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Article (Accepted Version)

Ferns, Gordon A A, Ghayour-Morbarhan, Majid, Unset and Unset (2018) Metabolic syndrome in Iran: a review. Translational Metabolic Syndrome Research, 1. pp. 10-22. ISSN 2588-9303

Metabolic Syndrome in Iran: A Review

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Key words: Iran, Metabolic Syndrome, Prevalence, adults, children, regional and ethnic variation criteria

Abbreviations:

AHAP; Amirkola Health and Ageing Project

ALT; Alanine aminotransferase

AST; Aspartate aminotransferase

ALP; Alkaline phosphatase

ATPIII; National Cholesterol Education Programme, Adult Treatment Panel-III

CMetSys; Continuous Metabolic Syndrome risk score

DASH; Dietary approaches to stop hypertension

GDM; Gestational diabetes mellitus

HDL-C; High density lipoprotein-cholesterol

HOMA; Homeostasis model assessment

IDF-AHA/NHLBI; International Diabetes Federation-American Heart Association/ National Heart Lung and Blood Institute

IDF; International Federation of Diabetes

IFG; Impaired fasting glucose

IGT; Impaired glucose tolerance

IHHP**;** Isfahan Healthy Heart Program

IR; Insulin-resistant

IS; Insulin-sensitive

JIS; Joint Interim Societies

KERCADRS; Kerman Coronary Artery Disease Risk Study

LDL-C; Low density lipoprotein-cholesterol

MetS; Metabolic Syndrome

NAFLD; Non-alcoholic fatty liver disease

NHANES; National Health and Nutrition Examination Survey

PCOS; Polycystic ovary syndrome

QUICKI; Quantitative insulin check index

ROC; Receiver operating characteristic

SuRNCD; Survey of risk factors of non-communicable diseases

TLGS; Tehran Lipid and Glucose Study

WHR; Waist-to-Hip Ratio

Declarations of Interest: Nil

1.0 Abstract

This overview of the prevalence of Metabolic Syndrome (MetS) in Iran considers the reports on regional and ethnic variation, international comparisons, and within specific groups, including children, diabetics and women at different stages of their life-course. The reported impact of lifestyle is also discussed. One particular controversy has been the definition of MetS, and this remains a difficulty across ethic groups and in children and adolescents. The changes in the criteria being applied to determine the presence of MetS, also makes trends in prevalence difficult to interpret.

2.0 Introduction

The prevalence of MetS varies with the criteria used to define it, and with demographic factors such as age, gender, ethnicity and socioeconomic status. Iran is ethnically [1], geographically and climatically [2] a highly diverse country, with a total population of approximately 80 million people. The interpretation of epidemiological data, on its changing prevalence in Iran must therefore take this into account. The numerous studies attempting to estimate the prevalence of MetS in different age groups and regions of Iran (see Table 1) are difficult to compare directly, as different criteria for MetS have been applied, the age ranges of those recruited do not fully align, and different sampling strategies have been used. Furthermore, if there have been temporal changes in the prevalence of MetS as suggested by some longitudinal studies, the prevalence rates may not be directly comparable. However, the prevalence of MetS in some regions within Iran is amongst the highest reported globally.

3.0 The reported general prevalence of metabolic syndrome in adults

3.1 In northern Iran

One of the first cohort studies to determine the prevalence of MetS in a defined urbanised region in Iran was the Tehran Lipid and Glucose Study (TLGS) [3], in which the MetS was defined by the presence of three or more of the following components: abdominal obesity, hypertriglyceridemia, low high density lipoprotein-cholesterol (HDL-C), high blood pressure (BP), and high fasting blood glucose (FBG). The age-standardized prevalence was reported as 33.7%.and increased with age in both sexes, but was significantly more common in women than in men (42% vs. 24%).

More recently (2009) in an urban population of 2941 adults > 20 years old from Zanjan province, located to the west of Tehran, MetS was defined using National Cholesterol Education Program, Adult Treatment Panel-III (ATP-III) criteria [4] and was present in 23.7% of subjects (23.1% of men and 24.4% of women) [5].

The prevalence of MetS and its association with body mass index (BMI), socio-demography, and lifestyle habits was investigated in a random sample of 984 women aged 30-50 years old living in Babol in 2009. ATPIII criteria were used to define MetS and its overall prevalence was 31.0%. Abdominal obesity was found in about 76.6% (n = 273) of subjects. Older age, higher waist circumference (WC), higher systolic (SBP) and diastolic (DBP) blood pressure, low educational attainment and farming as an occupation were associated with increased risk for MetS[6].

In 2016, the Shahroud eye cohort study sample comprised of 5190 middle aged individuals (40-64 years) from east of Tehran, was used to assess the prevalence of MetS. This was related to age and gender. The prevalence of MetS was 10.9% in men, 13.0% in women and 12.1% in total. The prevalence increased with age. Using multivariate logistic regression analysis, educational attainment and positive smoking habit, had significant effects on the risk of MetS [7].

The prevalence of MetS and its components was determined in an elderly population from Amirkola in 2016, using four different diagnostic criteria [8]. The study was part of the larger community-based Amirkola Health and Ageing Project (AHAP)[9] study, and comprised 1562 individuals (55.2% male). Applying an Iranian definition of MetS, 1160 persons (74.3%) had MetS, higher than for the other three definitions. The highest prevalence was observed in females in the age group of 65-74 and the lowest in males in the age group of 85-99 years old.

Amol is near the Caspian Sea, whilst Zahedan is in the southeast, near the border with Pakistan. In 2014, the prevalence of MetS was determined according to two definitions and compared the characteristics of the subjects who met the MetS criteria according to the different definitions. Participants were recruited from family registries of public health centers. MetS was defined according to both the ATPIII and International Diabetes Federation (IDF) criteria [10]. Using this approach, 3 groups could be identified: 1) Individuals without MetS, based on either definition, 2) Individuals with MetS according to one of the definitions, and 3) Individuals who met both ATPIII and IDF criteria for MetS. Subjects from Amol (n=5826) and Zahedan (n=2243) were enrolled into the study. The weighted prevalence of MetS according to the ATPIII and IDF criteria was 27.8% and 26.9% in Amol and 12% and 11.8% in Zahedan, respectively. Overall, 18.9% of the subjects fulfilled the criteria for both definitions of MetS, whilst 8.5% met the MetS criteria according to one definition only [11].

3.2 In Central Iran

The Isfahan Healthy Heart Program (IHHP) assessed the prevalence of the MetS using ATP III criteria in 12,514 adults (≥19 years) living in urban and rural areas in and around 3 cities in central Iran. The age-adjusted prevalence of MetS was 23.3%, with a higher prevalence in women compared to men (35.1% vs. 10.7%, $P<0.05$) and in urban residents compared to rural residents (24.2% vs. 19.5%, $P<0.05$) [12].

The use of the continuous MetSy risk score (CMetSyS)[13] has been recommended to define MetS. In 2014 the CMetSyS was applied to data from the baseline survey of the IHHP. The study population consisted of 8313 individuals (49.9% male, with a mean age 38.54±15.86 years). MetS was found in 21.86% of the population. Triglycerides and WC were the best predictive components. The CMetSyS was significantly associated with serum high sensitive C-reactive protein (Hs-CRP), BMI, leisure time, and workplace physical activity as well as age and gender [14].

3.3 In Southern Iran

The Kerman Coronary Artery Disease Risk Study (KERCADRS) is a cohort study of 6000 individuals resident in Kerman city [15]. Estimates of the prevalence of the different components and definitions of MetS were investigated. Using IDF criteria, the prevalence of MetS was 25.2% in men and 42.5% in women; the corresponding values were 31.0% in men and 38.0% in women using ATPIII criteria. The prevalence of MetS increased with age in both genders, peaking at the age of 51-60 years in both.

The prevalence of the MetS as well as cut-off points for WC for the diagnosis of MetS was investigated in 1802 people (735 men and 1067 women) aged ≥19 years from Zahedan in 2012. MetS was defined using ATP III, and the IDF criteria and WC cut-off points for IDF criteria. The prevalence of MetS according to ATP III, IDF and IDF -AHA/NHLBI were 21.0% (15.4% in men and 24.9% in women), 24.8 (20.0% in men, 28.1% in women) and 23.3% (19.7% in men, 25.8% in women), respectively [16].

The prevalence of MetS and its components was determined in a cross-sectional study of a rural population living in Kavar. The population comprised 13304 adults aged > 20 years (32.6% male). MetS was defined using ATP III criteria and its prevalence was compared to the rates estimated by modified ATPIII and IDF definitions. The prevalence of ATP III-defined-MetS was 25.1% compared to 27.7% and 28.3% using the modified ATP III and IDF definitions, respectively. The prevalence rate was higher among the females compared to the males by all the definitions (28.4% in females and 18.9% in males by ATP III criteria, $P < 0.001$) and increased with age ($P < 0.001$) [17].

Between October 2012 and April 2013, 377 adults aged ≥20 years (190 women and 187 men with a mean age of 43.8 ±11.0 years) were invited to a Petroleum Industry Health Organization Polyclinic, in Shiraz. MetS was defined using the revised ATPIII criteria, and 101 individuals were found to have MetS; 16.6% of men and 36.8% of women ($P < 0.001$). The prevalence increased by almost 15% with each decade of life ($P < 0.001$) [18].

The association between MetS and menopausal status in Iranian women was investigated in 490 pre- and 434 postmenopausal women from the Shiraz Women's Health Cohort Study. MetS was defined according to ATPIII and IDF criteria. Postmenopausal women had a modestly higher prevalence of MetS (60.2% versus 59.4%, respectively). WC, waist-to-hip ratio (WHR), blood pressure, and levels of fasting plasma glucose (FPG), total cholesterol, low density lipoprotein cholesterol (LDL-C), and triglycerides were higher in postmenopausal women compared to premenopausal women [19].

3.4 In Western Iran

The prevalence and characteristics of MetS amongst women of reproductive age was investigated in a cross-sectional study using a systematic randomized sampling method. In 406 women of reproductive age living in Abhar City, the prevalence rate of MetS was 28.1%. This figure increased with age and BMI. The majority of cases with MetS were either overweight or obese (53.5%). The greatest rise in prevalence of MetS was observed in the age range between 45 to 49 years (70.6%) [20]. Amongst 100 postmenopausal women, who were referred to the health centers in Gorgan, MetS was only marginally higher at 31%, using ATP III criteria [21].

3.5 National surveys of the prevalence of metabolic syndrome

The first national estimate on the prevalence of the MetS and its components in Iranians aged between 25-64 year old, living in urban and rural areas of all 30 provinces in Iran was undertaken in 2009. Several criteria were used for the definition of the MetS and its age-standardized prevalence was approximately 34.7% (95% Cl 33.1-36.2) based on the ATPIII criteria. Its prevalence was higher in women, and in those living in urban areas [22].

A systematic review of all available studies on MetS in the adult Iranian population, estimated the overall prevalence of MetS in 2015 was 36.9% (95% CI: 32.7-41.2%) based on the ATPIII criteria, 34.6% (95% Cl: 31.7-37.6%) according to the IDF, and 41.5% (95% Cl: 29.8-53.2%) based on the Joint Interim Societies (JIS) criteria [23]. The prevalence of MetS determined by JIS was significantly higher than for values determined by ATP Ill and IDF. The prevalence of MetS was 15.4% lower in men than in women (27.7% versus 43.1%) based on the ATP III criteria, and it was 11.3% lower in men based on the IDF criteria; however according to the JIS criteria, it was 8.4% more prevalent in men [24].

A further systematic review regarding MetS and its risk factors among Iranian adults aged > 19 years during 2005-2014 was also published in 2015. From the 43 studies, the rate of MetS varied from 10% to 60% depending on sex, age and region. The highest rate reported was among postmenopausal women in Shiraz, and was over 60%. The rate of MetS was higher among women compared with men across all, apart from a single study. A particularly high gender difference (43.3% vs. 17.1%) was observed in western Iran (Kordestan province). MetS was significantly more prevalent among older adults, postmenopausal women, less-educated people, those living in urban areas and those with low physical activity and unhealthy eating habits [25].

Whilst these national statistics are not directly comparable, there are some interesting conclusions that can nevertheless be drawn. The prevalence of MetS increases with age; in Iran, like many other Asian and Middle Eastern countries, MetS is more prevalent in women [26]; and the criteria used in the west are not appropriate for the Iranian population. There appear to be marked regional differences, and differences between urban and rural populations. What is less clear is whether the overall prevalence has increased significantly since 2003, despite the reported increase in prevalence of obesity [27].

4.0 Ethnic and International comparisons

The impact of age in the prediction of the non-adiposity related components of MetS, and to determine the optimal cut-off values for the prediction of MetS, was investigated in Turkman and non-Turkman residents of northern Iran. Subjects who were 25-70 years age (n=248) were recruited, and MetS defined using ATP-III criteria. The prevalence of MetS was 37.6% and was 14.7% higher in non-Turkman than in Turkman individuals, respectively. Mean FBG, triglycerides, WC and diastolic blood pressure (DBP) were also significantly higher in the non-Turkman group [28].

The prevalence of MetS and its components were compared between an adult population from Mashhad in north-eastern Iran (n=1,194) and a population from north-eastern France (n=1,386). MetS was defined by ATP III criteria. The prevalence of MetS was significantly higher in Iranian women (55.0%), followed by Iranian men (30.1%), French men (13.7%) and French women (6.6%). Iranian women had high rates of abdominal obesity (65.0%), hypertension (52.1%), hypertriglyceridemia (43.1%), and low high-density lipoprotein cholesterol (HDL-C; 92.7%). Iranian men had high rates of hypertension (48.9%), hypertriglyceridemia (42.8%), and low HDL-C (81.8%). French men had high rates of hypertension (44.7%) and moderate rates of hypertriglyceridemia (28.6%) and hyperglycemia (23.9%). There was a relationship between waist circumference and the lipid components of MetS in both countries [29].

The harmonised paediatric definition of the MetS defined by the IDF [30] has allowed a global comparison of the prevalence. The prevalence of MetS and its components was assessed in two large representative samples of adolescents in Germany and Iran, Data from 3,647 German adolescents aged 10-15 years old participating in the German PEP Family Heart Study[31] and 2,728 Iranians in the same age range participating in the CASPIAN Study were compared. MetS was four times more prevalent in Iranian (2.1%) compared to German (0.5%) adolescents [32].

These ethnic and international data are striking and important for several reasons. The obvious conclusion is that there are substantial differences in the prevalence of MetS between ethic and national groups, irrespective of the criteria used to define it. This is consistent with studies in other countries [33]. These appear to emerge early in adolescence. The sexual dimorphism of the phenotype appears to occur in late adolescence, but differs between populations in Iran and the West [34].

5.0 The Prevalence of metabolic syndrome in defined groups

5.1 Impact of physical activity

Two approaches to this question have been adopted: using a questionnaire to determine the extent of physical activity, and by assessing the prevalence of MetS in specific occupational groups with different levels of physical activity.

The association between different aspects of physical activity and MetS was investigated in a nationally representative sample of 3296 Iranian adults as part of the third national survey of risk factors of non-communicable diseases (SuRFNCD-2007). Physical activity was evaluated with respect to 3 domains: work, commuting, and recreational activities. Both duration and intensity of activity were assessed. MetS was defined using the IDF and the ATPIII criteria. The national prevalence of MetS was estimated to be between 24% and 30%, depending on sex and the criteria used. The prevalence of MetS increased incrementally among individuals with high-, moderate-, and low-category activity was 18.7±1.5%, 25.8±2.0%, and 27.9±2.0%, respectively ($P < 0.001$). These rates were 12.6±1.6%, 26.0±1.5%, and 34.1±3.2% among individuals with vigorous activity, with non-vigorous activity, and without activity, respectively ($P < 0.001$). The risk for MetS increased 1.28-fold with every 30-min/d reduction in vigorous-intensity activity ($P < 0.001$) [35].

A cross-sectional study evaluated the prevalence of MetS among 1488 office workers in Qom province in Central Iran, by using a multi-stage cluster sampling. MetS was defined based on blood HDL-cholesterol, triglyceride, and FBG levels and waist circumference, and blood pressure. Its prevalence was 35.9% overall, higher in men (37.2%) than in women (20.6%), and increased with age [36].

The prevalence of MetS has also been investigated in 234 Iranian male seafarers working for the National Iranian Tanker Company (NITC) in 2015. MetS was diagnosed according to the reports of National Committee of Obesity. The mean age of the participants was 36.0±10.3 years. The prevalence of MetS was 14.9% [37].

Among 429 bus and truck drivers from Kashan, and using the ATPIII criteria, the prevalence of MetS was 35.9%. Hypertension, diabetes, overweight and obesity were seen in 42.9%, 7%, 41% and 23% of the drivers, respectively. .[38] Among 12138 long distance drivers, resident in West Azerbaijan province, 3697 subjects were found to have MetS , using IDF criteria. The crude and age-adjusted rates of MetS were 30.5% and 32.4% respectively. 5027 subjects (41.4%) were overweight (BMI >= 25.01-30 kg/m2), and 2592 (21.3%) were obese (BMI ≥ 30.01 kg/m2) [39]

These data are consistent with an increasing risk of MetS and obesity being associated with low levels of physical activity.

5.2 Association with impaired glucose tolerance and diabetes mellitus

The prevalence of MetS was determined using two established criteria for ATPIII and IDF and a new definition for MetS, from a population sample of 950 diabetic type 2 patients in Kerman in central Iran. The prevalence of MetS in this sample was 73.4, 64.9, and 70.4%,respectively [40].

A similar study in Type 2 diabetics from Gorgan, in northern Iran used ATP-III criteria, and reported a prevalence of MetS in this group was 51.50%, with a higher prevalence in women [41].

Gestational diabetes mellitus (GDM) affects nearly 5% of pregnancies and women with a history of GDM have a higher risk of type 2 diabetes mellitus (T2DM) [42]. The incidence of abnormal blood glucose level and MetS was investigated in 110 women with a history of GDM who had delivered during 2004-2010 in three hospitals of Zanjan City. The patients were recalled to perform an oral glucose tolerance test and other tests required for a diagnosis of MetS. Of the 110 women, 36 (32.7%) developed T2DM and 11 (10%) had impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). 22 women (20%) had developed MetS [43].

MetS is highly prevalent in type 2 diabetics and is a strong risk factor for cardiovascular diseases in these patients [44].

5.3 Association with polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is characterized by ovarian dysfunction, hyperandrogenism and PCO morphology by ultrasound.[45]. Its clinical manifestations may also include obesity, insulin resistance (IR) and an increased risk of type 2 diabetes and cardiovascular events [46].

The prevalence of MetS was investigated in 215 women from Rasht in northern Iran with PCOS (defined by the Rotterdam 2003 criteria) [47]. Subjects were recruited between March 2010 and July 2012. The prevalence of MetS in women with PCOS was 28.8%, higher than reported by other studies in Iranian women with PCOS [48]. The prevalence of MetS has also been assessed among Iranian women diagnosed within different phenotypic subgroups of PCOS based on the Rotterdam criteria [49]. The study recruited women with PCOS who were referred to infertility clinics, and was conducted between January 2006 and June 2008, in Isfahan. The subjects underwent metabolic screening according to ATP III guidelines and IR screening was based on the homeostasis model assessment (HOMA) of insulin resistance. The prevalence of MetS and IR were 24.9% and 24.3%, respectively. A significant difference in the prevalence of MetS was reported for anovulatory women with PCOS with or without hyperandrogenism (23.1% and 13.9%, respectively; $P = 0.001$).

The frequency of IR was compared between 136 individuals with PCOS and 423 healthy controls. PCOS and MetS were diagnosed using the Rotterdam 2003 criteria and JIS, respectively. IR was defined using the HOMA-IR). In this population sample, MetS was no more frequent in a representative sample of Iranian women with PCOS than in healthy controls. However, the prevalence of IR in PCOS was higher than in controls [50].

The presence of IR and MetS were assessed in 63 overweight or obese PCOS patients subdivided into insulin-resistant (IR) and insulin-sensitive (IS) groups. Fasting insulin concentration and HOMA-IR were higher ($p<0.001$), and quantitative insulin check index (QUICKI), glucose-to-insulin ratio ($p<0.001$), and HDL-C ($p=0.012$) were lower in the IR group. MetS ($p=0.034$) and obesity ($p=0.038$) were more prevalent in IR group [51].

PCOS is therefore associated with metabolic abnormalities that are also components of MetS. It is unclear whether it would be clinically effective to screen all women with PCOS for MetS and IR, as their prevalence may vary by PCOS phenotype, ethnicity and age.

5.4 Association with hypertension

The prevalence of the MetS and its different features were compared among hypertensive and normotensive subjects, derived from a representative sample of adults living in 3 cities in Iran. Among the 12,514 subjects, selected by multi-stage random sampling, 13.9% were hypertensive. The prevalence of the MetS, using the ATPIII criteria, was significantly higher in hypertensive than normotensive subjects (51.6% versus 12.9%, respectively). The prevalence of MetS was also greater in normotensive and hypertensive subjects living in urban areas than those living in rural areas (14.2% and 53.9% versus 9.5% and 45.6%, respectively, $P < 0.05$). A combination of hypertension with MetS was more prevalent in women than men (72% versus 28% respectively, $P < 0.000$), and in subjects living in urban areas than those in rural areas (75.1% versus 24.9%, respectively [52].

5.5 The impact of diet

In a cross-sectional study using a representative sample of Isfahani female nurses, a dietary score was used for assessing compliance with a DASH diet and this was related to the presence of MetS defined according to the Joint Scientific Statement criteria. Individuals in the highest tertile of the DASH diet score [53] had 81 % lower odds of MetS than those in the lowest category (OR 0.19; 95 % CI 0.07-0.96). Participants with the greater adherence to the DASH diet were less likely to have enlarged waist circumference, hyperglyceridemia, low HDL-C levels, and high blood pressure, respectively. Adherence to the DASH eating plan was inversely associated with the odds of MetS and most of its features among a group of Iranian women [54].

The relationship between dietary intake and MetS was investigated in 984 middle-aged (30-50 years) women from the urban area of Babol, in northern, Iran. Dietary patterns were evaluated using a food frequency questionnaire. The ATP III criteria were used to define MetS. A good dietary pattern, rich in fruits, legumes, vegetables, cereals, and fish, as well as high intake of dairy products and eggs decrease the likelihood of MetS. The adjusted OR for MetS in women with low fat intake was higher than in women with high and moderate fat (OR= 2.92; 95%, CI= 1.36, 6.28) [55].

The relationship between the presence of MetS and compliance with a Mediterranean diet was investigated in 158 patients with T2DM, aged 28-75 years old. Food frequency questionnaires comprised an 11-item score to determine the adherence to a Mediterranean diet; 55.4% of participants had good adherence to Mediterranean diet. The presence of MetS in women was significantly higher than in men ($p < 0.001$). Nuts, legumes and seeds consumption were associated with a significant lower risk of MetS ($p < 0.05$), but no association was observed between MetS and adherence to a Mediterranean diet [56].

The beneficial effects of a Mediterranean diet [57] and DASH type diets[58] on the features of MetS have been established; these data from Iran are consistent with these western studies.

6.0 The prevalence of metabolic syndrome in children and adolescents

MetS in children and adolescents is becoming a global public health concern because it tracks into adulthood [59] and is then associated with an increased risk for type 2 diabetes mellitus and cardiovascular disease [60].

A national study was conducted among 4811 students (2248 boys and 2563 girls) aged 6-18 y, living in six different provinces in Iran, recruited to determine the prevalence of paediatric MetS and its best predictive anthropometric index. Two definitions for MetS were used: type A, based on criteria analogous to ATP III; type B was defined according to the cut-offs obtained from NHANES III. Both types A and B define high FBG as > 100 mg/dl and SBP/DBP as > 90th percentile. The mean age of students was 12.07±3.2 y. Type A MetS was seven times more prevalent than type B MetS (14% vs 2%, respectively, $p < 0.0001$), and there was no significant gender difference. Waist circumference (WC) and waist-to-hip ratio (WHR) had the strongest and weakest associations, respectively, with the MetS [61]. The impact of environmental factors on the prevalence of MetS among young people is limited. The association of these factors with MetS was also investigated in this sample of Iranian children; MetS was detected in 14.1% of participants. A birth weight of > 4000 g in boys and < 2500 g in girls increased the risk of having the MetS. Poorly educated parents and a positive parental history of chronic disease were other risks factors associated with MetS. Low levels of physical activity significantly increased the risk of having MetS. The risk of MetS increased with the consumption of solid hydrogenated fat and bread made with white flour. However, an increased frequency of consumption of fruits and vegetable, as well as dairy products decreased the risk of having MetS [62].

Another nationally representative sample (recruited from 23 provinces in Iran) of 5738 adolescents (2875 girls) aged from 10 to 18 years (mean 14.7±2.4 years) and obtained as part of the third study of the school-based surveillance system entitled CASPIAN III., was used to study the prevalence of different components of MetS, and their discriminative value was assessed using receiver operating characteristic (ROC) curve analysis; 17.4% of participants were underweight and 17.7% were overweight or obese. Using IDF criteria for the adolescent age group, 24.2% of participants had one risk factor, 8.0% had two, 2.1% had three, and 0.3% had all the four components of MetS. The prevalence of MetS was 15.4% in the overweight/obese participants, the corresponding figure was 1.8% for the normal-weight students, and was 2.5% in the whole population studied [63].

The relationship between MetS, using ATP III criteria, and its individual components were related to socio-economic factors obtained using a self-administered questionnaire amongst 538 14-18 year-old adolescents living in Shiraz. Approximately 6% of the adolescents had MetS, with significantly more males than females (9.3% vs 2.4%, $p<0.001$) being affected, an unusual finding for an Iranian population. There were positive associations between the components of MetS and parental education, school location and household monthly income [64]. The CASPIAN III study has recently reported that increasing socioeconomic status was associated with an increased risk of MetS [65].

The prevalence of MetS and IR was determined in 338 children and adolescents (172 girls) aged 10-18 years old from Qazvin, in northern Iran. They were selected using a multistage cluster random sampling technique. MetS was defined according to the IDF criteria. IR was estimated by the homeostatic model assessment. The overall prevalence of MetS and IR were 3.4% and 18.2%, respectively [66].

A representative sample of 1425 Iranian elementary school children from Birjand was used to assess the best preventive measures for MetS in this age group. They were recruited through multiple-cluster sampling in 2013. MetS was defined according to ATP-III criteria based on the National Cholesterol

Education Program. The overall prevalence of MetS was 5.3% and increased with age. 43.5% of children had one or more components of the MetS. The prevalence of MetS was 0.9% in normal weight, 11.3% in overweight and 36.2% in obese children [67].

The prevalence of the MetS, and its component factors was determined among 622 high school girls (15 to 17 years old) living in Mashhad, Iran. A self-administered questionnaire was used to assess socio-demographic characteristics and dietary habits. Anthropometric assessments, blood pressure measurement and biochemical assessment were done. Applying BMI Z-score for age and gender (WHO 2007), 14.6 % and 3.4 % of subjects were classified as overweight and obese, respectively. A large WC (> 80 cm) was found in 9.5% of the girls. Based on ATP III criteria, the overall prevalence of the MetS was 6.5% and increased to 45.1% in obese subjects. A high socioeconomic status of the family, and a high consumption of carbohydrates were influencing factors in the prevalence of MetS [68].

The prevalence of MetS and the association between MetS and obesity was investigated in a population of 450 adolescents from northern Iran. High school students (50% boys), aged 15-18 years, were enrolled in the study. MetS was defined using modified NHANES III criteria. The prevalence of MetS amongst subjects was 3.3%. The associations between a BMI ≥85th percentile and MetS, and between a BMI ≥75th percentile and MetS were statistically significant. The association between an increased WC and MetS was also statistically significant, confirming the high prevalence of components of MetS among apparently healthy Iranian adolescents, even among those who were not overweight.[69]

The prevalence of obesity and MetS was investigated in 1221 adolescent girls (mean age 14.3±1.7 years) living in Rafsanjan. MetS was defined using ATPIII criteria;11.2% and 2.4% of subjects were overweight and obese respectively; 3.9% had MetS.[70]

In a systematically review of the prevalence of MetS among Iranian children and adolescents. aged 3-21-year-old. The prevalence range of MetS among children was 1-22% using the different definitions. The reported range of MetS defined by different criteria was as follows: ATP III; 3-16%, IDF; 0-8%, AHA; 4-9.5%, The NHANES III; 1-18%, de Ferranti; 0-22%. MetS is a common metabolic disorder among Iranian children and adolescents, with increasing trends during the last decades.[71]

7.0 Metabolic Syndrome and its associated conditions

The differences between patients with and without coronary artery disease (CAD), regarding the presence of MetS and its components, and selected lifestyle behaviours, including dietary intake, physical activity patterns, and smoking habits was investigated, in an attempt to determine whether MetS was an independent risk factor for CAD. The study used a case-control methodology for the collection and analysis of the data. Six hundred participants were recruited. MetS was associated with a 4.19-fold increased risk of CAD (P=0.0001). However, multivariate analysis showed that MetS did not add any additional predictive information beyond its components.[72]

The prevalence of MetS was investigated in a group of 100 healthy children and adolescents (6-16 years old, 58% female) with a body mass index (BMI) above the 85th percentile for their age and sex in Qazvin Province in northern Iran. Two definitions of MetS were compared: the ATP III criteria and a modified definition by Weiss et al.[73] The mean BMI of the group was 26.02±4.38 and 80% had obesity. IR was found in 81% of the study population. MetS was present in 50% of the overweight and 66.2% of the obese subjects by applying ATP III criteria. MetS was present in 25% of the overweight and 42.5% of the obese subjects using the definition of Weiss et al. There were no statistically significant differences between the two groups with MetS defined with MetS by the two criteria.[74]

The relationship between physical activity and MetS was investigated in a large national-representative sample of children. [75] School students (2,248 boys and 2,563 girls) aged 6-18 years, were recruited between 2003-4 using multi-stage random cluster sampling from six provinces in Iran. Physical activity was assessed using a standardized questionnaire. MetS was defined using ATPIII criteria. In all age groups, boys were more physically active than girls. The MetS was detected in 14.1% of participants, and its prevalence was higher in those subjects with the lowest levels of physical activity. In both genders, before and after adjustment for age and body mass index, low levels of physical activity significantly increased the risk of having the MetS [in boys: OR: 1.8, (CI: 1.1-2.1); and in girls, OR: 1.6 (CI 1.1-1.9)].

8.0 The Prevalence of the components of the metabolic syndrome

The prevalence and distribution of cardiovascular risk factors and MetS in 4,811 nationally representative children and adolescents aged 6-18 years with generalized, central, or combined types of obesity were investigated to determine if a phenotypically obese metabolically normal and a metabolically obese normal weight phenotype could be identified. Children were recruited through randomly selected schools within six provinces in Iran. Varying with age and gender, 6-9% of children had isolated central obesity, 7.5-11% had isolated generalized obesity, and 14-16.5% had combined obesity. The prevalence of dyslipidemia, high blood pressure, and MetS was higher in those children with combined obesity than in those with the other two types of obesity.[76] The most prevalent CVD risk factors in this population sample were a low HDL-C (28%), followed by hypertriglyceridemia (20.1 %), and overweight (17%). ROC analyses showed that in boys, who were in the 10-13.9 and 14-18-year-age groups, respectively, waist circumference (WC) and body mass index (BMI) were best for distinguishing CVD risk factors. Amongst girls, these indices were respectively BMI and waist to stature ratio (WSR); WC and WSR; and WC.[77]

The prevalence of obesity, central obesity and WHR obesity in individuals between 15-70 years old were determined in individuals who were chosen randomly from 23 clusters in Golestan province in northern Iran in 2013; and a comparison made by ethnic group (Turkman = 166, and non-Turkman = 298). Individuals with a BMI (Body Mass Index) of < 25, 25.0-29.9, 30-39.9 and >= 40 kg/m^2 were classified as normal, overweight, obese and pathologic obese. Central obesity was defined by waist circumference of WC > 102 cm in men and > 88 cm in women. WHR (Waist-to-Hip Ratio) ≥0.95 cm and ≥0.8 cm were classified as WHR obesity for men and women, respectively. General obesity and overweight were seen in 30.0% and 28.2% of subjects, respectively. For the non-Turkman group, obesity was significantly more common in women (men= 19.4% and women= 43.9%; P= 0.001) whereas it was not significantly different in the Turkman group (men= 16.4% vs women= 30.0%). Central obesity was also very common (40.7%) with a significant difference between genders (men= 22.9% vs women= 54.4%) (P= 0.001). Compared to Turkman men and women, the prevalence of central obesity was 12% and 19.2% and was more common in the non-Turkman group (P= 0.003). In the whole population sample, WHR obesity was common in 62.7% and 63.1% of men and women, respectively. Hence, general obesity, central obesity and WHR obesity are common in northern Iran and more common in non-Turkman than in the Turkman group.[78] This work was extended to investigate the prevalence of central obesity in the three predominant ethnic groups among 2993 individuals (Fars-native = 1627, Turkaman = 974 and Sisstani = 392) aged 15-65 years and living in urban and rural areas within 11 districts in Golestan province in northern Iran. The groups were matched for age and sex. Central obesity was defined using WHO criteria. The mean WC in the three ethnic groups were: Fars, 88.88±15.83 cm, Turkman, 89.11±14.12 cm and Sisstani, 84.41±13.74 cm. Central obesity was found in 36.9%, 34.9% and 27.6% of each ethnic group, respectively (P= 0.002) and was more common in women (54.5%) than men (15.7%). (P=0.001).[79]

The third national Surveillance of Risk Factors of Non-Communicable Diseases (SuRFNCD-2007), investigated 5,287 Iranian citizens, aged 15-64 years. Data were collected on demographics, diet, physical activity, smoking, history of hypertension, and history of diabetes. Anthropometric characteristics were measured and serum biochemistry profiles were determined on venous blood samples The prevalence of diabetes, hypertension, obesity, and central obesity were 8.7%, 26.6%, 22.3%, and, respectively. The prevalence of hypertriglyceridemia was 36.4%. These rates were higher among females (except hypertriglyceridemia) and urban residents.[80] The trends of overweight and obesity among Iranian adults (25-64 years old) within an 8-year period (1999-2007) were assessed using datasets of three cross-sectional national surveys: The National Health Survey-1999 (n = 21,576), National SuRFNCD-2005 (n = 70,945), and SuRFNCD-2007 (n = 4,186). The overall prevalence of obesity increased from 13.6% in 1999 to 19.6% in 2005 and 22.3% in 2007(P < 0.001). . The corresponding values for overweight subjects were, 32.2%, 35.8% and 36.3%, respectively (P < 0.001). The increase in prevalence of obesity was seen in both males and females, and both urban and rural residents.[81]

A systematic review of studies on the prevalence of overweight and obesity in the Iranian paediatric population from January 1990 to the end of December 2013 has shown a large variation for the reported values in different age and sex groups had large variations; from 1-16.1% and from 4.4-42.3% respectively for obesity and overweight).[82]

In a meta-analysis of 107 studies, the overall prevalence of obesity and overweight remained relatively constant in the 2000s in children and adolescents at about 5.1% and 10.8%, respectively. A meta-regression analysis showed that the prevalence of obesity and overweight did not vary significantly with respect to sex and age of study participants. Girls had a lower prevalence of obesity and higher prevalence of overweight than boys. Although the prevalence of childhood obesity in Iranian children was not very high, there is an escalating trend of excess weight among young children.[83]

The trends in the national prevalence of overweight and obesity amongst 6 year old children were compared for the northern, central and southern parts of Iran in 2011. The data were collected as part of a routine and mandatory national screening program on children entering elementary schools in 2007, 2008 and 2009. Data were available for 2,600,065 children. Among all the children 12.8%, 13.5% and 10.9% were overweight in 2007, 2008 and 2009, respectively. The corresponding figures for obesity were 3.4%, 3.5% and 3.4%, respectively. For all three surveys, the prevalence of overweight and obesity was highest in the southern region, but was constant over the three years. It was suggested that the higher prevalence of overweight in the southern region may be related to the lower socioeconomic status of this population.[84]

The latter hypothesis is consistent with data from Rasht; in which the prevalence and predictors of overweight and obesity by location of residence was assessed amongst randomly selected 2,577 urban school girls aged 12-17 years. Data on age, frequency of skipping breakfast per week, physical activity, hours of television viewing, self-perception about body condition, and home address were collected. Data on birth-weight of the girls, educational attainment of parents, weights and heights of parents, and employment status of mothers were obtained from parents using a self-administrated questionnaire. The overall prevalence of overweight and obesity was 18.6% and 5.9% respectively. Overweight or obesity was more common among girls from low-income areas compared to high-income areas (21.6% vs 17.1%, $p<0.001$). Maternal education was positively related to overweight/obesity of the girls, as was overweight or obesity in a parent.[85] However, the data of Motlagh et al [84] are odds with another cross-sectional nation-wide study.[86] In this study, 14880 school students aged 6-18 years, were selected using a multistage random cluster sampling from 30 provinces in Iran. The World Health Organization growth curve was used to categorize Body Mass Index (BMI). Obesity was defined as a BMI equal to or greater than the age-and gender-specific 95th percentile; abdominal obesity was considered as waist-to-height ratio ≥0.5. 13486 students completed the study (6543 girls and 75.6% urban residents), with a mean age of 12.45 years. The prevalence rate of general and abdominal obesity was 11.89% (13.58% of boys vs. 10.15% of girls) and 19.12% (20.41% of boys vs. 17.79% of girls), respectively. The highest frequency of obesity was found in the middle school students. The Southern and South Eastern provinces had the lowest prevalence of general obesity (2.6% and 5.6%) and abdominal obesity (7.4% and 8.8%). The highest prevalence of obesity was found in north and north west Iran with a frequency of 18.3% general obesity and 30.2% of abdominal obesity

Furthermore, another nationwide survey also challenges the association with a low socioeconomic status.[87] In a representative sample of 5,528 students aged 10-18 years from 27 provinces of Iran, a potential model of the relationship between various cardio-metabolic risk factors including obesity, unhealthy diet, low physical activity, dyslipidemia, and high blood pressure. The mean age of study participants was 14.7±2.41 years and the mean body mass index (BMI) was 19.4± 4.1. In this study a higher socioeconomic status was associated with an unhealthy diet, low physical activity and high BMI in both sexes. Age was directly related to low physical activity in both sexes. BMI was positively related to total cholesterol, triglyceride, low-density lipoprotein cholesterol, and mean arterial pressure

The prevalence of obesity and its association with hypertension was assessed in a sample of 2000 children and adolescents aged 11 to 17 years, from Shiraz, who were recruited from 2010-11. Approximately 7% and 11.8% of the students were obese and hypertensive, respectively. Obesity was found to be an important risk factor for hypertension. The prevalence of obesity had not changed over the previous 5 years, but that of hypertension had risen significantly.[88]

Reference percentile curves are often used to assess growth disorders in children. These may differ according to ethnicity and lifestyle patterns. A comparison was made between the curves of anthropometric measures obtained in two national studies of Iranian children and adolescents (10-18-years-old) collected between 2003-2004 and 2009-2010. Age-and gender-specific percentiles were determined and the model was smoothed. Comparison of two series of studies showed that the weight, BMI, WC, and waist-to-height ratio were lower in adolescent girls than boys especially in the higher percentiles. In both genders, weight, BMI, and WC percentiles had fallen.[89]

9.0 Defining regional reference ranges

9.1 Adiposity

9.1.1 Measures of adiposity in adults

The optimal cut-off values for waist circumference in Turkman and non-Turkman people in the northern Iran was determined using a representative sample of 248 subjects aged 25-70 years, from 25 clusters. ATP-III criteria were used for MetS. There were significant differences between Turkman and non-Turkman groups in almost all the parameters used to define MetS: HDL-C, low density lipoprotein-cholesterol (LDL-C), cholesterol, triglycerides (TG), and FBG. The cut-off values of WC for hyper TG, low HDL-C and diabetes were 6.0, 7.25 and 8.25 cm higher in the non-Turkman group than in Turkman group. [72]

A study was conducted to determine the best discriminators for the diagnosis of the MetS among six obesity indexes, and the optimal cut-off values for all obesity indexes were determined, using data from 5910 subjects from the Haraz cohort study in northern Iran. The discriminatory power of six obesity indexes, including, body mass index (BMI), waist circumference (WC), waist to hip ratio (WHR), waist to height ratio (WHtR), abdominal volume index (AVI) and conicity index (CI) were compared for the diagnosis of at least two other components of MetS. The Youden index was used to determine the optimal cut-off values. The optimal cut-off points in men were 26.0 kg/m(2) for BMI, 90 cm for WC, 0.90 for WHR, 0.53 for WHtR, 16.6 (cm(2)) for AVI and 1.24(m(3/2)/kg(1/2)) for CI. The optimal values in women were 29.0 kg/m(2) for BMI, 91 cm for WC, 0.86 for WHR, 0.58 for WHtR, 17.0(cm(2)) for AVI and 1.23 (m(3/2)/kg(1/2)) for CI. The prevalence of overweight or obesity was 46.1% to 54.1% in women and 49.5% to 53.6% in men based on various obesity indexes. The area under the ROC curves (AUCs) varied from 0.671(0.651-0.690) for CI to 0.718(0.700-0.736) for WC in men and from 0.668 (0.646-0.690) for BMI to 0.755(0.735-0.774) for WHR and CI in women. [73]

Several criteria have been proposed to define abdominal obesity. The prevalence of overweight and obesity was estimated using different criteria in 844 female teachers living in Yazd city, in central Iran, in 2015. Anthropometric, demographic data and lifestyle factors were collected using a self-reported questionnaire. The prevalence of general overweight and obesity were 44.5% and 27.5%, respectively using BMI cut-offs. The prevalence of abdominal obesity based on WC measurements was 42.2% based on Iranian national criteria. The prevalence of abdominal obesity using WHR data, ranged from 23% based on criteria developed for Omani women to 93.5% based on Iranian criteria. The WHtR, prevalence of abdominal adiposity ranged between 83.5-92.9% based on two different suggested criteria for Iranian females. Applying the Iranian criteria gave the highest number of significant associations for abdominal obesity based on WC and WHR; however this was not the case for WHtR. [74]

Central obesity is commonly assessed using gender- and ethnicity-specific waist circumference RC) cut-off values, the WC cut-offs by the IDF developed for European populations, may not be appropriate for Iranian populations. The optimal cut-off points for the diagnosis of MetS in Iran were evaluated in a population of 2752 adults (1046 men). Subjects with two or more of the following risk factors from the IDF criteria were considered as having multiple risk factors: hyperglycemia (FBG >= 100 mg/dL or diagnosed diabetes), high blood pressure (SBP >= 130 mmHg, DBP >= 85 mmHg, or using antihypertensive drugs), low HDL (<50 mg/dL for females and <40 mg/dL for males), and high TG (>150 mg/dL). The WC cut-off with the highest sensitivity and specificity for predicting the presence of multiple risk factors were 91.5 cm in men and 85.5 cm in women. Sensitivity and specificity were 77% (86%) and 58% (50%) in men (women), respectively. The prevalence of MetS was estimated to be approximately 27% in Tehran. The authors conclude that the WC cut-offs recommended by the IDF are not appropriate for use in Iran. [75]

The optimum BMI cut-off point for the Iranian population based on MetS risk factors were investigated together with the BMI cut-off points with and without waist WC as a cofactor of risk and compared the differences, as part of the Shiraz Heart study. Subjects (n = 12283) were between the ages of 20-65 years old. All the features of MetS were found in 38.9% of the sample population, which was more prevalent among women than men (41.5% vs. 36%). The optimum BMI cut-off point for predicting MetS was 26.1 kg/m^2 and 26.2 kg/m^2 for males and females, respectively. When excluding waist circumference, the optimum BMI cut-off for acquiring metabolic risk factors in males decreased to 25.7 kg/m^2 and increased for women to 27.05 kg/m^2.[90]

Cross-sectional data from 3277 Iranian adults >20 years adults living in Zanjan, in north western Iran were analysed to identify cut-offs for WC that confer increased risk of MetS. After excluding WC, the, existence of two or more of the remaining four risk factors of the modified ATPIII criteria for MetS were defined as multiple risk factors. The cut-off values that had the maximal sensitivity and specificity for predicting the presence of MetS (multiple risk factors) were 87 cm in men and 82 cm in women. Cut-offs corresponding to a BMI of 25 and 30 kg/m^2 to predict MetS were 84 and 97 cm in men and 78 and 91 cm in women, respectively. The authors suggest that lower cut-off values for WC should be considered in the identification of individuals at high risk of MetS in the Iranian population.[91]

There is a lack of compelling evidence that waist circumference (WC) is a cardiovascular disease (CVD) risk factor in some ethnic groups[92], The optimal cut-off points of WC for predicting incident CVD and MetS was investigated in an Iranian population of 6,504 participants recruited from three areas in central Iran and were followed up for 7 years. After 394,418 person-years of follow-up, 427 incident primary CVD events (233 in men) were identified. For CVD, the optimum cut-off points for WC were 99 and 103.5 cm in men and women, respectively, but these had a low sensitivity (AUC: 0.59, 95%CI 0.55-0.63 in both men and women). Using cut-offs of 93 and 97 cm resulted in acceptable sensitivity. Regarding MetS, 92.6 and 97.8 cm were identified as optimum (AUC: 0.67, 95%CI 0.65-0.69 in men and 0.65, 95%CI 0.63-0.67 in women). The best cut-off values derived from the Cox regression model were 90 and 97 cm for men and women respectively.[93]

The cut-off value for WC that could be used as a surrogate index for central obesity were also independently investigated in 907 women (mean age 34.4±7.6 years) to determine the optimal values for predicting IR in Iranian women of reproductive age. IR was evaluated by the HOMA-IR and its cut off value was defined as the 95th percentile of HOMA-IR value for 129 subjects, without any metabolic abnormality. The optimal cut-off value for WC in relation to HOMA-IR was calculated based on the receiver operating characteristics (ROC) curve analysis using the Youden index and the area under curve (AUC). After adjustment for age the odds ratios (OR) of an elevated HOMA-IR rose with increasing WC; the age adjusted OR of IR for women with WC > 95 cm in comparison to those subjects with WC < 80 cm, was 9.5 (95% CI 5.6-16.1). The optimal cut-off value for WC predicting IR was 88.5 cm; with a sensitivity and specificity of 71% and 64%, respectively. These cut-offs are substantially lower than were proposed in the previous study, but may be related to the differences in age.[94]

9.1.2 Measures of adiposity in children

A cross-sectional survey was undertaken in a representative sample of 14,880 school students [6640 girls (49.2%) and 75.6% urban residents] , selected by multistage random cluster sampling from urban and rural areas of 30 provinces in Iran. Anthropometric measures including body mass index (BMI), waist circumference (WC), hip circumference (HC), and wrist circumference were measured under standard protocols by using calibrated instruments. Age-and gender- specific reference values were determined for anthropometric measures by the maximum penalized likelihood approach. Participants' mean age was 12.47±3.36 years.[95]

The development of age- and gender-specific reference curves for waist and hip circumferences was undertaken using a cross-sectional population survey in 2003-04 and a nationally representative sample of 21111 school-students living in urban (84.6%) and rural (15.4%) areas of 23 provinces in Iran. Smoothed reference curves for waist and hip circumference (WC, HiC) and waist-to-hip ratio (WHR) were developed by the LMS method. WC and HiC percentile values increased with age. For girls, the 50th to 95th percentile curves for WC increased sharply between 8-13 years and 11-15 years, respectively, and began to plateau after this age, whereas in boys, these curves had a persistent and less sharp increase with age, until the age of 18 years. The WHR curves of girls decreased with age until 15 years and began to plateau thereafter, whereas for boys the 25th to 95th curves had a plateau pattern. Comparisons of the current reference curves with the British curves showed that in boys, the 5th and 50th percentile curves were similar, but the 95th percentile curve of in Iran were higher than for the British students. For girls, the 5th percentile curves of both studies were similar, but the 50th and 95th percentile curves of our study were higher than the British curves.[96]

The prevalence of obesity and overweight in children for different age categories was determined using three standard definitions of obesity. Studies have reported the prevalence of obesity or overweight of children < 6, 6-12, and 12-20 years old. The reported prevalence of the overweight and obesity with regard to age and gender, and also by the different standard references which are the Centers for Disease Control and Prevention (CDC), the World Health Organization (WHO) definition, and the International Obesity Task Force (IOTF) references were combined. Meta-regression analysis showed that the prevalence of obesity and overweight did not vary significantly by gender and age categories, but using the different definitions led to different estimates of the prevalence of overweight and obesity.[97]

The determinants of overweight and obesity were investigated among 6635 children (3551 boys and 3084 girls, 6-11-year-old) attending elementary school in Rasht. Data on weekly frequency of skipping breakfast, physical activity and hours of television viewing were collected. Information on birth weight, parental age, parental educational levels, parental weight and height, and mother's employment status were gathered through self- administrated questionnaires given to the parents. The overall prevalence of overweight was 11-5% and 15.0% for boys and girls, respectively; while the overall prevalence of obesity was 5.0% and 5.9% respectively. Children with more educated mothers had a higher prevalence of overweight than children with less educated mothers. Logistic regression analysis showed that children with overweight/obese parents, children with more educated mothers and children who often skipped breakfast were more prone to overweight and obesity [98].

9.2 Estimates of insulin resistance

The optimal cut-off for the HOMA of insulin resistance for the diagnosis of IR and MetS in non-diabetic residents of Tehran has been reported. Optimal national cut-offs were determined for the Iranian population for those with and without diabetes mellitus, using data from the third National SuRFNCD. 3,071 adult Iranian individuals aged 25-64 years were analysed. MetS was defined according to the ATPIII and IDF criteria. HOMA-IR cut-offs from the 50th to the 95th percentile were calculated and sensitivity, specificity, and positive likelihood ratio for MetS diagnosis were determined. The area under the curve (AUC) (95%CI) was 0.650 (0.631-0.670) for IDF-defined MetS and 0.683 (0.664-0.703) with the ATPIII definition. The optimal HOMA-IR cut-off for the diagnosis of IDF- and ATPIII-defined MetS in non-diabetic individuals was 1.775. The optimal cut-offs in diabetic individuals were 3.875 (sensitivity: 49.7%, specificity: 69.6%) and 4.325 (sensitivity: 45.4%, specificity: 69.0%) for ATPIII- and IDF-defined MetS, respectively [99].

The threshold values of the HOMA used to determine IR were assessed in a sample of Iranians and the associations of IR with MetS was investigated. A total of 1327 non-diabetic and non-hypertensive subjects (438 men, 838 women; aged 20-77 years) were recruited from four different locations in Tehran from 2005-2008. The lower limit of the top quintile of HOMA values in subjects without any metabolic abnormality was considered as the threshold for IR. This threshold was 1.7 in men and 1.8 in women. Overall, 41.1% of subjects (36.3% men; 41.5% women) had IR. The HOMA cut-off to determine MetS was 1.95 using the ATPIII definition, and 1.85 for IDF definition of MetS. IR was associated with MetS using either definition. The sensitivity of MetS to detect IR was 22.4% for IDF and 36.2% for ATPIII criteria. In multivariate models, HOMA was predicted by WC, and was inversely associated with age and serum HDL-C. The cut point for the HOMA to detect IR was lower than reported for other populations. The authors conclude that IR is a robust correlate of MetS; but definitions of MetS are insensitive measures of IR in the Iranian population [100].

Non-alcoholic fatty liver disease (NAFLD) is characterised by intrahepatic fat accumulation, IR and serum liver enzyme abnormalities in individuals with obesity and MetS.[101] The optimal cut-off points for HOMA-IR and QUICKI in the diagnosis of MetS and NAFLD, using baseline data of 5511 subjects aged ≥18 years from a cohort study recruited in northern Iran. The optimal cut-off points for HOMA-IR in the diagnosis of MetS and NAFLD were 2.0 and 1.79 in men and were 2.5 and 1.95 in women, respectively. The optimal cut off points for QUICKI in the diagnosis of MetS and NAFLD were 0.343 and 0.347 in men and were 0.331 and 0.333 in women, respectively [102].

The prevalence of NAFLD and its associated metabolic abnormalities were investigated in 966 school-aged children and adolescents aged 7-18 years in Iran. Anthropometric and laboratory measurement and abdominal ultrasonography for liver echogenicity and size were undertaken in all subjects. A questionnaire was also used to obtain information on demographical and medical history, dietary habit, alcohol consumption and cigarette smoking. Fatty liver was diagnosed by ultrasound in 7.1% of children. NAFLD was significantly associated with increasing age, alanine aminotransferase (ALT), fasting insulin, total- and LDL-cholesterol, triglycerides and IR. In multiple logistic regression analysis, serum ALT, total cholesterol and WC were independent metabolic factors predictive of NAFLD after adjustment for other variables. There was a strong relationship between NAFLD and the abnormal metabolic variables in children [103].

A cross-sectional study aimed to determine the prevalence of the MetS, abnormalities of liver enzymes and sonographic fatty liver, as well as the inter-related associations in normal weight, overweight and obese children and adolescents. A sample of 1107 students (56.1% girls), aged 6-18 years were recruited from Isfahan. Liver sonography was performed among 931 participants. These variables were compared among participants with different BMI categories. From lower to higher BMI category, ALT, total cholesterol, LDL-C, triglycerides and SBP increased incrementally, and HDL-C decreased significantly. Elevated ALT, aspartate aminotransferase (AST) and alkaline phosphatase (ALP) were present in 4.1%, 6.6% and 9.8%, respectively of the normal weight group. The corresponding values were 9.5%, 9.8% and 9.1% in the overweight group, and 16.9%, 14.9% and

10.8% in the obese group. For all BMI categories, ALT increased significantly with an increasing number of components of the MetS. The odds ratio for elevated liver enzymes and sonographic fatty liver increased significantly with a greater number of the components of the MetS and higher BMI categories before and after adjustment for age [104].

The prevalence of fatty liver in obese Iranian children and its association with MetS and IR was investigated in 102 obese Iranian children, referred to pediatric clinics from 2011-2012. The evaluation of fatty liver was made by a pediatric endocrinologist, a pediatric gastroenterologist and an expert radiologist. The grade of fatty liver was higher in older children (P = 0.001). It was also greater in taller and heavier children (P <0.000), and those in whom the BMI was greater (P = 0.002). Severity of fatty liver according to liver sonography was positively related with WC, hip circumference, serum TG, serum FBG, serum fasting insulin, serum ALT, SBP and HOMA index and negatively related with the level of ALP [105].

The prevalence and causes of elevated ALT levels were determined among apparently healthy Iranian blood donors in Tehran. A total of 1959 (1465 male) were randomly selected among blood donors. BMI, viral markers and ALT levels were measured. If ALT was elevated (> 40 U/L), it was rechecked twice within 6 months. Individuals with ≥ 2 times elevated ALT levels (persistently elevated ALT) were invited for further evaluation. Fifty-two persons (2.65%) were found to have persistently elevated serum ALT. Among these subjects, non-alcoholic steato-hepatitis (NASH) was diagnosed in 46 (88.4%), chronic hepatitis C virus (HCV) infection in four (7.7%), alcoholic liver disease in one (1.92%), and drug-induced liver disease in one (1.92%). The prevalence of NASH and HCV infection in the studied population was 2.35% and 0.4%, respectively. The mean BMI of individuals with NASH was 30.58 kg/m(2), compared with 27.28 kg/m(2) of those without NASH (P < 0.001) [106].

To determine the homeostasis model assessment (HOMA-IR) cut off values to identify IR and MetS in Qazvin, in central Iran, 480 men and 502 women aged 20-72 years old were recruited to this cross-sectional study from September 2010 to April 2011. The criteria used to define MetS were the ATPIII, IDF and new JIS criteria. The lower limit of the top quintile of HOMA values in normal subjects was considered as the threshold of IR. The threshold of HOMA for IR was 2.48. Fifty one percent of the subjects were IR using this cut-off. The cut points for diagnosis of JIS, IDF, ATP III and Persian IDF defined MetS were 2.92, 2.91, 2.49 and 3.21, respectively [107].

10.0 Prospective cohort studies.

A study was designed to investigate the prevalence and trends of MetS and its components in a cohort of Iranian adults (n=6500) aged ≥35 years from 2001 to 2013. Subjects were randomly selected from three provinces in central Iran. Socio-demographic characteristics, anthropometry, blood pressure, and various biochemical indices were collected in 2001, 2007, and 2013. Secular trend and age-adjusted trend of MetS and its components were calculated over the period 2001-2013. The standardized prevalence of MetS, hypertension, low HDL-C, central obesity, and diabetes/impaired glucose tolerance (IGT) increased over the 12 years by 6.9%, 5.5%, 12.0%, 2.3%, and 18.7%, respectively, while the prevalence of hypertriglyceridemia decreased by 15.5%. The prevalence of MetS, low HDL-C, and central obesity were higher in females than males. The increasing prevalence of these metabolic abnormalities was higher in the rural population than in the urban population [108].

The prevalence of MetS and its individual components was determined within the Iranian adult population in 2011 and the changes occurring between 2007-2011 was assessed. Data were from two rounds of the Surveillance of Risk Factors of Non-communicable Diseases national surveys conducted in 2007 and 2011. MetS was defined according to IDF criteria. In 2007, the prevalence of MetS among adults aged 25-64 years was 35.95%, which decreased to 32.96% in 2011. Despite this overall decline, the prevalence of central obesity, raised triglycerides, and reduced HDL-C have remained constant. There was a trend towards a decline in the proportion of individuals with increased blood pressure, and the proportion of adults with increased fasting plasma glucose (FPG) increased. In 2011, the prevalence of central obesity, raised triglycerides, reduced HDL-C, increased blood pressure and increased FPG was 51.88, 36.99%, 54.72% 38.92%, and 24.97% respectively. Between 2007-11, the prevalence of MetS was reported to have fallen slightly in Iran, although the prevalence of increased FPG has increased significantly [109].

Some recent studies have shown a stability or declining trend in obesity in the Iranian population, while others still report increasing trends. The trends in general and abdominal obesity have been assessed in adults living in Tehran over a median follow-up period of 10 years. Data from participants in the four phases of the TLGS from 1999 to 2011 (n =10 368), aged ≥20 years were analysed. The crude prevalence of general obesity and central obesity increased from 23.1 % and 47.9 % at baseline, to 34.1 % and 71.1 % at the end of follow-up period, respectively. Risks of obesity and central obesity increased over the whole study period for men and women. These rising trends were observed in all sub-groups regardless of age, marital status and educational level [110].

The incidence of MetS and its most powerful components as predictors of MetS were investigated in a cohort study in central Iran. 2000 participants aged 20 to 74 years were initially selected using multistage random cluster sampling method from urban areas of Yazd in 2005 and re-investigated in 2015. MetS was defined using a modified version of the ATPIII definition [111]. The prevalence of MetS was 44.8% at baseline. Subjects without MetS were followed up in 2015. At this time, MetS had developed in 56.1% of these subjects. Incidence of MetS in males and females was 56.1/ 1000 person-years and 58.7/ 1000 person-years, respectively. The incidence of MetS increased with age and higher socio-economic status and decreased with increasing level of education. In females and males the most powerful component for incidence of MetS was a high FBG (HR = 16.6, 95% CI: 1.91-22.82) and hypertriglyceridemia (HR = 1.64, 95% CI: 1.02-2.6), respectively [112].

11.0 Conclusions

MetS is a common condition in Iran, with a higher prevalence in women. Whilst the prevalence of several of the components of the MetS appears to be rising, it is unclear whether this is also true for the MetS as defined by several criteria. There is a significant variation in the prevalence of MetS by region and ethnicity, and this is likely to be multifactorial, with socioeconomic status and diet playing an important role.

The features of MetS develop early in adolescence and may be detected using simple anthropometric measurements. However the precise cut-off values for these need to be agreed nationally and applied to population screening. This would be worthwhile, as lifestyle interventions appear to be effective.

Unravelling the genetics and proteomics of the MetS is likely to be complex[114-116], and will rely on an international consensus on its phenotype, if large multinational studies are to be feasible.

Table 1 Studies of the prevalence of Metabolic Syndrome in Adults in Iran

Date	Region	n	Age (y)	Criteria	Preval-ence (%) Total	Male (%)	Female (%)	Urban (%)	Rural (%)
2003 [3]	Tehran	10368	>20		33.7	24	42		
2004 [12]	Three centres	12514	>19	ATPIII	23.3	10.7	35.1	24.2	19.5
2007 [22]	Multi-centre	3024	25-64		37.4				
2009 [5]	Western	2941	>18	ATPIII	23.7	23.1	24.4		
2009 [6]	Northern Iran	984	30-50	ATPIII		-	31.0		
2007 2011 [109]	National survey	-	25-64	IDF	35.95 32.96				
2012 [29]	North East	1194	>18	ATPIII	29.1	31.1	55.0		
2012 [16]	South East	1802	>19	ATPIII IDF IDF/ AHA/ NHLBI	21 24.8 23.3	15.4 20.0 19.7	24.9 28. 25.8		
2014 [11]	Northern Iran South East	5826 2243	>18	ATPIII IDF ATPIII IDF	27.8 26.9 12.0 11.8				
2014 [14]	Central	8313	>18	ATPIII	21.9				
2015 [18]	Southern Iran	377	>20	ATPIII	26.8	16.6	36.8		
2015 [17]	Southern Iran	13304	>20	ATPIII Modified ATPIII IDF	25.1 27.7 28.3	18.9	28.4		
2015 [15]	South East	6000	>18	ATPIII IDF	35.0	31.0 25.2	38.0 42.5		
2015 [113]	North East	9829	35-65	ATPIII	38.8				
2016 [90]	South West	12283	20-65	WHO	38.9	36	41.5		
2016 [8]	Northern Iran	1562	>18	Local criteria	74.3				
2016 [7]	Northern Iran	5910	40-64	ATPIII		10.9	13.0		
2017 [28]	Northern Iran	248	25-70	ATPIII	37.6				
2005 2017 [112]	Central	2000	20-74	ATPIII	44.8				

ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III ; IDF = International Diabetes Federation; AHA = American Heart Association; NHLBI = National Heart Lung and Blood Institute; NHANES = National Health and Nutrition Examination Survey; WHO = World Health Organization

Table 2 Studies of the prevalence of Metabolic Syndrome in Children in Iran

Date	Region	n	Age (y)	Criteria	Preval-ence (%) Total	Male (%)	Female (%)	Urban (%)	Rural (%)
2006 [61]	Multi-centre	4811	6-18	ATPIII NHANES-III	14 2				
2009 [68]	North East	622	15-17	ATPIII		-	6.5		
2009 [70]	Central Iran	1221	10-15	ATPIII		-	3.9		
2010 [32]	Multi-centre	2728	10-15	IDF	2.1				
2012 [69]	Northern Iran	450	15-18	NHANES-III	3.3				
2013 [63]	Multicentre	5738	10-18	IDF	2.5				
2015 [67]	East I*ran*	1425	6-10	ATPIII	5.3				
2015 [66]	North western	338	10-18	IDF	3.4				
2016 [64]	Southern Iran	538	14-18	ATPIII	6	9.3	2.4		

ATPIII = National Cholesterol Education Programme, Adult Treatment Panel-III ; IDF = International Diabetes Federation; AHA = American Heart Association; NHLBI = National Heart Lung and Blood Institute; NHANES = National Health and Nutrition Examination Survey; WHO = World Health Organization

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