	0.002	0.001	0.049	0.428	0.398	0.038	0.024	0.516	0.484
	HOMA score	Correlation	0.570	0.532	0.363	0.189	0.181	0.350	0.408	0.150	0.144
		Sig.	0.001	0.001	0.038	0.293	0.313	0.046	0.018	0.404	0.423
Indian	Glucose	Correlation	0.155	0.241	0.248	0.201	0.164	0.208	0.314	0.215	0.203
		Sig.	0.441	0.226	0.211	0.314	0.415	0.297	0.110	0.281	0.309
	Insulin	Correlation	0.351	0.351	0.432	0.381	0.347	0.016	0.373	0.376	0.321
		Sig.	0.073	0.072	0.025	0.051	0.076	0.938	0.055	0.053	0.102
	HOMA score	Correlation	0.356	0.393	0.463	0.393	0.344	0.089	0.438	0.386	0.332
		Sig.	0.069	0.043	0.015	0.043	0.079	0.658	0.022	0.047	0.091
Iranian	Glucose	Correlation	0.036	0.022	-0.019	0.018	-0.025	0.223	0.032	0.090	0.039
		Sig.	0.849	0.906	0.919	0.923	0.895	0.228	0.862	0.632	0.833
	Insulin	Correlation	0.559	0.719	0.543	0.376	0.346	0.479	0.592	0.410	0.369
		Sig.	0.001	<0.001	0.002	0.037	0.057	0.006	<0.001	0.022	0.041
	HOMA score	Correlation	0.549	0.702	0.521	0.369	0.332	0.502	0.578	0.415	0.368
		Sig.	0.001	<0.001	0.003	0.041	0.068	0.004	0.001	0.020	0.042

BMI, body mass index; WC, waist circumference; HOMA, homeostatic model of assessment

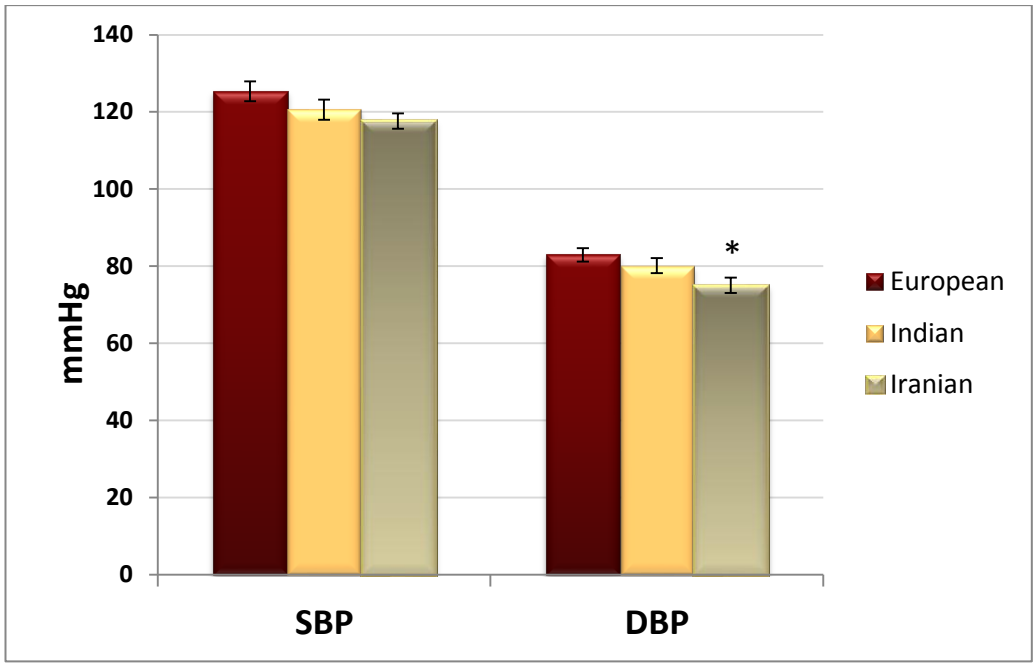


Figure 15: Systolic and diastolic blood pressure measured in three ethnic groups. European *participants had higher systolic and diastolic blood pressure relative to Indian and Iranian groups. Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with Indian group.*

4.4.3 Systolic and diastolic blood pressure

Analysis of the raw data indicated that European participants had a trend to higher mean systolic and diastolic blood pressure relative to Indians and Iranians [Figure 15 & Table 11]. However, this trend changed after adjusting data for age and gender [Figure 16 & Table 12]. Namely, Indian participants then had a higher mean (± SEM) resting systolic blood pressure (123.8 ± 2.6 mmHg) relative to European (120.5 ±2.6 mmHg, P=0.422) and Iranian (117.9 ± 2.4 mmHg, P=0.094) groups, although differences were not significant statistically. Similarly, the age & gender adjusted mean (±SEM) value of diastolic blood pressure measured in Indian group (82.0 ± 2.0 mmHg) was higher than those measured in Europeans (80.7 ± 2.1 mmHg, P = 0.692) and Iranians (75.2 ± 1.9 mmHg, P=0.014). Interestingly, the difference between SBP / DBP in Indians and Iranians became more significant after additional adjustment for WC [P value for SBP<0.05, P value for DBP=0.008].

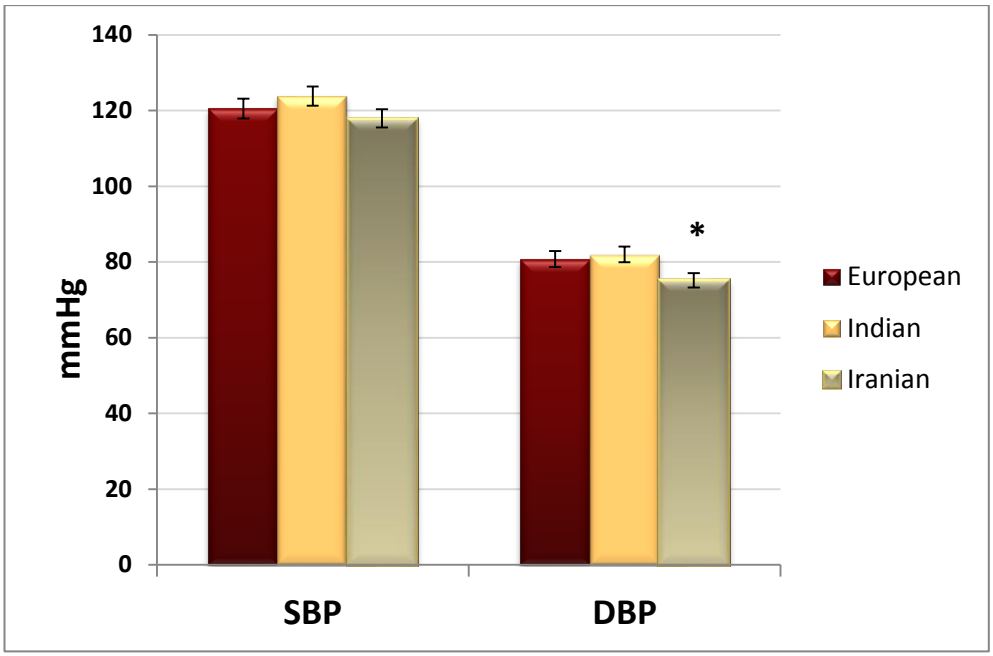


Figure 16: Systolic and diastolic blood pressure measured in three ethnic groups, after adjusting for age and sex. *Indian participants had higher systolic and diastolic blood pressure relative to European and Iranian groups. Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with Indian group.*

There were significant correlations (r) between systolic blood pressure and BMI (0.23, P= 0.023), WC (0.33, P=0.001) and body fat measurements including total body fat mass (0.24, P= 0.020, total body fat percentage (0.229, P=0.029), total fat/lean (0.24, P=0.019), truncal fat mass (0.300, P= 0.003), truncal body fat percentage (0.29, P=0.004) and truncal fat/lean (0.281, P= 0.006) after controlling for age and gender. However, among these variables, diastolic blood pressure was only significantly correlated with WC (0.263, P=0.010).

There were also borderline associations between diastolic blood pressure and truncal fat assessments including truncal fat mass (0.20, P=0.054) and truncal body fat percentage (0.19, P=0.060) .No significant dietary effect was observed in any of the correlation analyses (all p values > 0.05). By multiple regression analysis, diastolic blood pressure was predicted by WC (β= 0.365, p<0.001), ethnicity (P= 0.007; for Europeans: β=6.604; for Indians: β=7.378; for Iranian: β=0, as the reference group), sodium intake (β=0.004, P=0.028), and thiamin intake (β= - 6.324, P= 0.04). While, WC (β= 0.003, p=0.023) and HOMA (β= 0.021, p<0.007) were found as significant predictors of systolic blood pressure.

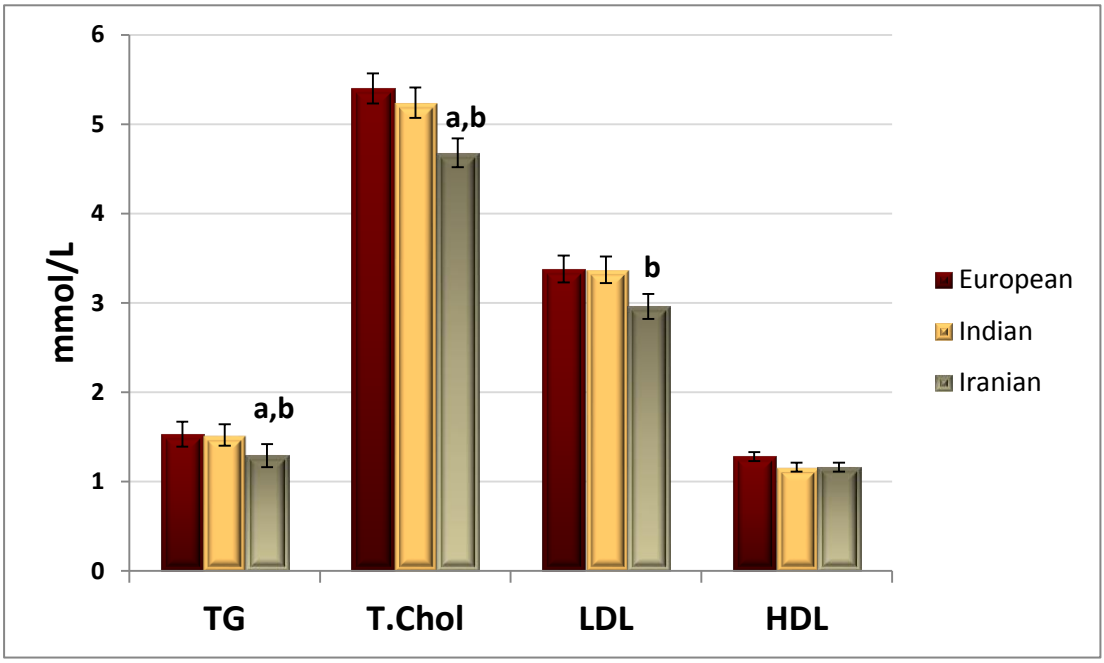


Figure 17: lipid profile assessed in three ethnic groups, after adjusting for age and gender. *Iranian participants had lower total cholesterol, LDL, HDL and triglyceride relative to Indian and European groups. Data are presented as mean ± SEM .a, Significant difference (P<0.05) in comparison with European group. b, Significant difference (P<0.05) in comparison with Indian group.*

4.4.4 Lipid profile, hs-CRP and renal function test

After adjusting for age and gender, participants in European group had higher mean (±SEM) total cholesterol (5.4±0.2 vs. 4.7±0.2 mmol/L, P=0.003), LDL (3.4±0.1 vs. 3.0±0.1 mmol/L, P=0.05), triglyceride (1.6±0.1 vs. 1.2±0.1 mmol/L, P=0.037) and trend to lower HDL (1.3±0.05 vs. 1.7±0.04 mmol/L, P=0.102) and relative to Iranians [Table 12 & Figure 17]. This trend was similar to what observed when lipid profile data was analysed without adjustment [Table 11].

Similarly, the age & gender adjusted mean (±SEM) values of total cholesterol (5.4±0.2 vs. 5.2±0.2 mmol/L, P=0.14), LDL (3.4±0.1 vs. 3.4±0.1 mmol/L, P=0.98), HDL (1.3±0.05 vs. 1.2±0.05 mmol/L, P=0.125) and triglyceride (1.6±0.1 vs. 1.5±0.1 mmol/L, P=0.98) estimated in the European group were higher than those in the Indian group. In comparison with the Indian group, Iranian participants had significantly lower mean values when they were compared for total cholesterol (P=0.015), LDL (P=0.04), and log- transformed TG (P=0.028).

Partial correlation analysis showed positive and significant associations between the levels of triglyceride and, BMI (r=0.30, P= 0.003), WC (r=0.30, P= 0.004), total body fat mass (r=0.23, P= 0.024) and truncal adiposity measurements including truncal fat mass (r=0.28, P= 0.006) and truncal body fat percentage (r=0.28, P=0.006) after controlling for age and sex [Table 23].

These variables also tended to be significantly but negatively correlated with HDL-cholesterol [BMI: r= - 0.28, P= 0.006), WC: r= - 0.30, P= 0.003, total body fat mass: r= - 0.21, P= 0.045, truncal fat mass: r= - 0.30, P= 0.003 and truncal body fat percentage: r= - 0.37, p<0.001]. There was no significant relationship between total cholesterol or LDL-cholesterol and the measures of general and truncal fatness.

As presented in Table 24, the degree of associations between the lipid profile and different body fat measurements varied among three ethnic groups. In Europeans, HDL-cholesterol and triglyceride were significantly correlated with WC, BMI and truncal fat content. But, the levels of HDL and triglyceride measured in Iranians were significantly associated with truncal body fat percentage (HDL: r=0.47, P=0.008; triglyceride: r= -0.60, P=0.001). In Indians, HDL-cholesterol (but not triglyceride), was correlated with BMI (r= - 0.41, P= 0.031), WC (r= - 0.49, P= 0.010), total body fat mass (r= - 0.53, P= 0.005) total body fat% (r= - 0.42, P= 0.029) total fat/lean (r= - 0.42, P= 0.030) truncal fat mass (r= - 0.42, P= 0.031, truncal fat /truncal mass (r= - 0.39, P= 0.044).

In regression analysis, ethnicity was found to be a significant predictor of total cholesterol (P<0.001), HDL (P=0.002) and LDL (P=0.017), TG (Ln, P=0.019), after controlling for age, sex and BMI.

Table 23: The overall correlations between lipid profile and different body fat measurements after controlling for age and sex

variables		BMI	WC	Total body fat mass	Total body fat%	Total fat/lean	Truncal body fat%	Truncal fat mass	Truncal fat /truncal mass	Truncal fat/lean
Total cholesterol	Correlation	0.068	0.023	0.105	0.102	0.122	- 0.015	0.084	0.095	0.116
	Sig.	0.511	0.825	0.313	0.327	0.240	0.889	0.418	0.362	0.262
LDL-chol.	Correlation	0.038	- 0.006	0.084	0.121	0.131	- 0.23	0.070	0.119	0.140
	Sig.	0.717	0.953	0.416	0.242	0.205	0.823	0.502	0.249	0.176
HDL-chol.	Correlation	- 0.281	- 0.303	- 0.206	- 0.122	- 0.148	- 0.366	- 0.298	- 0.197	- 0.210
	Sig.	0.006	0.003	0.045	0.238	0.154	<0.001	0.003	0.054	0.041
Triglyceride	Correlation	0.298	0.295	0.232	0.078	0.126	0.280	0.278	0.117	0.136
	Sig.	0.003	0.004	0.024	0.454	0.222	0.006	0.006	0.260	0.188

BMI, body mass index; WC, waist circumference; LDL-chol, low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol

Table 24: Correlations between lipid profile and different body fat measurements in three ethnic groups after controlling for age and sex.

Ethnicity / variables			BMI	WC	Total body fat mass	Total body fat%	Total fat/lean	Truncal body fat%	Truncal fat mass	Truncal fat /truncal mass	Truncal fat/lean
European	Total cholesterol	Correlation	0.016	- 0.117	0.060	- 0.023	- 0.012	- 0.233	- 0.006	- 0.072	- 0.042
		Sig.	0.930	0.518	0.741	0.900	0.946	0.193	0.975	0.692	0.816
	LDL-chol.	Correlation	- 0.079	0.029	- 0.033	- 0.091	- 0.089	- 0.165	- 0.061	- 0.090	- 0.071
		Sig.	0.664	0.875	0.853	0.613	0.623	0.360	0.737	0.618	0.694
	HDL-chol.	Correlation	- 0.453	- 0.464	- 0.314	- 0.316	- 0.155	- 0.324	- 0.403	- 0.170	- 0.195
		Sig.	0.008	0.007	0.075	0.449	0.389	0.066	0.020	0.345	0.276
	Triglyceride	Correlation	0.456	0.456	0.363	0.202	0.228	0.096	0.357	0.141	0.176
		Sig.	0.008	0.008	0.038	0.259	0.202	0.597	0.041	0.435	0.327
Indian	Total cholesterol	Correlation	0.129	0.023	0.090	- 0.013	0.092	0.242	0.149	- 0.006	0.109
		Sig.	0.522	0.908	0.655	0.948	0.648	0.223	0.457	0.976	0.588
	LDL-chol.	Correlation	0.162	0.020	0.125	0.089	0.186	0.246	0.188	0.089	0.201
		Sig.	0.419	0.920	0.533	0.660	0.353	0.215	0.348	0.658	0.316
	HDL-chol.	Correlation	- 0.415	- 0.489	- 0.527	- 0.420	- 0.419	0.162	- 0.415	- 0.391	- 0.367
		Sig.	0.031	0.010	0.005	0.029	0.030	0.419	0.031	0.044	0.060
	Triglyceride	Correlation	0.215	0.301	0.251	- 0.063	0.021	0.037	0.212	- 0.057	0.009
		Sig.	0.281	0.127	0.206	0.754	0.919	0.853	0.288	0.777	0.966
Iranian	Total cholesterol	Correlation	0.70	- 0.109	0.045	0.127	0.108	- 0.304	- 0.033	0.061	0.071
		Sig.	0.707	0.559	0.811	0.497	0.563	0.096	0.859	0.743	0.704
	LDL-chol.	Correlation	0.052	- 0.109	0.068	0.163	0.152	- 0.307	- 0.019	0.095	0.113
		Sig.	0.782	0.561	0.717	0.380	0.413	0.093	0.920	0.611	0.546
	HDL-chol.	Correlation	- 0.206	- 0.230	- 0.178	- 0.101	- 0.129	- 0.600	- 0.302	- 0.253	- 0.253
		Sig.	0.266	0.212	0.337	0.589	0.490	<0.001	0.99	0.170	0.170
	Triglyceride	Correlation	0.236	0.178	0.111	0.028	0.031	0.470	0.222	0.154	0.137
		Sig.	0.202	0.337	0.554	0.883	0.870	0.008	0.229	0.408	0.463

BMI, body mass index; WC, waist circumference; LDL-chol, low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol

After adjusting for age and gender, European participants revealed trends to a higher mean (±SD) value of hs-CRP relative to Indians (4.6±0.8 vs. 3.5±0.8 mg/L, P=0.85) and Iranians (4.6±0.8 vs. 2.8±0.8 mg/L, P=0.65), although they were not statistically significant [Table 12]. Females participating in the present study had a significantly higher mean value of hs-CRP than that measured in males (4.6±4.6 vs. 2.6±3.5, P (Ln) =0.001).

There was evidence of weak but significant correlations (r) between hs-CRP and, BMI (0.35, P=0.001), WC (0.28, P=0.006), HC (0.27, P=0.007), total body fat mass (0.33, P=0.001), total body fat percentage (0.24, P=0.019), total body fat /lean (0.27, P=0.009), truncal fat mass (0.30, P=0.003), truncal fat/lean (0.24, P=0.021) and truncal fat/truncal mass (0.21, P=0.045) after controlling for age and sex. However, these associations were not constant in three ethnic groups [Table 25].

In partial correlation analysis, hs-CRP was also correlated with glucose (r=0.22, P=0.03), insulin (r= 0.28, P= 0.007) and HOMA (r=0.28, P=0.006), after controlling for age and sex. However, these associations remained significant only in Indians (HOMA: r=0.42, P=0.03) and Iranians (HOMA: r=0.47, P=0.008; insulin: r=0.45, P=0.01) when data was analysed for three ethnic groups, separately. There was no correlation between hs-CRP and systolic or diastolic blood pressure (P values >0.05). The bivariate correlation analysis showed that hs-CRP was significantly associated with triglyceride (r=0.21, P= 0.04) and total cholesterol (r=0.22, P=0.03). However, there was no significant association between hs-CRP and these serum lipids, after controlling for age and gender. Furthermore, hs-CRP measured in Indians was significantly correlated with LDL-chol. (r=0.40, P=0.04) and HDL-chol (r= - 0.47, P=0.01), after analysing data based on ethnicities.

Microalbuminuria (an albumin /creatinine ratio ≥ 30 and <299 µg/mg) was detected in 11.4 % of participants in European group (4 of 35 subjects), compared to 12.1% of those in Indian group (4 of 33 subjects). Additionally, clinical albuminuria (albumin /creatinine ratio ≥ 300 µg/mg) was present in 1 European subject (0.03%), but no participant in Indian group. All participants in Iranian group had an albumin /creatinine ratio in the normal ranges (< 30 µg/mg).

Table 25: Correlations between hs-CRP and different body fat measurements in three ethnic groups after controlling for age and sex.

Ethnicity/ variables			BMI	WC	HC	Total body fat mass	Total body fat%	Total fat/lean	Truncal body fat%	Truncal fat mass	Truncal fat / truncal mass	Truncal fat/lean
hs-CRP	Overall	Correlation Sig.	0.345 0.001	0.282 0.006	0.273 0.007	0.326 0.001	0.241 0.019	0.268 0.009	0.052 0.616	0.297 0.003	0.206 0.045	0.237 0.021
	European	Correlation Sig.	0.103 0.567	0.041 0.820	0.060 0.741	0.093 0.607	- 0.066 0.716	0.008 0.965	- 0.370 0.034	- 0.017 0.926	- 0.185 0.302	- 0.094 0.604
	Indian	Correlation Sig.	0.456 0.017	0.373 0.05	0.443 0.021	0.442 0.021	0.494 0.009	0.555 0.003	0.284 0.152	0.489 0.01	0.580 0.002	0.638 <0.001
	Iranian	Correlation Sig.	0.744 <0.001	0.724 0.001	0.753 <0.001	0.789 <0.001	0.594 <0.001	0.609 <0.001	0.465 0.008	0.799 <0.001	0.580 0.001	0.583 0.001

BMI, body mass index; WC, waist circumference; HC, hip circumference; hs-CRP, high sensitive C-reactive protein

4.5 The effects of ethnicity on endothelial dysfunction

In this study, European, Indian and Iranian participants were also compared for soluble forms of VCAM-1 and E-selectin, as biomarkers of endothelial dysfunction.

The age & gender adjusted mean value (±SE) of VCAM-1 measured in Iranians was higher than Indians (223.3± 12.8 vs. 191.0±13.0 ng/mL, P (Ln) = 0.01) and Europeans (223.3± 12.8 vs. 198.4±13.4 ng/mL, P (Ln) = 0.20). There were no significant difference between VCAM-1 measured in males and females participating in this study (F: 203.5±73.6, M: 195.2±67.0, P=0.56) in overall. The only significant difference detected was between the mean VCAM-1 measured in Iranian's men and women [Figure 18].

In Europeans and Iranians, there was no significant correlation between VCAM-1 and different anthropometric or metabolic measurements after controlling for age and sex. However, the levels of VCAM-1 measured in Indians was positively associated with BMI (r = 0.56, p = 0.002), WC (r = 0.58, p = 0.002), HC (r = 0.48, p = 0.011), total body fat mass (r=0.46, P= 0.015) and truncal fat mass (r=0.39, P=0.041). There was no significant correlation between VCAM-1 and intake of different nutrients.

After adjusting for age and gender, European participants had a significantly higher mean (±SE) value of E-selectin relative to Indians (23.7±1.4 vs. 16.4±1.4 ng/mL, P (Ln) =0.002) and Iranians (23.7±1.4 vs. 16.9±1.30 ng/mL, P (Ln) =0.004). Also, E-selectin concentrations were significantly higher in men than in women (20.8±7.87 vs. 17.2±7.69 ng/mL, P=0.026). This trend was consistent across ethnicities [Figure 19]. In regression analysis, ethnicity remained a significant predictor of circulating levels of E-selectin (Ln, P=0.003) (for Europeans: β=0.450, $p<0.01$; for Indians: β=-0.166, P=0.254; Iranian as the reference group), after controlling for age, sex and BMI. The elevated level of E-selectin in European group were significantly correlated with insulin (r = 42, P = 0.016) and HOMA score (r = 0.39, P = 0.026). No significant association was observed between E-selectin and different components of metabolic syndrome in Indians and Iranians. Also, there were significant associations between E-selectin and dietary intakes of protein (ρ=0.24, P=0.02), cholesterol (ρ=0.21, P=0.04) and sodium (ρ=0.25, P=0.01).

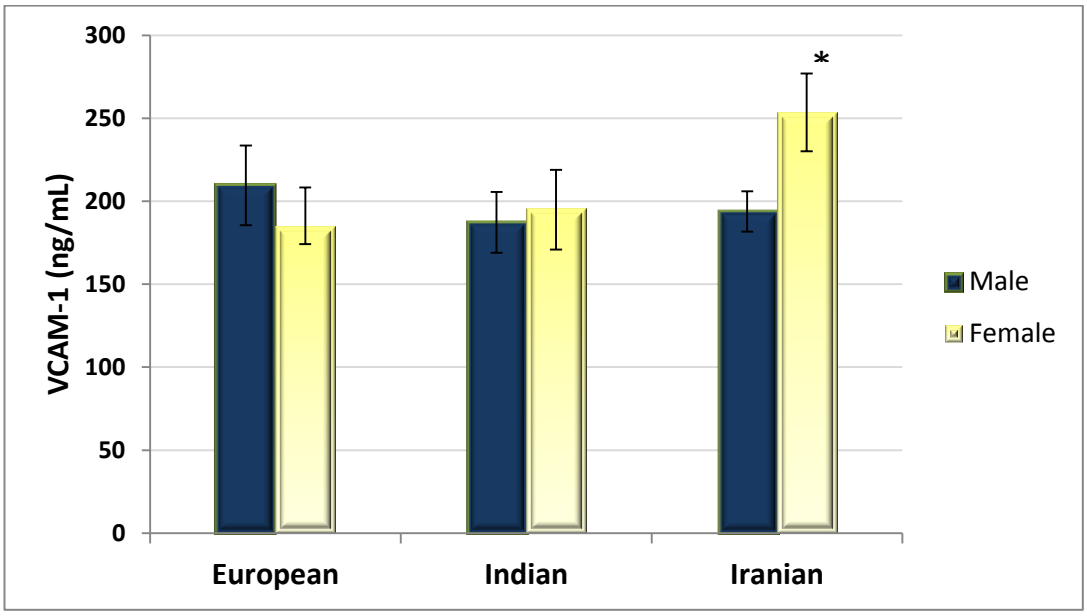


Figure 18: Comparison between the mean VCAM-1 measured in men and women in three ethnic groups. *Data are presented as mean ± SEM. *, Significant difference (P<0.05) in comparison with Iranian males.*

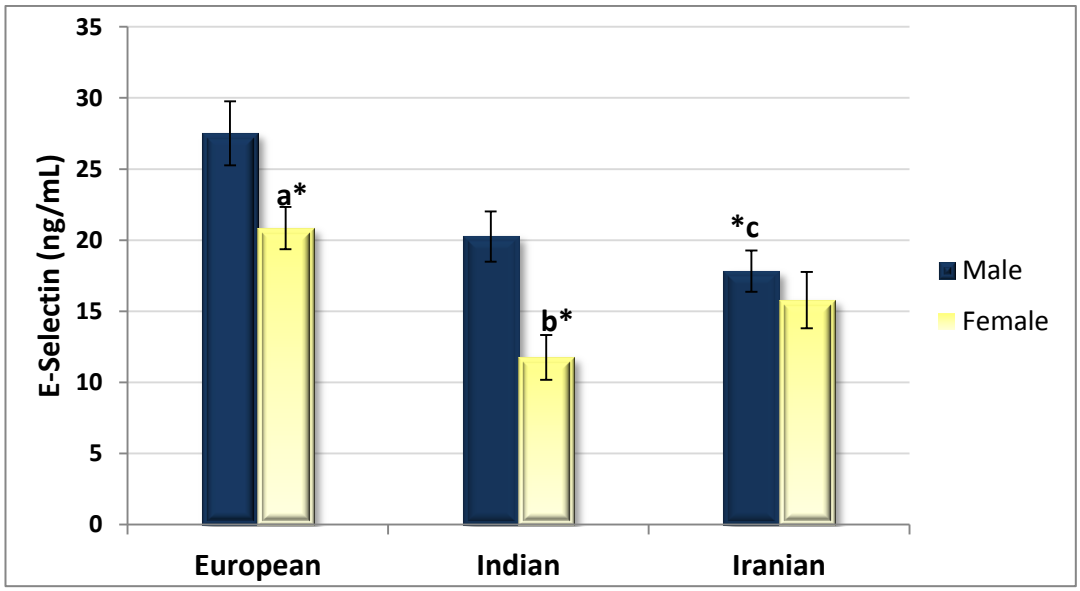


Figure 19: Comparison between the mean of E-Selectin measured in men and women in three ethnic groups. *Data are presented as mean ± SEM. a*, Significant difference in comparison with European males (p<0.05); b*, Significant differences in comparison with Indian males (P=0.002) and European females (P=0.001). c*, Significant difference in comparison with European males (P=0.001).*

4.6 Assessment of adiponectin in three ethnic groups

The mean value (±SD) of adiponectin was the highest in the European group compared to Indians (22.2±16.8 vs. 8.2±2.8, p<0.001) and Iranians (22.2±16.8 vs. 8.9±3.4, p<0.001). There was no significant difference between adiponectin measured in Indians and those in Iranians using a non-parametric test (8.2±2.8 vs. 8.9±3.4, p=0.306). There was also a significantly lower adiponectin level in men and in women participating in this study (M: 9.3±6.0 vs. W: 17.8±15.2, p<0.001). For all ethnicities, women had a higher mean value of adiponectin than men [Figure 20].

In overall, circulating levels of adiponectin was found to be negatively correlated with TG (r= - 0.24, p<0.020), insulin (r= - 0.23, p<0.023), truncal body fat percentage (r= - 0.43, p<0.001) and total carbohydrate intake (r= - 0.25, p<0.015), and positively with HDL-chol (r= 0.56, p<0.015) and vegetable and legume (r= 0.31, p<0.002).

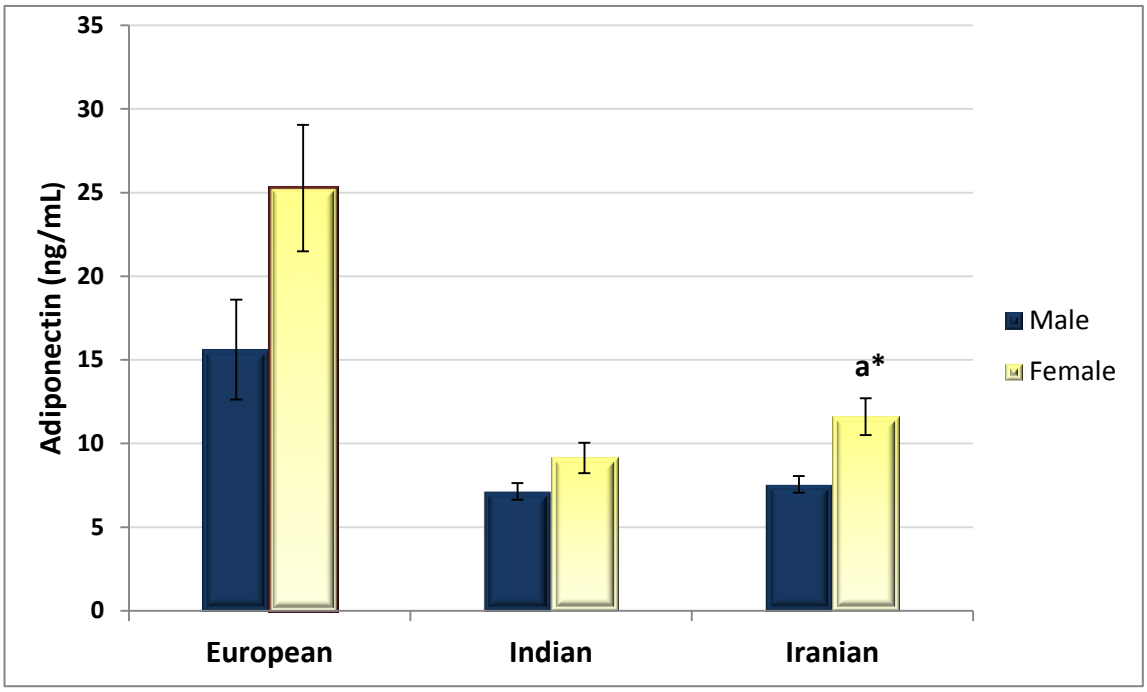


Figure 20: Comparison between the mean of Adiponectin measured in men and women in three ethnic groups. *Data are presented as mean ± SEM. a*, Significant difference (P=0.001) in comparison Iranian males.*

There was no significant association between adiponectin and, different anthropometric and metabolic measurements in European and Indian groups, after controlling for age and sex. However, the adiponectin measured in Iranians was negatively correlated with glucose ($r = -0.39$, $P=0.03$), insulin ($r = -0.37$, $P=0.039$), HOMA score($r = -0.43$, $P=0.015$) and truncal body fat percentage ($r= -0.36$, $P=0.044$).

The results of the regression models showed that the levels of adiponectin (Ln) were predicted (55.5%) by ethnicity (for Europeans: $\beta=0.758$, $p<0.001$; for Indians: $\beta=-0.004$, $P=0.967$; Iranian as the reference group), W/H ratio ($\beta= 1.98$, $P=0.013$), SBP ($\beta=0.013$, $P=0.002$), DBP ($\beta= -0.014$, $P=0.008$), insulin ($\beta= -0.024$, $P=0.009$), truncal body fat percentage ($\beta= -0.032$, $p<0.001$) and total carbohydrate intake ($\beta= -0.001$, $P=0.009$).

Chapter 5

Discussion of Results

As mentioned in the first chapter, the main objective of this research was to study the effects of ethnicity on metabolic syndrome risk factors. It was hypothesed that ethnicity plays a significant role in developing metabolic syndrome components including general and central obesity, hypertension, dyslipidaemia, hyperglycemia and insulin resistance.

Specifically, this study:

- compared metabolic syndrome criteria among a cross-section of immigrants from three ethnic groups in Western Australia using four common international definitions of metabolic syndrome,
- described the effects of ethnicity on the endothelial dysfunction in the ethnic groups under study,
- investigated the impact of diet on metabolic syndrome among the three ethnic groups, and finally
- explored the correlation between adiponectin and different components of metabolic syndrome amongst ethnic groups.

Accordingly, these objectives are addressed and discussed in this chapter.

5.1 Comparison of different definition of metabolic syndrome

In this study, the highest overall prevalence was shown by IDF definition and followed by ATP III, WHO and EGIR. These findings were consistent with other studies, like the AusDiab in Australia (Cameron et al. 2007), Esteghamati et al. (2010) in Iran and Zainuddin et al. (2011) in Malaysia. However, the results derived from a research in India showed that the highest prevalence of metabolic syndrome was identified by IDF and then followed by WHO and ATP III (Deepa et al. 2007).

There was also the excellent alignment between the definitions of IDF and ATPIII in all ethnic groups. This may be due to the fact that unlike the WHO and EGIR definitions, IDF and ATPIII considers central obesity as the main criterion. Also, hyperinsulinemia and insulin resistance are not prerequisite criteria in IDF or ATP III.

The overall prevalence of metabolic syndrome was significantly higher in females than males using all definitions. This finding was consistent with studies carried out in India (Ramachandran et al. 2003; Gupta et al. 2004) and Iran (Ayatollahi and Ghoreshizadeh 2010), but not with the results of the AusDiab study conducted on a national sample population of 11247 Australian adults. Studies carried out in European countries showed a variety of dominancy between males and females. The studies carried out in France (Dallongeville et al. 2005), Germany (Assmann et al. 2007), Greece (Skoumas et al. 2007) and Italy (Bo et al. 2005) showed a higher prevalence of metabolic syndrome among males, however the prevalence in Netherlands (Dekker et al. 2005), Portugal (Santos and Barros 2003) and Spain (Lorenzo et al. 2006) were greater in females than males. Accordingly, the discrepancy in the prevalence of metabolic syndrome amongst males and females observed in the AusDiab and the current study may be due to the differences in the ethnic composition of individuals participating in these studies and the samples sizes. Also, AusDiab was a population-based survey including a range of normal, overweight and obese participants; while individuals participating in the study were only overweight and obese volunteers.

In the current study, WHO- and EGIR-defined participants were more insulin resistant than participants categorised as having metabolic syndrome based on IDF and ATPIII definitions. These results were not surprising, because as mentioned before insulin resistance is an essential component for metabolic syndrome according to WHO and EGIR, but not IDF and ATPIII definitions. It was also found that the highest percentages of participants with insulin resistance were revealed using WHO definition. Given the key role of insulin resistance as a main underlying contributor for developing of cardiovascular diseases, the findings support the results of AusDiab (Cameron et al. 2007), indicating the highest association between WHO definition and cardiovascular risk among four definitions.

Although the overall criteria for metabolic syndrome offered by different organisations are similar, they differ in some important respects. For example, in contrast to IDF and ATPIII, the WHO criteria includes impaired glucose tolerance (IGT), on account of some potential advantages (Grundy et al. 2004). Firstly, IGT detected by an oral glucose tolerance test (OGTT) could be considered a metabolic risk factor in individuals with normal fasting glucose. Secondly, it is known that IGT is directly associated with an accelerated risk for developing type 2 diabetes. Thirdly, performing OGTT is strongly recommended in individuals with impaired fasting glucose (IFG) for recognition of diabetes, which is in turn a known risk factor for cardiovascular diseases. Therefore, by including OGTT, the value for cardiovascular disease risk prediction significantly increased.

In this study, the percentage of participants with insulin resistance revealed by IDF definition was slightly lower than WHO. In line with the findings, the AusDiab survey indicated that after WHO, the greatest odd ratio for having a 10 year cardiovascular disease risk > or = 15% was observed for those defined as having metabolic syndrome based on IDF. Also, according to AusDiab results, the IDF definition showed the highest population attributable risk (PAR) of high cardiovascular risk due to metabolic syndrome. As discussed above, the lower power of IDF definition in predicting the risk of CVD can be in part due to omitting the IGT among the risk factors of metabolic syndrome; however this omission was to avoid the additional inconvenience and the cost of OGTT. Therefore, although the IDF definition seems to be slightly less accurate than the WHO definition in identifying individuals with higher risk of CVD, it can be more practical from clinical aspect.

Previous studies showed that the percentage of fat mass, particularly truncal fat is one of the most important predictor of metabolic syndrome (Nguyen-Duy et al. 2003). In this study, truncal fat mass was significantly related to waist circumference in all ethnic groups (see Section 4.4.1). The result also supports the prior findings suggesting ethnicity as a major determinant of truncal fat accumulation (Wu et al. 2007). Despite these findings, among different definitions of metabolic syndrome, only the cut-off points of waist circumference offered by IDF is defined according to ethnic diversity. Therefore, the IDF definition seems to be also more reliable than others in estimating the prevalence of metabolic syndrome in different ethnic groups.

This point is particularly important for establishing appropriate prevention strategies in countries like Australia; receive emigrants from different countries and ethnic groups.

5.2 Comparison of metabolic syndrome criteria

5.2.1 Anthropometric variables

A. Body mass index

The results of comparative studies comparing the BMI of Indians and Caucasians in European and non-European countries were controversial. While, in some studies Indians had higher BMI than Caucasians, it was different in others (Raji et al. 2001). The findings were in line with the results reported by Raji et al. (2001), probably because both studies were conducted on participants with similar age ranges.

From another point, many studies have consistently shown that Indians have a higher body fat percentage and accordingly higher metabolic risks in comparison to Caucasians for a given BMI, age and gender (Forouhi et al. 1999; Chandalia et al. 2007; Rush et al. 2007; Nair et al. 2008; Rush, Freitas, and Plank 2009).

Although, there are several existing studies on Indians and Caucasians, there are few studies comparing metabolic syndrome between Iranians and Caucasians in a common environment. The higher BMI in Europeans found in the study is not consistent with a study comparing Caucasians and Iranian migrants in Sweden, which found a higher BMI in Iranians than Europeans (Koochek et al. 2008). The possible explanation for this discrepancy is that this study has focused on elderly Iranians and accordingly is not representative of all age groups. Moreover, this study is influenced by the natural facts of decreasing metabolism and increasing body fat during the aging process.

Body mass index has been used characteristically as an index evaluating total body fat mass. According to the presented classifications by WHO, the BMI cut-off points of 25 and 30 kg/m^2 have been recommended for overweight and obesity categories respectively. However, further studies revealed that the unique BMI cut-off point is

not appropriate for all population and genders. Therefore, an accurate cut-of point needs to be defined for each ethnic group separately.

Since, the study did not include a very large population; it was limited to recommend the certain BMI cut-off point for each ethnic group. However, the results suggest an appropriate ranking for the cut-off points in different ethnic groups evaluated in this study, since it is carried out in unique environment.

After adjustment for BMI, females participating in this study had significantly higher total body fat percentages than males overall and in all ethnic groups separately. Given the significant differences between male and females, it could be inferred that the BMI cut-off point should be gender specific.

Moreover, according to the results, Indian and Iranian females had the highest and the lowest body fat percentage among three ethnic groups. Given that BMI is accepted as an index for general fatness, the findings suggest that the BMI cut-off points for the Indian and Iranian females would be defined lower and higher than European females respectively. In addition, the Indian and European males had the highest and the lowest body fat percentage amongst the participants. So, the BMI cut-off point for Iranians should be defined higher and lower than Indians and Europeans respectively.

B. Waist and hip circumferences

Unlike BMI, waist circumference is an index evaluating central obesity and truncal body fat mass. Subsequent to the official recommended cut-off points for WC by International Diabetes Federation (IDF), many studies tried to find much more accurate cut-off points in specific populations (Misra et al. 2006; Nilsson et al. 2008; Dhanaraj et al. 2009; Shabnam et al. 2012). However, there is still no general consensus on the WC cut-off points in ethnic groups and genders. The International Diabetes Federation (IDF) recommended the WC cut-off points of ≥94cm and ≥80 cm for both European and Iranian males and females respectively; and ≥90cm and ≥80cm for Indian males and females respectively. However, several studies

suggested lower WC cut-off points in Indians than those recommended by ATP III and IDF (Raji et al. 2001; Misra et al. 2006; Dhanaraj et al. 2009).

In addition, in separate comparison of males and females in three ethnic groups, Indian and Iranian females had the highest and the lowest truncal fat among of the female participants. This suggests that the cut-off points for Indian and Iranian women should be defined lower and higher than European women respectively. This was consistent with the lower cut-off point for Indian females already recommended by IDF and some studies. However, it challenged the conception that the WC cut-off points are the same in European and Iranian females.

Analysing the truncal body fat in males in the same WC showed that Iranian males had higher and lower truncal fat percentage in comparison to European and Indian males. Accordingly, the WC cut-off point for Iranian males is suggested to be higher than that in Indian males, but lower than European males.

So, overall conclusions from these findings are:

The suggested cut-off points for BMI and WC in different ethnic groups are:

- Indian females < European females < Iranian females
- Indian males < Iranian males < European males

5.2.2 Glucose, insulin and HOMA score

In this study, the mean values of glucose, insulin and HOMA in Caucasians were higher than two other groups. But, Indian participants had the highest mean of HOMA score, after adjustment for age, gender and WC, a trend similar to what was found for truncal fat measurements. These results were consistent with other studies (McKeigue, Miller, and Marmot 1989; Raji et al. 2001) reporting higher prevalence of insulin resistance in Indians compare to Caucasians.

The results of both regression and correlation analyses showed significant associations between HOMA and different measurements of adiposity. However, HOMA tended to be more correlated with the measurements of truncal fat than total

fatness. The inverse correlation between truncal adiposity and insulin sensitivity has been also reported in other studies (Evans et al. 1984; Kelley et al. 2000a). Although, the mechanism behind this association is not fully understood, the excess release of non-esterified fatty acids (NEFA) by truncal adipose tissue and subsequent decreases in glucose utilisation and insulin sensitivity has been suggested as a possible reason (Randle et al. 1963; Jensen et al. 1989). Indians had been shown to have higher truncal fat relative to Europeans and Iranians at the same age, gender and WC (Section 4.4.1). These findings support previous studies suggesting that the higher rates of insulin resistance in Indians compared to Caucasians may be in part due to their higher truncal adiposity (Misra et al. 2004).

However, in the current study, ethnicity was found as a significant predictor of insulin resistance after controlling for different measurements of fatness. In line with the findings, it has been proposed that Asian Indians are also susceptible to insulin resistance independent of fat tissue volume or distribution (Chandalia et al. 1999). In this study, it was shown that the degree of association between HOMA and different body fat measurements varied significantly across three ethnic groups. Since, it is known that there are significant differences in functional characteristics of adipose tissue in different sites of the body (Arner, Engfeldt, and Lithell 1981; Jansson, Smith, and Lonnroth 1990), the findings suggest that there may be also functional heterogeneity in regional adipose tissue of individuals with different ethnicities. Accordingly, tendency for insulin resistance in some ethnic groups, including Indians, may be due to a hereditary adipose tissue dysfunction resulting in excessive response of adipocytes to factors contributing in the development of insulin resistance. Further studies are required to investigate the effects of ethnicity on the function of adipocytes in different regions, and also compare the impact of increase/decrease in truncal adipose tissue on the insulin resistance state in individuals with different ethnicity.

5.2.3 Systolic and diastolic blood pressure

Previous studies comparing the blood pressure levels of Indians with Caucasians were mainly conducted on South Asians, reporting different results. While, in some studies South Asian men had a higher systolic and diastolic blood pressure than Caucasians (Miller et al. 1988; McKeigue, Shah, and Marmot 1991), others reported

higher blood pressure in Caucasians (McKeigue et al. 1988; Bhopal et al. 1999; Perumal et al. 2012). The discrepancy between these results could be partly due to the fact that the term 'South Asian' is not essentially equal to Indian but includes people from the Indian subcontinent including India, Pakistan, Bangladesh and Sri Lanka, and there is obvious heterogeneity between South Asian subgroups (Agyemang and Bhopal 2002). The results of the Newcastle Heart Project study conducted in UK (Bhopal et al. 1999) showed that among three South Asian groups, Indians had higher blood pressure than Pakistanis, and the lowest blood pressure was observed in Bangladeshis. Other than the difference in the composition of South Asian groups, the inconsistent findings may be also because of sample population variations and differences in study methods. For example, in a study conducted by Chaturvedi et al. (2007) in UK 84 Asian Indian and 83 European men aged 45 years and older were recruited, however in another study in New Zealand (Perumal et al. 2012), the CVD risk profile of 47091 Europeans and 8830 Indian people aged 35-74, who completed PREDIC (a web-based computerised decision support system) risk assessments were reported.

The findings showed diastolic blood pressure was significantly lower in Iranians compare to Indians. This was supported by the regression analysis result showing ethnicity as a significant predictor of diastolic blood pressure after controlling for other variables. Also, Indian and Iranian ethnicities had the highest and the lowest regression coefficients among three ethnic groups, respectively. Since, current study is the first clinical assessment comparing Indians and Iranians in unique society; it was impossible to compare the findings to other similar studies in this regard.

There was also significant association between diastolic blood pressure and the dietary intake of sodium in regression analysis. The relation of nutritional factors with hypertension has been assessed in several clinical and epidemiological studies (Ascherio et al. 1996; Swaminathan 2003). It is known that there is a positive relationship between arterial blood pressure and sodium intake (Cheung et al. 2000; Hu and Tian 2001; Dumler 2009). However, higher systolic and diastolic blood pressure observed in the Indian group was accompanied with a significantly lower intake of sodium in comparison to European and Iranian descents.

On the other hand, Iranian participants with the highest average of sodium intake had the lowest mean systolic and diastolic blood pressure among three ethnic groups. It seems that these inconsistencies could be explained by higher intake of other minerals. It has been shown that the increased levels of blood pressure resulted from high sodium intake can be modified by the intakes of other dietary factors having inverse effects (Ono, Ando, and Fujita 1994; Akita et al. 2003). Blood pressure is inversely associated with intakes of magnesium, calcium and potassium (Ascherio et al. 1996; Swaminathan 2003; Karppanen and Mervaala 2006), and Iranian and European participants in the study had higher intakes of these minerals than Indians.

In line with the findings, in a survey conducted in Iran, there was a significant inverse association between calcium intake and both systolic and diastolic blood pressure in Iranian boys and girls (Azizi, Mirmiran, and Azadbakht 2004). These results are compatible with the possibilities that in addition to ethnicity, imbalanced dietary intake of minerals may contribute to higher levels of blood pressure reported in some ethnic groups.

According to the results, SBP was positively correlated with BMI, WC, total body fat percentage, truncal body fat percentage and truncal fat/lean ratio, after controlling for age and gender. As discussed before (Section 4.4.1) for the same BMI, WC, HC and age, Indian individuals participating in the current study had higher percentages of total body fat, total body fat/lean and truncal body fat relative to Europeans and Iranians. Given the significant associations between SBP and different total and truncal adiposity measurements discussed previously, these findings could probably explain the higher SBP observed in the Indian participants.

5.2.4 Lipid profile, hs-CRP and renal function

A. Lipid profile

In the current study, ethnicity was found to be a significant predictor of serum lipids, after controlling for age, sex and BMI. It is known that ethnic difference in lipid profile may be due to ethnic-specific lifestyle factors as well as genetic variation (Chang et al. 2011; Bentley et al. 2014).

The results indicated that the age & sex-adjusted mean values of total cholesterol, LDL-chol and triglycerides in Iranian participants were lower than those in other ethnic groups. These findings were inconsistent with other studies conducted in Iran, showing relatively high levels of these lipid measurements in Iranian adults and adolescents (Azizi et al. 2002; Azizi et al. 2003; Kelishadi et al. 2004). For example, in a survey conducted by Azizi et al (2003), mean values of 210 mg/dl (5.43 mmol/l), 133 mg/dl (3.44 mmol/l) and 173 mg/dl (1.95 mmol/l) were reported for total cholesterol, LDL- cholesterol and triglycerides concentrations of 6246 participants aged 20-64years living in Tehran, respectively. These results are much higher than those found in this study (total cholesterol: 4.75 mmol/l; LDL-chol: 3.00 mmol/l; triglycerides: 1.30 mmol/l) which was conducted in Australia. However, mean HDL-chol observed in Azizi et al.'s study was almost equal to that in our study (1.11 vs 1.12 mmol/l). These findings suggest that the levels of total cholesterol, LDL-chol and triglycerides in Iranian population may be affected mainly by lifestyle factors rather than genetics.

It is known that lifestyle factors, including unhealthy diet and physical inactivity play key roles in developing dyslipidaemia in some populations (Kelishadi et al. 2004; Ghosh 2007; Kelishadi et al. 2012; Huffman et al. 2012). There are several studies reporting high levels of serum lipids and lipoproteins (except HDL-chol) in people consuming foods rich in saturated and trans fatty acids, and cholesterol (Ghosh 2007; de Roos, Schouten, and Katan 2001). However, the health hazards of trans-fatty acids are more than do saturated fats (de Roos, Schouten, and Katan 2001). Because, in addition to increasing total cholesterol and LDL- cholesterol (like saturated fatty acids), they decrease serum HDL- cholesterol concentrations. Trans-fatty acids are present mainly in margarines and partially hydrogenated vegetable oils produced commercially in food manufactures.

Mandatory labelling of trans-fatty acid on packaged food products as well as increasing awareness of customers of the unfavourable effects of saturated fat on lipid profile have led to significant decrease in consuming saturated fat and trans-fatty acids in western countries. However, hydrogenated and partially hydrogenated vegetable oils are still widely used in Asian countries such as Iran, resulted in

consuming trans-fatty acids as about twice as those in developed countries (Mozaffarian et al. 2007).

In this study, the levels of total and LDL cholesterol measured in Indian participants were significantly higher than Iranians, while they had significantly lower dietary fat and cholesterol intake. This could be due to the fact that serum lipids may be also affected by consumption of dietary factors such as fibre (Brown et al. 1999), magnesium (Olatunji and Soladoye 2007) and calcium (Ditscheid, Keller, and Jahreis 2005), which were consumed in lesser amounts by Indian than Iranian participants. Moreover, despite of significantly lower cholesterol in Iranian participants compared to Europeans, there was no significant difference between them in the intakes of different dietary components. This discrepancy could be also explained by a tendency for higher physical activity in Iranians than those determined in European participants.

In the current study, there was no significant relationship between total cholesterol or LDL-cholesterol and the measures of general and truncal fatness. Consistent with these results, in an intervention study conducted on 578 (222 cases and 356 controls) Iranian adults, despite a significant increase in BMI of both intervention and control groups, significant decrease in dietary intake of cholesterol in intervention group was accompanied with concomitant decrease in their serum total cholesterol concentrations compared to control group (Mirmiran et al. 2008). These findings confirm that the levels of total cholesterol and LDL-chol are influenced more by dietary fat and cholesterol intake than by the body fat.

In contrast to total and LDL cholesterol, the levels of triglyceride and HDL-chol were significantly correlated with the measures of general and truncal fatness. However, the degree of associations between these lipid profile and different body fat measurements varied among three ethnic groups. These findings were consistent with another study conducted by Valsamaki et al. (2004) showing significant relationships between TG (positively) and HDL – chol (negatively), and visceral adiposity, which can be influenced by genetic factors as well.

In this study, HDL–chol measured in Indian participants was negatively correlated with total and truncal adiposity. Additionally, the results showed that (Section 4.4), Indians are susceptible to have a higher percentage of total and truncal body fat for the same BMI compared to Caucasians. These results are in line with other studies comparing anthropometric features of South Asians, Europeans and Afro-Caribbean people in West London (McKeigue, Shah, and Marmot 1991). These findings support this hypothesis that the lower HDL-chol in Indians than that in Europeans reported in previous research (Raji et al. 2001; Valsamakis et al. 2004) and the current study may be due to their relatively high percentages of total body and abdominal fat.

The lower HDL-chol relative to Europeans was also found in the Iranian participants, although the difference was not significant statistically. It is known that genetic variation may also cause a different response of the body to acquired factors. An elevation of 1unit in BMI has been shown to be associated with an overall decrease in HDL- chol of 0.08 mmol/l (Anderson et al. 1987). However, the amount of increase/decrease in HDL-chol resulted from the changes in BMI is not the same among different ethnic groups, and they may present different degree of sensitivity. In an epidemiological study evaluating changes in anthropometric measurements and lipid profile during a period of 3.6 years in Iranian adults, an increase in BMI of 1 unit leaded to a decrease in HDL-chol of 0.10-0.13 mmol/l (Bozorgmanesh et al. 2008), which was higher than value observed in Caucasians (Anderson et al. 1987). These findings may explain the higher prevalence of low HDL-chol phenotype found in some ethnic groups including Iranians (Azizi et al. 2002; Sharifi et al. 2008; Schwandt, Kelishadi, and Haas 2010).

B. hs-CRP

Acute phase reactants including CRP have been shown to play an important role in the atherosclerotic inflammatory process (Zwaka, Hombach, and Torzewski 2001). According to the guideline issued by American Heart Association, hs-CRP levels of 0 to <1mg/L, 1-3mg/L, >3-10 mg/L are associated with low risk, intermediate risk and high risk for cardiovascular diseases, respectively (Pearson et al. 2003). In the current study, European and Indian participants had higher mean concentrations of

hs-CRP relative to Iranians. Although, the differences between groups were not significant statistically, the mean values >3 mg/L found in Europeans (4.64±0.83 mg/l) and Indians (3.50±0.81 mg/L) indicated that they are at higher risk of cardiovascular events relative to Iranians who had mean hs-CRP<3 mg/L.

Regardless of ethnicity, hs-CRP determined in our participants was correlated with different measures of obesity. In agreement with the results, excess fat tissue has been indicated to induce the production of inflammatory markers such as CRP (Yudkin et al. 1999). However, according to our results hs-CRP tended to be significantly more correlated with total body fat than with truncal adiposity. As mentioned before (Section 4.4.1), the European and Iranian participants had the highest and the lowest total body fat percentages, the same pattern as that observed for hs-CRP.

In the current study, female participants had a significantly higher mean value of hs-CRP compared to males. This was in line with some previous studies assessing gender difference in CRP levels (Khera et al. 2005; Lakoski et al. 2006). Furthermore, CRP has been also suggested as a better predicting marker for the risk of cardiovascular diseases in women than men (Qasim et al. 2011). For all ethnicities, females participating in the study had a higher total body fat compared to males; however they were less likely to accumulate fat in the abdominal area (indicated by truncal body fat percentage) (see Section 4.4.1). Also, as mentioned above hs-CRP measured in the participants was significantly more correlated with total body fat than with truncal fat. These findings would also help explain the significantly higher hs-CRP reported in females participating in the present study than that measured in males.

Given the findings mentioned above, among different biomarkers of metabolic syndrome, hs-CRP was significantly associated with those being more correlated with total body fat including glucose, insulin and HOMA. This was consistent with the results of several studies conducted in different countries, age and ethnic groups (Chambers et al. 2001; McLaughlin et al. 2002; Zuliani et al. 2009). In the current study, there were overall associations between hs- CRP and some serum lipids (TG, total chol.); however they did not remain significant after controlling for age and

gender. The results also showed no significant correlation between hs- CRP and systolic and diastolic blood pressure. It is suggested that inflammation may contribute to initiation of hypertension via secretion of some mediators, such as CRP (Bautista 2003). However, the results of human studies investigating the link between CRP and blood pressure have been controversial. While, analysis of the Third National Health and Nutrition Examination Survey (NHANES III) data collected from 1988 to 1994 showed a positive relationship between CRP and blood pressure across a wide range of blood pressure categories (King et al. 2004), no significant association was found in some other studies (Bautista et al. 2005).

Interestingly, it was observed that the degree of associations between CRP and biomarkers associated with the metabolic syndrome were not constant across ethnicities. It has been shown that the serum CRP levels in populations can be affected by genetic variation (Crawford et al. 2006). According to the results, there was significant associations between hs-CRP and HOMA, as a marker of insulin resistance, in Iranian and Indian groups, but not in Europeans. Similarly, the associations between hs-CRP and various body fat measurements tended to be stronger and more significant in Iranians and Indians than in Europeans. Additionally, there was no overall association between hs-CRP and serum lipids, after controlling for age and gender. However, hs-CRP measured in Indians was significantly correlated with LDL-chol (positively) and HDL-chol (negatively), when data was analysed for three ethnic groups, separately. On the other hand, as discussed above, hs-CRP has been found to be more correlated with total body fat rather than truncal fatness. As a result, there is a possibility that it would not reflect the risk of cardiovascular disease accurately.

Given the strong link between metabolic syndrome components and the occurrence of cardiovascular diseases, these findings suggest that hs-CRP may be more accurate to predict cardiovascular events in Iranians than in Indians and Europeans.

Microalbuminuria was detected in a greater number of European participants than Indian participants. Although, the difference was not statistically significant, the higher rate of microalbuminuria with a lower mean age (38.2 versus 55.6 year) in Indian is considerable. This finding agrees with the findings of the United Kingdom

Asian Diabetes Study (UKADS) which compared microalbuminuria and proteinuria in south Asian and white European ethnicity. Similar to the present study, younger south Asian participants had statistically significant higher proteinuria in comparison to white European (Raymond et al. 2011). Accordingly, the difference between Indian and other ethnic groups suggest Indians present microalbuminuria and related disorders more commonly than other ethnic groups. Further studies needed to focus more from this view in metabolic syndrome amongst Indian compare to other ethnic groups.

5.3 The effects of ethnicity on endothelial markers

Cellular adhesion molecules including E-selectin and VCAM-1 have been postulated to participate in the pathogenesis of atherosclerosis (Cybulsky and Gimbrone 1991; Li et al. 1993; Kawakami et al. 2006). These adhesion molecules are detectable in the serum in their soluble forms. Increased concentrations of soluble adhesion molecules have been shown in patients with coronary artery atherosclerosis (Blann, Amiral, and McCollum 1996; Damnjanovic et al. 2009) and peripheral artery diseases (De Caterina et al. 1997).

In the current study, the serum level of E-selectin in Europeans was significantly correlated with insulin and HOMA. This was in line with the results of previous studies reporting the elevated levels of E-selectin in patients with different cardiovascular diseases risk factors, including insulin resistance, hypertension, dyslipidemia and diabetes mellitus (Hackman et al. 1996; Abe et al. 1998; Matsumoto et al. 2000; Palomo et al. 2003; Glowinska et al. 2005; Boulbou et al. 2005; Song et al. 2007; Maggio et al. 2012). European volunteers participating in the study had significantly higher insulin, HOMA and serum lipids levels as well as total body fat percentage relative to Iranians (see Section 4.4). Moreover, it has been found that there is a close correlation between the increased level of E-selectin and general obesity (Matsumoto et al. 2002). An elevation of 1 unit in BMI has been shown to be associated with an approximate 2% increase in E-selectin level (Miller and Cappuccio 2006). Therefore, the higher E-selectin levels detected in Europeans participating in this study compared to Iranians is not surprising.

However, the differences between European and Indian participants were statistically significant only when they were compared for glucose, but not for other measurements mentioned above (see section 4.4). In this study, ethnicity was found as a significant predictor for circulating level of E-selectin after controlling for age, gender and BMI. To the best of our knowledge, this is the first report showing the association between ethnicity and E-selectin in these ethnic groups.

VCAM-1 was another endothelial marker assessed in this study. In the present study, the trends found for VCAM-1 were contrary to what was observed for E-selectin. The ethnic-related differences in the circulating VCAM-1 concentrations have been found among some ethnic groups. In a study conducted on 261 white, 188 African origin and 215 South Asian individuals living in England, participants with African ancestry had significantly lower VCAM-1 concentration relative to two other groups. There was no significant difference between the VCAM-1 concentrations measured in white and South Asian participants (Miller et al. 2003). However, there has been no study to compare the levels of circulating VCAM-1 in Iranians with any other ethnic groups. Also, we are unable to explain these findings based on the differences in metabolic syndrome components observed among three ethnic groups. Because, as mentioned above, the relationship between VCAM-1 and cardiovascular risk factors is still a matter of controversy. Therefore, further studies are required to confirm these results and provide the most possible justifications in this regard.

According to the data, there was no significant association between VCAM-1 and different metabolic measurements of FBG, insulin, HOMA, lipid profile and blood pressure after controlling for age and gender. As mentioned above, the correlations between E-selectin and the risk factors of cardiovascular diseases have been confirmed by several studies. However, the results of research examining the relationship between VCAM-1 and the metabolic measurements mentioned above have been controversial.

For example, the elevated levels of VCAM-1 have been reported in older men with uncomplicated essential hypertension by DeSouza et al. (1997), but in a study conducted by Ferri et al. (1999) there was no significant difference between VCAM-1 levels evaluated in hypertensive and normotensive men, in either obese or non-

obese groups. Or, in another study examining the association between blood pressure and cellular adhesion molecules levels of P-selectin, E-selectin, ICAM-1 and VCAM-1 in a multi- ethnic population, only the correlation between circulating levels of E- selectin and blood pressure remained significant after adjustment for age (Miller et al. 2004).

Similarly, the results of a study evaluating the relationship between insulin resistance and different soluble adhesion molecules including E-selectin, ICAM-1 and VCAM-1, has shown that the degree of insulin resistance was significantly associated with all of these markers. However, the correlation between VCAM-1 and insulin resistance was abolished after adjustment for age and gender as possible confounders (Chen, Holmes, and Reaven 1999). Moreover, it was shown that the relationship between cellular adhesion molecules and cardiovascular risk factors is adhesion molecule specific and may differ with age and gender (Miller et al. 2004). Given these findings, it seems that among different cellular adhesion molecules mentioned above, E-selectin has a strong association with metabolic syndrome markers; and may possibly be a better marker for predicting of cardiovascular diseases.

5.4 The assessment of ethnicity on Adiponectin

Adiponectin is an adipocytokinase secreted specifically and plentifully by adipocytes, and plays an important role in preventing obesity-linked disorders, particularly insulin resistance. The findings of the current study highlight that the European group had significantly higher adiponectin levels than Indians and Iranians. The lower adiponectin level found in Indians than Europeans was consistent with other multiethnic studies undertaken on Indian and Caucasian subjects (Smith et al. 2006; Mente et al. 2010; Vuksan et al. 2012). It has been shown that Indians have higher rates of cardiovascular events compared to Caucasians (Anand et al. 2000; Vuksan et al. 2012); however the underlying causes are not fully understood. It is known that adiponectin has an anti-diabetic, anti-atherogenic and anti-inflammatory effects, and a decrease in the circulatory adiponectin level may have a role in developing type 2 diabetes and metabolic syndrome (Lindsay et al. 2002; Matsuzawa et al. 2004; Mente et al. 2010).

There was no study comparing the adiponectin level and metabolic syndrome risk factors between Europeans and Iranians in one environment. The level of adiponectin determined in normal Iranians living in Iran (Shojaie, Sotoodah, and Shafaie 2009) was obviously lower than those reported in Caucasians participating in different studies (Mente et al. 2010; Pischon et al. 2005). Namely, the level of adiponectin in relatively healthy Iranians was almost equal to those in Caucasians with cardiovascular events, indicating that in the basis of adiponectin, Iranians are more prone to the cardiovascular diseases and metabolic syndrome compared to Europeans. Existing evidence confirmed a higher risk of cardiovascular events and type 2 diabetes mellitus among Iranians having a lower level of adiponectin (Shojaie, Sotoodah, and Shafaie 2009; Mohammadzadeh and Zarghami 2009).

It has also been shown that the level of adiponectin can be affected by genetic, environmental factors resulting in obesity, and dietary habits. In the current study, serum adiponectin concentration was inversely correlated with truncal body fat percentage. Furthermore, truncal body fat percentage remained a significant predictor of circulatory adiponectin after controlling for other factors. In agreement with these results, Staiger et al. showed that serum concentration of adiponectin is associated with proportion of fat accumulated in the abdominal area (Staiger et al. 2003). Given the anti-atherogenic effects of adiponectin, the findings also confirm other studies demonstrating that the susceptibility for atherosclerosis is mainly determined by the localisation of fat mass rather than general obesity (Tanko et al. 2003; Ferreira et al. 2004). As mentioned before (see Section 4.4.1), Indian subjects participating in this study had a higher truncal body fat percentage relative to Europeans. This can be a probable explanation for the lower level of adiponectin detected in Indians when compared to European participants.

In all ethnicities, women participating in this study had a higher mean value of adiponectin than men. This finding was consistent with another study in this regard (Staiger et al. 2003). Given the relationship of fat distribution and adiponectin discussed above, the significant difference in circulatory level of adiponectin between men and women participating in this study can be explained partly by the significant difference between their truncal body fat percentages. As indicated before (see Section 4.4.1), for all ethnicities, men had a lower total body fat compared to

women; however they were more likely to accumulate fat in the abdominal or visceral area. Furthermore, the higher adiponectin level found in female humans and rodents suggest that adiponectin regulation may be affected by sexual hormones, such as oestrogen and testosterone (Combs et al. 2003; Xu et al. 2005).

In the current study, the adiponectin showed inverse correlation with glucose, insulin and HOMA score in Iranians, but not in Indians and Europeans. These findings were partially in line with the results of Giahi et al.'s study (2008) showing a positive correlation between adiponectin and insulin sensitivity in diabetic and non-diabetic Iranian men, although the association was statistically significant only in non-diabetics. Similarly, in other studies conducted on native Canadians and Alaskan Eskimo, the level of adiponectin was negatively correlated with insulin and HOMA-IR (Hanley et al. 2003; Goropashnaya et al. 2009). It was shown that the effect of adiponectin on insulin sensitivity can be modified by ethnicity. Namely, each given decrease in adiponectin may result in different amount of increase in HOMA score across ethnic groups (Mente et al. 2010). This may explain the different association between adiponectin and insulin resistance among ethnic groups in the current study.

In this study, adiponectin showed a negative association with the total carbohydrate intake. Additionally, the intake of carbohydrate was found to be a significant predictor of serum adiponectin after controlling for other factors. These results were consistent with previous studies investigating the relationship between high carbohydrate diet and adiponectin level (Nakamura et al. 2004; Pischon et al. 2005; Laughlin et al. 2007). Legumes and vegetables are other dietary factors which were suggested to have a role in relation to adiponectin. It was shown that there is a positive correlation between consumption of legumes and the level of adiponectin (Detopoulou et al. 2010). Iranian subjects participating in this study had a tendency toward an increased intake of carbohydrate relative to Europeans. In addition, the amount of vegetables and legumes consumed by Iranians and Indians were significantly lower than those in Europeans. These findings indicate that apart from race differences, the significantly lower adiponectin observed in Iranians compared to Europeans may be due to their different dietary habits.

To sum up, the European participants had generally higher mean values of total and truncal body fat percentages, glucose, insulin, HOMA, serum lipids and blood pressure (SBP & DBP) relative to Indians and Iranians. The tendency for a higher risk of cardiovascular diseases found in European participants were confirmed with their higher levels of hs-CRP and E-selectin relative to those of Indians and Iranians. Also, in overall, Iranian participants seem to be healthier than two other groups.

In this study, the mean values of BMI/WC measured in Indian participants were just slightly lower than those in Europeans and Iranians. However, the patterns observed for some measurements changed when data were adjusted for these non-significant differences. Namely, after adjustment, Indian participants had the highest total and truncal body fat, HOMA and blood pressure among three ethnic groups. These results suggest that a better health situation found in the Indian group relative to Europeans may be in part due to these slight differences. Accordingly, Indians may be at a higher risk for metabolic syndrome than others in populations with exactly similar BMI and WC measurements. The next chapter is the concluding chapter of the thesis and presents the strengths, and recommendations of the study.

Chapter 6

Recommendations, Significance and Conclusions

6.1 Brief overview

This final chapter presents the recommendations, significance and conclusions drawn from the research and supported by the literature. Metabolic syndrome is a cluster of risk factors leading individuals to diabetes and cardiovascular diseases. Given the personal and socio-economic impacts of these widespread chronic diseases, gathering sufficient and accurate knowledge and evidence concerning the metabolic syndrome plays a key role in defining effective prevention programs.

Despite many studies having been undertaken globally and offering various definitions for the metabolic syndrome, there is still no general consensus on how to apply the accurate definitions and their diagnostic criteria, among different ethnic groups. Given this gap, research in a region such as Australia comprising people with different ethnicity living in a unique environment provides an opportunity to clear up some controversies around this issue.

Therefore, in order to achieve the **first objective**, metabolic syndrome criteria among a cross-section of immigrants from three ethnic groups in Western Australia using four common international definitions of metabolic syndrome was compared. Subsequently, the effects of ethnicity on different components of metabolic syndrome were investigated.

The findings of this study showed that using various definitions for metabolic syndrome lead to a wide range of prevalence estimates. This in turn can influence the prevention strategies for chronic diseases in the populations. Accordingly, there is still a need for clear consensus on a uniform definition of metabolic syndrome. In this study, the percentage of participants defined as having metabolic syndrome by WHO was lower than those with metabolic syndrome based on ATP III and IDF; however, the highest percentage of participants with insulin resistance was

discovered by WHO definition. Given the association between insulin resistance and other cardiovascular risk factors, these findings suggest that the WHO definition may have more accuracy to recognise individuals with higher risk of CVD compared to other three definitions of metabolic syndrome. Moreover, although the IDF definition seems to have slightly lower power in predicting the risk of CVD than WHO, it may be more practical from a clinical diagnostic perspective.

It is known that among different components of metabolic syndrome, obesity (general & central) has a central role. Therefore, establishing optimal cut-off points for BMI and waist circumference, as anthropometric indices of total and truncal body fat, is necessary. While, several studies have shown that recommended cut-off points for BMI and waist circumference vary according to ethnicity and gender, there has been no general agreement so far about the specific values being applied for men and women in different ethnic groups.

The results showed that European participants had higher total body fat percentage relative to Indians and Iranians; however this trend changed after adjusting for age and BMI. For a given age and BMI, the Indian group had higher mean value of total body fat percentage and total body fat/lean ratio, relative to Europeans and Iranians. In addition, there was no significant difference between the mean BMI of men and women participating in this study, but in all three ethnic groups, women had significantly higher total body fat, body fat percentage and total fat/lean mass ratio compared to men. This pattern was also observed for men and women in all ethnic groups, when they were evaluated for the age & WC adjusted mean values of truncal fat mass and truncal fat/lean ratio.

In this study, despite the higher mean values of glucose, insulin and HOMA in Caucasians relative to two the other groups, Indian participants had the highest mean of HOMA score, after adjustment for age, gender and WC. Regression and correlation analyses showed that insulin resistance (indicated by HOMA) was related to different measurements of adiposity. However, HOMA tended to be more correlated with the measurements of truncal fat than generalised fatness. In the current study, ethnicity was found as a significant predictor of insulin resistance after controlling for different measurements of fatness. This suggests that the higher rates

of insulin resistance reported in Indians may be in part due to their higher truncal adiposity resulted from ethnic differences.

Similarly, the European participants had higher means of systolic and diastolic blood pressure compared to Indians and Iranians, but after adjusting for age and gender, the mean values of systolic and diastolic blood pressure in Indians were higher than two other groups. The regression analysis showed ethnicity as a significant predictor of diastolic blood pressure after controlling for other variables.

According to the results, SBP was positively correlated with different measurements of total and truncal adiposity, after controlling for age and gender. Additionally, the difference in SBP/DBP between Indians and Iranians became more significant after adjustment for WC. It was shown that for the given WC and age, Indian individuals participating in this study had higher percentages truncal body fat relative to Europeans and Iranians. These findings could partly explain the higher SBP observed in Indian participants.

The results indicated that European and Iranian participants had the highest and the lowest age & sex-adjusted mean values of total cholesterol, LDL-cholesterol and triglycerides among three ethnic groups, respectively. In the current study, ethnicity was also shown as a strong predictor of total cholesterol, HDL-cholesterol, LDL-cholesterol and TG, after controlling for other variables. It is known that the ethnic difference in lipid profile may be due to genetic variation as well as ethnic–specific lifestyle factors, such as dietary pattern and physical activity. We found no significant correlation between total or LDL-cholesterol and the measures of general and truncal fatness. Accordingly, the serum levels of these lipids are thought to be more influenced by dietary factors and physical activity. However, HDL-cholesterol and TG were significantly correlated with visceral adiposity, which can be affected by both acquired and genetic factors.

These findings support the hypothesis (see Section 1.2) that ethnicity plays a significant role in developing metabolic syndrome risk factors affecting components such as, body mass index (BMI), central obesity, hypertension, dyslipidaemia, fasting blood glucose and Insulin resistance. Based on the guidelines issued by

American Heart Association, the hs-CRP mean values >3 mg/L found in the European and Indian groups indicated that based on hs-CRP levels, they are at higher risk of cardiovascular events relative to Iranians who had mean hs-CRP<3 mg/L.

Regardless of ethnicity, not only, hs-CRP determined in the participants was correlated with several different measures of obesity, but also it tended to be significantly more correlated with total body fat than with truncal adiposity. This finding would help explain the significantly higher hs-CRP reported in Europeans relative to Indians and Iranians, and in the females participating in the present study than those measured in males.

Additionally, the degree of associations between CRP and different metabolic syndrome components assessed in this study varied across ethnic groups. Since, the associations between hs-CRP and different components of metabolic syndrome assessed in Iranians were stronger than those observed in Indians and Europeans, these findings suggest that the prognostic value of hs-CRP for predicting cardiovascular diseases may be more accurate in Iranians than two other groups.

The **second specific objective**, evaluated the effects of ethnicity on the endothelial function in the ethnic groups. In this study, European, Indian and Iranian participants were compared for soluble forms of E-selectin and VCAM-1, as biomarkers of endothelial dysfunction. The mean values of E-selectin measured in Europeans were significantly higher than those in Iranians and Indians. This was in line with the results of hs-CRP suggesting that Europeans may be at a higher risk for cardiovascular diseases compared to two other groups. However, comparison between VCAM-1 measured in three ethnic groups showed a pattern contrary to what was observed for E-selectin. In this study, ethnicity was found as a significant predictor for circulating level of E-selectin after adjusting for age, gender and BMI. Since, E-selectin has a strong association with metabolic syndrome components and markers; it seems that among different cellular adhesion molecules, it would be a more reliable marker for prediction of cardiovascular diseases risk.

It is known that the increased risks of metabolic syndrome in different populations can be because of the factors related to health behaviours. Accordingly, individuals

participating in this study were also evaluated for their dietary habits and nutrients intakes, **as the third specific objective**.

In the current study, there was no significant difference between the amounts of carbohydrate taken by three ethnic groups; however they showed differences in regard to the intake of other nutrients. Namely, participants in Indian group had significantly lower intakes of protein, magnesium and sodium compared to Europeans and Iranians. Indian participants also had the lowest intakes, when three ethnic groups were compared for total daily energy intake, dietary fat, and calcium.

The highest consumption of vegetables & legumes per day was consumed by Europeans, while participants in Iranian group consumed the highest amounts of fruits and breads & cereal foods in comparison with Europeans and Indians.

Additionally, the relationship between these differences in nutrient intakes and different metabolic syndrome components were evaluated. The results highlighted a significant positive association between diastolic blood pressure and the dietary intake of sodium in regression analysis. However, the higher systolic and diastolic blood pressure observed in the Indian group was accompanied with a significantly lower intake of sodium in comparison to European and Iranian descents [Table 13 &Table 16]. On the other hand, Iranian participants with the highest average of sodium intake had the lowest mean systolic and diastolic blood pressure among three ethnic groups. We suggest that these inconsistencies may be explained by higher intake of other minerals (magnesium, calcium and potassium) modifying the effects of sodium. Iranian and European participants in this study had higher intakes of these minerals than Indians. These findings suggest that in addition to ethnic susceptibility, and total & truncal adiposity, imbalanced dietary intake of minerals may contribute to higher levels of blood pressure reported in some ethnic groups.

The levels of total and LDL cholesterol measured in Indians participating in this study were significantly higher than Iranians, while they had significantly lower dietary fat and cholesterol intake. This could be due to the fact that serum lipids may be also affected by consumption of dietary factors such as fibre (Brown et al. 1999), magnesium (Olatunji and Soladoye 2007) and calcium (Ditscheid, Keller, and Jahreis

2005), which were consumed in lesser amounts by Indian than by Iranian participants. Also, there was no significant relationship between total cholesterol or LDL-cholesterol and the measures of general and truncal fatness. These findings were consistent with other intervention studies indicating that the levels of total cholesterol and LDL-chol are influenced considerably more by dietary factors than by the body fat (Mirmiran et al. 2008).

Among different metabolic biomarkers evaluated in this study, there was a negative association between adiponectin and the total carbohydrate intake. Additionally, the intake of carbohydrate was found to be a significant predictor of serum adiponectin after controlling for other factors. These results were consistent with previous studies investigating the relationship between high carbohydrate diet and adiponectin level (Nakamura et al. 2004; Pischon et al. 2005; Laughlin et al. 2007). Legumes and vegetables are other dietary factors which were suggested to have a role in relation to adiponectin. It was shown that there is a positive correlation between consumption of legumes and the level of adiponectin (Detopoulou et al. 2010). As presented in Table 16, Iranian subjects participating in this study had a tendency toward an increased intake of carbohydrate relative to Europeans. In addition, the amount of vegetables and legumes consumed by Iranians and Indians were significantly lower than those in Europeans. These findings indicate that apart from race differences, the significantly lower adiponectin observed in Iranians compared to Europeans may be due to their different dietary habits.

As the final specific aim, the relationship between adiponectin and different components of metabolic syndrome amongst ethnic groups was explored. According to the results, Iranian and Indian individuals participating in the current study had a significantly lower adiponectin compared to Europeans. It was also found that other than the race differences, the significantly lower adiponectin observed in Indians and Iranians relative to Europeans can be in part due to their different truncal body fat percentages and dietary habits respectively. Also, ethnicity was demonstrated as a main predictor of serum adiponectin after controlling for other factors.

6.2 Significance of the study

It is well known that the metabolic syndrome and its related outcomes present a significant burden of disease all over the world. Despite many studies trying to define accurate diagnostic criteria and cut-offs for metabolic syndrome particularly among different ethnic groups, there is still no general consensus about the definition and criteria. The controversies were mostly due to the differences in methods applied for these researches such as using different samples from dissimilar ethnic groups as well as doing their studies in different countries and regions.

This study was undertaken in the same region compromising immigrants from different ethnicities. This condition along with including the criteria of living in Australia for at least 5 years were to minimise the potential biases resulting from the factors related to the environment and lifestyle, which may have roles in developing of metabolic syndrome.

This is the first experimental study in Australia comparing a wide range of elements such as routine biomedical factors, some specific endothelial markers, anthropometric measurements, dietary and body fat measurements using dual energy X-ray absorptiometry in three different ethnic groups. Accordingly, the effects of ethnicity on different cardiovascular risk factors have been investigated much more comprehensive than other similar studies.

Three ethnic groups including immigrants with a background from European countries, India and Iran were chosen for this study since they either were major ethnic group in Australia and can thus have a significant impact on health nationally or there are existing similar studies about migrants from these ethnic groups in the origin or other countries.

It is significant that unlike most of the other studies this research follows a multi-approach to metabolic syndrome. Therefore, the results of the current study can be considered for both decision makers and health professionals in the societies to improve related prevention programs in this regard.

6.3 Limitations

The current study should be interpreted within the context of its limitations. First of all, this study was conducted with a pilot-scale sample size. Although different methods of recruitment were undertaken for this purpose, only a limited number of eligible participants could be recruited. The small sample size precludes generalising the results to a wider population. Although the selection of 14 suburbs with the most population of targeted ethnic groups could decrease biases to minimum, this method could not omit the whole biases in this regard. There were also financial limitations in conducting this study with a larger sample size. Without these limitations, there was a good opportunity to enhance the power of study.

The ability to examine oral glucose tolerance tests (OGTT) was also limited because of volunteers' time limitation. The prevalence of impaired glucose tolerance was reported as 10.6% in Australia according to the AusDiab study. Due to limitation in performing oral glucose tolerance test, the prevalence of metabolic syndrome for the WHO definition reported in the current study may be underestimated by up to 10.6%. However, some of the participants with impaired glucose tolerance may have been characterized as metabolic syndrome cases in the analyses, because they may have met other components of the WHO definition.

Another limitation of the current study is that the insulin sensitivity is determined by HOMA-IR formula rather than the insulin sensitivity index derived from hyperinsulinemic euglycemic clamp as the gold standard method. Other studies show that the correlations between the insulin sensitivity index and HOMA-IR range from 0.69 to 0.79 (Bonora et al. 1998; Matsuda and DeFronzo 1999). However, HOMA-IR calculation is more practical for studies involving large number of participants.

6.4 Recommendations

The results of the current study as well as a review of different studies in the literature show the importance of ethnicity on metabolic syndrome criteria and components using four common definitions. This part suggests a range of particular and brief recommendations in this regard for different parties involving the metabolic syndrome.

6.4.1 Recommendation for the World Health Organisation

Since, ethnicity plays a key role in metabolic syndrome demonstrations, it is recommended to the WHO to improve the definition of metabolic syndrome through consider the ethnicity as principal criteria in further definition/s. Namely, not only the cut-off points of BMI and WC, but also other components such as fat profile cut-offs would be considered according to the ethnical specifies and differences. As it mentioned in section 2.2.1, only the definition recommended by the International Diabetes Federation (IDF) has considered the criterion of WC according to the population specifics.

Moreover, because of the role of body fat in metabolic syndrome, it seems that the amount of fat would be considered as a criterion in new definitions of metabolic syndrome. However, it should be defined on gender and ethnic based.

It is also recommended that in the management of metabolic syndrome at global scale needs to follow the policy of "think globally and act locally".

6.4.2 Recommendation for health economic and insurance organisations

Due to the importance of the health economy and the heavy impact of burden of diseases related to metabolic syndrome, it is recommended that the economic policies in health sector would be based on the more accurate criteria and definitions. These policies help them to decrease the costs in health sector from both commonwealth and out of pocket proportions via well-timed screening as well as prevention programs which are much inexpensive than further treatments.

6.4.3 Recommendation for the scientific organisations and researchers

It is recommended that to improve and complete their current strategic and action plans through considering the effects of ethnicity on different preventable diseases for further research. This approach may cause a convergence between different research outcomes of and subsequently decreases the controversies in this regard.

6.4.4 Recommendation for the department of health in Australia and other health policy makers in multi-cultural countries

The recommendation to the department of health in multi-cultural countries particular Australia is that they should plan screening programs according to the ethnic basis for different diseases particular those related to the metabolic syndrome. This plan can decrease the health sector costs where the diagnosis and subsequently related preventive intervention programs are done at the beginning stages. It also may improve the quality of life leading to an increase of life expectancy index.

It is also recommended that the reference range of BMI and WC for detecting metabolic syndrome in both Indian men and women would be lower than those in the same gender of two other groups. Furthermore, the recommended cut-off points of BMI and WC in European women should be lower than that in Iranians women; however higher cut-off points need to be applied for European men compared to Iranian men.

6.5 Conclusion

This study highlights that, different components of metabolic syndrome including general and central obesity, insulin resistance, dyslipidaemia and hypertension may be affected by ethnicity. These findings support the hypothesis that ethnicity plays a significant role in developing metabolic syndrome risk factors.

Based on the adjusted measurements of comparing the total and truncal fatness in men and women of three ethnic groups, it is recommended that the reference range of BMI and WC for detecting metabolic syndrome in both Indian men and women would be lower than those in the same gender of two other groups. Also, the recommended cut-off points of BMI and WC in European women should be lower than that in Iranians women; however higher cut-off points need to be applied for European men compared to Iranian men.

The initial analysis showed that European and Iranian individuals participating in this study had the highest and the lowest mean values of total and truncal fat, serum

glucose, insulin and lipids, HOMA and blood pressure, respectively. These results were compatible with hs-CRP and E-selectin data analyses, indicating that Europeans may be at a higher risk of cardiovascular events. The initial patterns observed for most risk factors reformed then when data were adjusted for potential confounders (age and sex). Namely, Indian participants had the highest degree of total and truncal fatness and insulin resistance (indicated by HOMA), and systolic and diastolic blood pressure in new analysis, and the changes were more significant after additional adjustment for WC. However, there was no difference between the patterns observed for hs-CRP and E-selectin before or after adjustment for these variables.

The results of the regression analysis showed ethnicity as a main predictor of hs-CRP, E-selectin and adiponectin. The results found that the degree of associations between different components of metabolic syndrome and these biomarkers vary between ethnic groups. This may cause bias in predicting the risk of cardiovascular events in populations having a specific risk factor dominantly. These results along with the findings mentioned above suggest that biomarkers of cardiovascular diseases may have different levels of accuracy across ethnic groups. This important point should be considered when these biomarkers are used to compare the risk of cardiovascular diseases among ethnic groups.

It is hoped that the results of the study will provide a new path to further investigations with a larger sample size to extend these encouraging outcomes regarding metabolic syndrome among different ethnic groups.

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Appendices

Appendix 1

Does your family's ethnic background and life style make you

Overweight & unwell?

See the back for more information

Recent studies indicate that your family's ethnic background plays a key role in your health situation

A Curtin University research team is looking for volunteers to participate in research on the link between ethnicity and chronic diseases risk factors, particularly heart disease and diabetes

Who is invited?

Volunteers who meet the following criteria are invited to participate:

- ***Have a cultural background from Europe, China, India or Iran***
- ***Have lived in Australia for at least 5 years***

Plus one or more criteria mentioned below:

- ***Body Mass Index 25 or more***
- ***Waist circumference: >90 cm for Male and >80 cm for Female***
  (>2.4 尺 for Male and >2 尺 for Female in Chinese measurement)

Participation in the study involves two questionnaires, one blood sample and a whole body scan which measures body composition. All tests will be taken at Curtin University and take only up to 1 or 1.5 hours

To register your interest in participating in this study please contact:

Dr. Majid Meshkini
Tel: 9266 1382 or 0413 246 859
majid.meshkini@postgrad.curtin.edu.au

For more information or register on-line please visit:

http://cih.curtin.edu.au/research/student_research_doctoral_surveys_mmeshkini.cfm

This study has been approved by the Curtin University Human Research Ethics Committee; you may contact hrec@curtin.edu.au for further details

Appendix 2

Screening Checklist

Name: ……. ID: Sex: ☐Male ☐Female

Address:…….

Your country background: ……..

The main language you spoken at your home: ……..

Phone No.: H: ……..…W:……..… Mobile: .....….……

EMail: ...…… DOB: ……. Age: …...…...

Weight: ……..... Height: …….. W/H circumference: …… BP: ……

Medical History	Yes	No	Details
Are you a Smoker			
Females: Pregnancy, lactating, post-menopausal, gestational diabetes			
Have you had your glucose or insulin, cholesterol, TG, measured recently? Can you remember the results?			
Have you had, or have, a history of diabetes in your family?			
Medications			
Supplements			
Major operations			
Major illnesses/diseases: Do you have • Diabetes &High BP • Kidney disease (renal problems) • Liver disease &Hepatitis • HIV& Blood diseases • Heart disease& GI problems			
Did you have faints or blackouts?			
Do you have any allergies?			
What type of alcoholic drink do you usually drink?			
How many standard alcoholic drinks do you drink per day? How many days per week?			
Do you exercise regularly?			
Can we keep your contact details for future reference in clinical research?			

Appendix 3

Curtin University
Centre for International Health

Participation Information sheet

A comparison of overall health between migrants of Asian and European background: A West Australian study of Chronic Disease, Diet & Metabolic Syndrome Risk Factors

The following document provides some information regarding to a medical research with the title above and carrying out at Curtin University. Please feel free to ask any questions at any time.

Introduction:

This project evaluates the relationship between health risk factors and ethnic groups in Western Australia. The researchers are Associate Professor Jaya Earnest, Professor Moyez Jiwa and Dr Majid Meshkini. The study explores different risk factors among people of European, Chines, Indians and Iranian ethnicity. The reasons these groups are selected is because Europeans and Chinese are the largest group of migrants in Australia and there has been previous research on Indian and Iranian migrants.

The study will involve one clinical visit to Curtin University and two questionnaires to be completed by the participants because there is a need to show the biophysical and biochemical differences between the four different ethnic groups. More details about the study are mentioned below.

Background Information:

In recent decades, evidence of chronic disease such as heart disease, cancer and diabetes have risen significantly and has now reached epidemic proportions worldwide. These diseases are cause an estimated 35 million deaths annually - 60% of all deaths globally. Similarly, the rise of obesity as one of the most important causes of chronic disease, is affecting approximately 1.6 billion adults globally. In the stages before developing chronic diseases, there are some known signs called metabolic syndrome. Metabolic syndrome is a collection of disorders and conditions that develop into a wide range of life threatening diseases. Factors affecting metabolic syndrome include body specification like height, weight, waist circumference and other criteria such as blood pressure and blood fat including triglycerides and cholesterol. According to recent studies the prevalence of metabolic syndrome in Australia is 30.7%. This study aims to find out more details about risk factors beween ethnicity and chronic disease among the 4 migrant groups that will be studies.

Required commitment to the study: There will be a total of one visit at Curtin University.

Study procedures:

The first part of clinical visit will be a primary visit of 1 hour which will do at Health Service Centre. The procedures will be explained and primary measurements including body weight, height, waist circumference and blood pressure will be recorded. If participants meet the inclusion criteria, a written consent of each volunteer will be obtained. Approved participants will fill in two questionnaires: the Dietary Questionnaire and Physical Activity Survey, then a blood sample will be taken by a qualified nurse. Participants will be required to fast overnight for about 10-14 hours.

The second part of clinical visit will take 20 minutes. The DEXA test (Dual Energy X-ray Absorptiometry) (a safe test) to measure the body composition, will also be taken in the School of Physiotherapy.

Inclusion criteria:

- Aged 18 or more
- Parents of the volunteers must be from one of the countries mentioned below
    - European countries
    - China
    - India
    - Iran
- Participants have lived in Australia for at least 5 years
- Have working knowledge of written and spoken English

Plus one or more criteria mentioned below:

- Are Overweight: Body Mass Index of 25 or more (Weight $_{Kg}$ /Height$^{2}_{M}$)
- Waist circumference: 90 cm for Male and 80 cm for Female or more

Exclusion criteria:

- Pregnancy
- Breastfeeding

Possible adverse effects:

The blood samples may cause minor discomfort and possible bruising for some participants. This bruising however is minor and will dissipate after a few days.

General benefits & benefits to volunteers:

This clinical study will be important to evaluate metabolic syndrome in individuals. The findings of this study will suggest a possible link to genetic factors and various ethnic groups and may play a critical role in the prevention of these chronic diseases for those who are at risk. Your involvement in this study will be useful to the health of the general population in Australia and specifically in the area of migrant health, chronic disease and metabolic syndrome.

For your services as a volunteer in this study, you will receive copies of all your blood analyses results including Fasting Blood Sugar, Fat profile, Insulin, C-RP and DEXA test etc. We will advise you to refer to your GP if there is a finding of abnormality in your tests.

For your time in participating in the study, you will **have the option or choice** of:

1. receiving a $50 gift card voucher for travelling and parking expenses or

2. entering your name into a **raffle** for three $500 prizes which will be drawn at the end of study.

You will be informed about the date and time via the contact details provided by you at registration time. All participants **who choose** to enter the raffle have an approximately **1 in 50** chance to win. Those who opt for the gift voucher option will not be included in the raffle and draw.

Participants Privacy:
Your participation in this study is completely voluntary and you are free to withdraw from the study at any time. All results and personal information are strictly confidential and are only accessible by the researchers. Participants' privacy is reserved during all procedures including during publication of results. Your individual results will be emailed or sent by registered post.

Ethics Consideration:
This study has been approved by the Curtin University Human Research Ethics Committee (Approval Number HR179/2008). The Committee is compromised of members of the public, academics, lawyers, doctors and pastoral carers. It's main role is to protect participants, if needed, verification of approval can be obtained either by writing to the Curtin University Human Research Ethics Committee, c/- Office of Research and Development, Curtin University of Technology, GOP Box U1987, Perth, 6845 or by telephoning 9266 2784 or by emailing hrec@curtin.edu.au

Any questions may be answered or clarified by contacting:

1. Dr. Majid Meshkini on telephone no: 0413 246 859
   Email: majid.meshkini@postgrad.curtin.edu.au
2. Associate Professor Jaya Earnest on telephone no: 9266 4151
   Email: J.Earnest@curtin.edu.au
3. Professor Moyez Jiwa on telephone no: 9266 1768
   Email: M.Jiwa@curtin.edu.au

Appendix 4

WRITTEN INFORMED CONSENT FORM

Project Title: **A comparison of overall health between Asians and Australians from European background: A West Australian study of Chronic Disease, Diet & Metabolic Syndrome Risk Factors**

I, _____ hereby consent to be a volunteer for the study "A comparison of overall health between Asians and Australians from European background: A West Australian study of Chronic Disease, Diet & Metabolic Syndrome Risk Factors". I understand that the screening and examination process will involve: weight, height, waist/hip measurements, blood pressure, pulse wave analysis, DEXA (Dual Energy X-Ray Absorptiometry), a safe method to determination of body composition, filling Dietary Questionnaire, Physical Activity Questionnaire and screening questionnaire, and blood samples for assessments. I consent to having a total of 18 ml of blood drawn by a trained phlebotomist in fasting condition on the assessment day, which will be assessed for various biochemical assessments. The potential risks of all the procedures have been explained to me. I understand that my participation in this project is voluntary and I can withdraw from the project at any time.

Signature: _____

Name: _____

Witness: _____

Date: ___/___/___

_____

Any questions or misunderstandings may be answered or clarified by contacting Dr. Majid Meshkini on telephone 9266 3226 or email: majid.meshkini@postgrad.curtin.edu.au or Dr. Jaya Earnest on telephone 9266 4151 or email: J.Earnest@curtin.edu.au

Appendix 5

Dietary Questionnaire

QUESTIONS ABOUT WHAT YOU USUALLY EAT AND DRINK

Please fill in the date you completed this questionnaire:

DAY	MTH	YEAR
0 0	JAN	2004
1 1	FEB	2005
2 2	MAR	2006
3 3	APR	2007
	MAY	2008
	JUN	2009
	JUL	2010
	AUG	2011
	SEP	2012
	OCT	2013
	NOV	2014
	DEC	2015

INSTRUCTIONS:

This questionnaire is about your **usual** eating habits **over the past 12 months**. Where possible give only **one answer per question** for the type of food you eat **most often.**
(If you can't decide which type you have most often, answer for the types you usually eat.)

- Use a soft pencil only, preferably 2B.
- Do not use **any** biro or felt tip pen.
- Erase mistakes fully.
- Make no stray marks.

Please MARK LIKE THIS: ○●○○

1. How many pieces of fresh fruit do you usually eat per day? *(Count 1/2 cup of diced fruit, berries or grapes as one piece.)*

- ○ I didn't eat fruit
- ○ less than 1 piece of fruit per day
- ○ 1 piece of fruit per day
- ○ 2 pieces of fruit per day
- ○ 3 pieces of fruit per day
- ○ 4 or more pieces of fruit per day

2. How many different vegetables do you usually eat per day? *(Count all types, fresh, frozen or tinned.)*

- ○ less than 1 vegetable per day
- ○ 1 vegetable per day
- ○ 2 vegetables per day
- ○ 3 vegetables per day
- ○ 4 vegetables per day
- ○ 5 vegetables per day
- ○ 6 or more vegetables per day

3. What type of milk do you usually use?

- ○ none
- ○ full cream milk
- ○ reduced fat milk
- ○ skim milk
- ○ soya milk

4. How much milk do you usually use per day? *(Include flavoured milk and milk added to tea, coffee, cereal, etc.)*

- ○ none
- ○ less than 250 ml *(1 large cup or mug)*
- ○ between 250 and 500 ml *(1-2 cups)*
- ○ between 500 and 750 ml *(2-3 cups)*
- ○ 750 ml *(3 cups)* or more

5. What type of bread do you usually eat?

- ○ I don't eat bread
- ○ high fibre white bread
- ○ white bread
- ○ wholemeal bread
- ○ rye bread
- ○ multi-grain bread

6. How many slices of bread do you usually eat per day? *(Include all types, fresh or toasted and count one bread roll as 2 slices.)*

- ○ less than 1 slice per day
- ○ 1 slice per day
- ○ 2 slices per day
- ○ 3 slices per day
- ○ 4 slices per day
- ○ 5-7 slices per day
- ○ 8 or more slices per day

7. Which spread do you usually put on bread?

- ○ I don't usually use any fat spread
- ○ margarine of any kind
- ○ polyunsaturated margarine
- ○ monounsaturated margarine
- ○ butter and margarine blends
- ○ butter

8. On average, how many teaspoons of sugar do you usually use per day? *(Include sugar taken with tea and coffee and on breakfast cereal, etc.)*

- ○ none
- ○ 1 to 4 teaspoons per day
- ○ 5 to 8 teaspoons per day
- ○ 9 to 12 teaspoons per day
- ○ more than 12 teaspoons per day

9. On average, how many eggs do you usually eat per week?

- ○ I don't eat eggs
- ○ less than 1 egg per week
- ○ 1 to 2 eggs per week
- ○ 3 to 5 eggs per week
- ○ 6 or more eggs per week

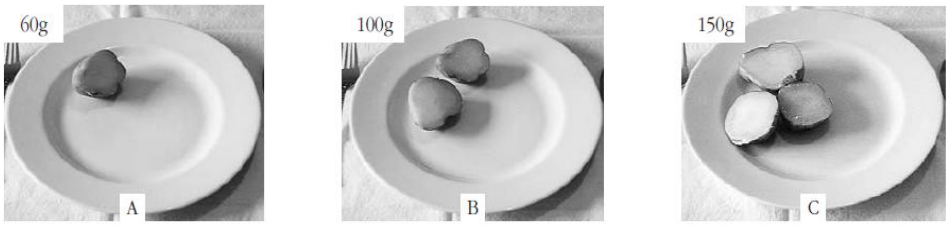
10. What types of cheese do you usually eat?

- ○ I don't eat cheese
- ○ hard cheeses, e.g. parmesan, romano
- ○ firm cheeses, e.g. cheddar, edam
- ○ soft cheeses, e.g. camembert, brie
- ○ ricotta or cottage cheese
- ○ cream cheese
- ○ low fat cheese

DO NOT WRITE IN THIS AREA.

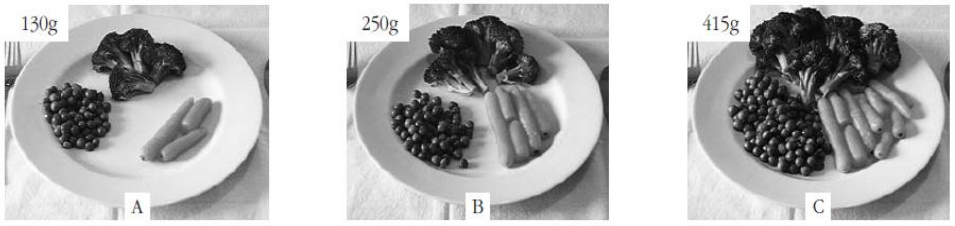
For each food shown on this page, indicate ***how much on average you would usually have eaten at main meals during the past 12 months.*** *When answering each question, think of the* ***amount*** *of that food you usually ate, even though you may rarely have eaten the food on its own.*
If you usually ate more than one helping, fill in the oval for the serving size closest to the ***total amount*** *you ate.*

11. When you ate potato, did you usually eat: ○ I never ate potato



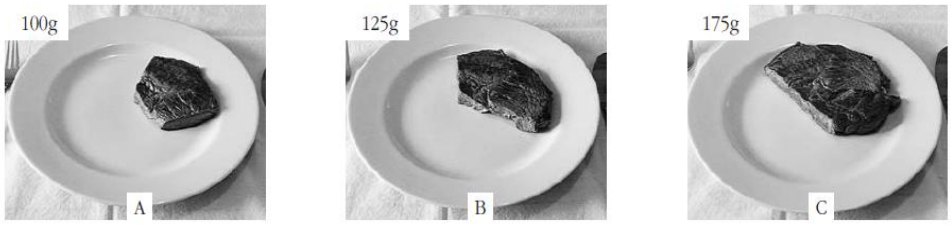
○ Less than A ○ A ○ Between A & B ○ B ○ Between B & C ○ C ○ More than C

12. When you ate vegetables, did you usually eat: ○ I never ate vegetables



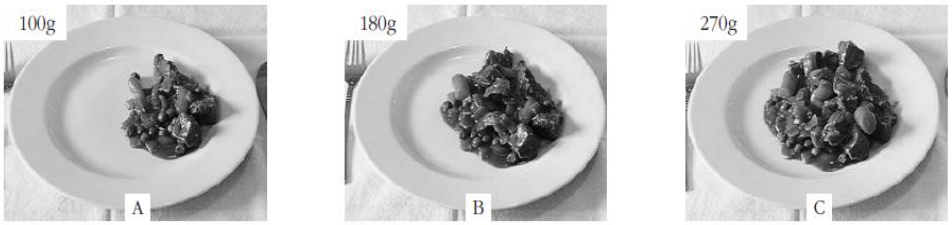
○ Less than A ○ A ○ Between A & B ○ B ○ Between B & C ○ C ○ More than C

13. When you ate steak, did you usually eat: ○ I never ate steak



○ Less than A ○ A ○ Between A & B ○ B ○ Between B & C ○ C ○ More than C

14. When you ate meat *or* vegetable casserole, did you usually eat: ○ I never ate casserole



○ Less than A ○ A ○ Between A & B ○ B ○ Between B & C ○ C ○ More than C

15. Over the last 12 months, on average, *how often* did you eat the following foods? *Please completely fill one oval in every line.*

Please MARK LIKE THIS: ○●○○ NOT LIKE THIS: ✔ ✘ ⊖ ◯

Times You Have Eaten		NEVER	less than once	1 to 3 times	1 time	2 times	3 to 4 times	5 to 6 times	1 time	2 times	3 or more times
			per month		per week				per day		
CEREAL FOODS, SWEETS & SNACKS											
All Bran™	A1	○	○	○	○	○	○	○	○	○	○
Sultana Bran™, FibrePlus™, Branflakes™	A2	○	○	○	○	○	○	○	○	○	○
Weet Bix™, Vita Brits™, Weeties™	A3	○	○	○	○	○	○	○	○	○	○
Cornflakes, Nutrigrain™, Special K™	A4	○	○	○	○	○	○	○	○	○	○
Porridge	A5	○	○	○	○	○	○	○	○	○	○
Muesli	A6	○	○	○	○	○	○	○	○	○	○
Rice	A7	○	○	○	○	○	○	○	○	○	○
Pasta or noodles (include lasagne)	A8	○	○	○	○	○	○	○	○	○	○
Crackers, crispbreads, dry biscuits	A9	○	○	○	○	○	○	○	○	○	○
Sweet biscuits	A10	○	○	○	○	○	○	○	○	○	○
Cakes, sweet pies, tarts and other sweet pastries	A11	○	○	○	○	○	○	○	○	○	○
Meat pies, pasties, quiche and other savoury pastries	A12	○	○	○	○	○	○	○	○	○	○
Pizza	A13	○	○	○	○	○	○	○	○	○	○
Hamburger with a bun	A14	○	○	○	○	○	○	○	○	○	○
Chocolate	A15	○	○	○	○	○	○	○	○	○	○
Flavoured milk drink (cocoa, Milo™, etc.)	A16	○	○	○	○	○	○	○	○	○	○
Nuts	A17	○	○	○	○	○	○	○	○	○	○
Peanut butter or peanut paste	A18	○	○	○	○	○	○	○	○	○	○
Corn chips, potato crisps, Twisties™, etc.	A19	○	○	○	○	○	○	○	○	○	○
Jam, marmalade, honey or syrups	A20	○	○	○	○	○	○	○	○	○	○
Vegemite™, Marmite™ or Promite™	A21	○	○	○	○	○	○	○	○	○	○
DAIRY PRODUCTS, MEAT & FISH											
Cheese	B1	○	○	○	○	○	○	○	○	○	○
Ice-cream	B2	○	○	○	○	○	○	○	○	○	○
Yoghurt	B3	○	○	○	○	○	○	○	○	○	○
Beef	B4	○	○	○	○	○	○	○	○	○	○
Veal	B5	○	○	○	○	○	○	○	○	○	○
Chicken	B6	○	○	○	○	○	○	○	○	○	○
Lamb	B7	○	○	○	○	○	○	○	○	○	○
Pork	B8	○	○	○	○	○	○	○	○	○	○
Bacon	B9	○	○	○	○	○	○	○	○	○	○
Ham	B10	○	○	○	○	○	○	○	○	○	○
Corned beef, luncheon meats or salami	B11	○	○	○	○	○	○	○	○	○	○
Sausages or frankfurters	B12	○	○	○	○	○	○	○	○	○	○
Fish, steamed, grilled or baked	B13	○	○	○	○	○	○	○	○	○	○
Fish, fried (include take-away)	B14	○	○	○	○	○	○	○	○	○	○
Fish, tinned (salmon, tuna, sardines, etc.)	B15	○	○	○	○	○	○	○	○	○	○
FRUIT											
Tinned or frozen fruit (any kind)	C1	○	○	○	○	○	○	○	○	○	○
Fruit juice	C2	○	○	○	○	○	○	○	○	○	○
Oranges or other citrus fruit	C3	○	○	○	○	○	○	○	○	○	○
Apples	C4	○	○	○	○	○	○	○	○	○	○
Pears	C5	○	○	○	○	○	○	○	○	○	○
Bananas	C6	○	○	○	○	○	○	○	○	○	○
Watermelon, rockmelon (cantaloupe), honeydew, etc.	C7	○	○	○	○	○	○	○	○	○	○
Pineapple	C8	○	○	○	○	○	○	○	○	○	○
Strawberries	C9	○	○	○	○	○	○	○	○	○	○
Apricots	C10	○	○	○	○	○	○	○	○	○	○
Peaches or nectarines	C11	○	○	○	○	○	○	○	○	○	○
Mango or paw paw	C12	○	○	○	○	○	○	○	○	○	○
Avocado	C13	○	○	○	○	○	○	○	○	○	○

Times You Have Eaten CONTINUED

		NEVER	less than once per month	1 to 3 times per month	1 time per week	2 times per week	3 to 4 times per week	5 to 6 times per week	1 time per day	2 times per day	3 or more times per day
VEGETABLES (INCLUDING FRESH, FROZEN AND TINNED)											
Potatoes, roasted or fried (include hot chips)	D1	○	○	○	○	○	○	○	○	○	○
Potatoes cooked without fat	D2	○	○	○	○	○	○	○	○	○	○
Tomato sauce, tomato paste or dried tomatoes	D3	○	○	○	○	○	○	○	○	○	○
Fresh or tinned tomatoes	D4	○	○	○	○	○	○	○	○	○	○
Peppers (capsicum)	D5	○	○	○	○	○	○	○	○	○	○
Lettuce, endive, or other salad greens	D6	○	○	○	○	○	○	○	○	○	○
Cucumber	D7	○	○	○	○	○	○	○	○	○	○
Celery	D8	○	○	○	○	○	○	○	○	○	○
Beetroot	D9	○	○	○	○	○	○	○	○	○	○
Carrots	D10	○	○	○	○	○	○	○	○	○	○
Cabbage or Brussels sprouts	D11	○	○	○	○	○	○	○	○	○	○
Cauliflower	D12	○	○	○	○	○	○	○	○	○	○
Broccoli	D13	○	○	○	○	○	○	○	○	○	○
Silverbeet or spinach	D14	○	○	○	○	○	○	○	○	○	○
Peas	D15	○	○	○	○	○	○	○	○	○	○
Green beans	D16	○	○	○	○	○	○	○	○	○	○
Bean sprouts or alfalfa sprouts	D17	○	○	○	○	○	○	○	○	○	○
Baked beans	D18	○	○	○	○	○	○	○	○	○	○
Soy beans, soy bean curd or tofu	D19	○	○	○	○	○	○	○	○	○	○
Other beans (include chick peas, lentils, etc.)	D20	○	○	○	○	○	○	○	○	○	○
Pumpkin	D21	○	○	○	○	○	○	○	○	○	○
Onion or leeks	D22	○	○	○	○	○	○	○	○	○	○
Garlic (not garlic tablets)	D23	○	○	○	○	○	○	○	○	○	○
Mushrooms	D24	○	○	○	○	○	○	○	○	○	○
Zucchini	D25	○	○	○	○	○	○	○	○	○	○

16. Over the last 12 months, how often did you drink beer, wine and/or spirits?

Times That You Drank

		NEVER	less than once a month	1-3 days per month	1 day per week	2 days per week	3 days per week	4 days per week	5 days per week	6 days per week	every day
Beer (low alcohol)	1	○	○	○	○	○	○	○	○	○	○
Beer (full strength)	2	○	○	○	○	○	○	○	○	○	○
Red wine	3	○	○	○	○	○	○	○	○	○	○
White wine (include sparkling wines)	4	○	○	○	○	○	○	○	○	○	○
Fortified wines, port, sherry, etc.	5	○	○	○	○	○	○	○	○	○	○
Spirits, liqueurs, etc.	6	○	○	○	○	○	○	○	○	○	○

When answering the next two questions, please convert the amounts you drank into glasses using the examples given below. For spirits, liqueurs, and mixed drinks containing spirits, please count each nip (30 ml) as one glass.

1 can or stubby of beer = 2 glasses
1 large bottle beer (750 ml) = 4 glasses
1 bottle wine (750 ml) = 6 glasses
1 bottle of port or sherry (750 ml) = 12 glasses

17. Over the last 12 months, on days when you were drinking, how many glasses of beer, wine and/or spirits altogether did you *usually* drink?

TOTAL NUMBER OF GLASSES PER DAY	1	2	3	4	5	6	7	8	9	10 or more
	○	○	○	○	○	○	○	○	○	○

18. Over the last 12 months, what was the *maximum* number of glasses of beer, wine and/or spirits that you drank in 24 hours?

MAXIMUM NUMBER OF GLASSES PER 24 HOURS	1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19 or more
	○	○	○	○	○	○	○	○	○	○

Thank You for completing this questionnaire

DO NOT WRITE IN THIS AREA.

Appendix 6

PHYSICAL ACTIVITY QUESTIONNAIRE

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Think *only* about those physical activities that you did for at least 10 minutes at a time.

1. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling?

   _____ **days per week**

   ☐ No vigorous physical activities ⟶ ***Skip to question 3***

2. How much time did you usually spend doing **vigorous** physical activities on one of those days?
   _____ **hours per day**
   _____ **minutes per day**

   ☐ Don't know/Not sure

Think about all the **moderate** activities that you did in the **last 7 days**. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal. Think only about those physical activities that you did for at least 10 minutes at a time.

3. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis?
   Do not include walking.

   _____ **days per week**

   ☐ No moderate physical activities ⟶ ***Skip to question 5***

4. How much time did you usually spend doing **moderate** physical activities on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

Think about the time you spent **walking** in the **last 7 days**. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure.

5. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time?

_____ **days per week**

☐ No walking ⟶ ***Skip to question 7***

6. How much time did you usually spend **walking** on one of those days?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

The last question is about the time you spent **sitting** on weekdays during the **last 7 days**. Include time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television.

7. During the **last 7 days**, how much time did you spend **sitting** on a **week day**?

_____ **hours per day**
_____ **minutes per day**

☐ Don't know/Not sure

This is the end of the questionnaire, thank you for participating.