AMERICAN UNIVERSITY OF BEIRUT

# METABOLICALLY HEALTHY AND UNHEALTHY OBESE IN THE LEBANESE POPULATION, ARE THEY DIFFERENT? THE ROLE OF TRADITIONAL AND NON-TRADITIONAL RISK FACTORS

by

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# AN ABSTRACT OF THE THESIS

Nancy Nakhoul for Master of Sciences
Major: Health Research (SHARP)

Title: Metabolically Healthy And Unhealthy Obese In The Lebanese Population, Are They Different? The Role Of Traditional And Non-Traditional Risk Factors

**Background**: Obesity prevalence is increasing worldwide, contributing significantly to the global burden of cardiovascular disease. A subset of obese subjects remains with a favorable metabolic profile labeled metabolically healthy obese. The prevalence and predictors of this group are not well defined in the literature and studies have shown mixed results concerning its cardiovascular and mortality outcomes.

**Objectives**: The objectives of our study are to determine the prevalence of healthy non obese individuals, metabolically healthy obese and unhealthy obese in the Greater Beirut area. In addition we aim to assess differentials in demographics and socioeconomic factors and explore associations in the traditional and non-traditional cardiovascular risk factors between the different groups.

**Research design and Methods:** This is a cross-sectional study involving secondary data analysis from a representative sample of 501 participants residing in Greater Beirut area. Data on BMI and metabolic health defined by the ATP III criteria contributed to the outcome variables. We divided the cohort into four mutually exclusive groups: healthy non-obese (BMI <30 $Kg/m^2$, having one or none of the metabolic factors, referred thereafter as Healthy), unhealthy non-obese (BMI <30 $Kg/m^2$ having two or more of the metabolic factors), metabolically healthy obese (BMI ≥30 $Kg/m^2$, having one or none of the metabolic factors, referred thereafter as MHO), and metabolically unhealthy obese (BMI ≥30 $Kg/m^2$, having two or more of the metabolic factors, referred thereafter as MUHO). However, for the objectives of this study, we focused attention on three groups and on comparisons made between MHO vs. Healthy and MHO vs. MUHO. Firstly, descriptive analysis was carried out to determine the prevalence of the three groups of interest. Then, we provided data on demographics, socioeconomics, lifestyle factors, medical history, and macronutrients intake and body composition. Laboratory data including glucose, lipids, HbA1C, CRP, microalbumin/creatinine ratio, insulin, C-peptide level, TSH, creatinine, 25 (OH) vitamin D and cortisol level were measured. HOMA-IR score was also calculated. Univariate analysis was carried out to compare the different factors between MHO vs. Healthy and MHO vs. MUHO using simple logistic regression. Finally to account for confounding factors, a multivariate logistic regression was carried out with the dependent factors being MHO vs. Healthy and MHO vs. MUHO.

**Results:** Out of the total 501 patients, 41.5% were obese and 75.2% were metabolically unhealthy. The prevalence of MHO was 8% (95% CI: 5.8-10.7%; n=40), the MHO group composed 19 % of all the obese subjects. The prevalence of MUHO was 33.5% (95% CI: 29.4-37.9%; n=168), and that of healthy non-obese was 16.4% (13.2-19.9%; n= 82).

MHO subjects were more married, had higher waist circumference, HOMA-IR score, CRP and cholesterol level when compared to healthy non-obese.
On the other hand, MHO subjects were younger and more married than MUHO subjects. In addition, MHO had significantly lower HOMA score, CRP level and waist circumference than MUHO subjects.
In the multivariate adjusted analysis the factors associated with the healthy non-obese phenotype were marital status [adjusted OR: 4.95, 95%CI (1.27- 19.29)], HOMA score [adjusted OR: 0.33, 95%CI (0.20 -0.55)] and CRP levels [adjusted OR: 0.93, 95%CI (0.86-0.99)] when comparing MHO to healthy. The factors associated with the MUHO phenotype were age [adjusted OR: 1.04, 95%CI (1.01-1.07)], marital status [adjusted OR: 4.13, 95%CI (1.44-11.85)] and HOMA score [adjusted OR: 1.35, 95%CI (1.00 - 1.82)] when comparing MHO to MUHO, after adjusting for the other factors including gender, crowding index, and cholesterol level.

**Conclusion:** In our study, MHO phenotype was found to be at an intermediate state of metabolic health falling in between being healthy non-obese and metabolically unhealthy obese, especially in terms of abdominal obesity, insulin resistance and inflammation. Subsequently, it may be important to harmonize the definition of MHO and include waist circumference, HOMA-IR score and CRP level in its definition, beside hypertension lipids and diabetes related factors. After harmonization of the definition, studies will be needed to determine its prevalence in different countries and explore new predictors. In conclusion, whether MHO is an independent phenotype or a transient one before developing MUHO phenotype with time remains a question for future research.

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# ILLUSTRATIONS

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| BMI | Body Mass Index |
| BP | Blood Pressure |
| BPA | Bisphenol A |
| CAD | Coronary Artery Disease |
| CI | Confidence Interval |
| CRP | C-Reactive Protein |
| CVD | CardioVascular Disease |
| DALY | Disability-Adjusted Life years |
| DBP | Diastolic Blood Pressure |
| DM | Diabetes Mellitus |
| F | Female |
| FPG | Fasting Plasma Glucose |
| HDL-C | High Density Lipoprotein-Cholesterol |
| HOMA-IR | HOmeostasis Model Assessment- Insulin Resistance |
| IL-6 | Interleukin-6 |
| LDL-C | High Density Lipoprotein-Cholesterol |
| M | Male |
| MetS | Metabolic Syndrome |
| MH | Metabolic Health |
| MHO | Metabolically Healthy Obese |
| MUHO | Metabolically Unhealthy Obese |
| NA | Not Applicable |

| | |
|---|---|
| NAv | Not Available |
| NCEP ATPIII | National Cholesterol Education Program Adult treatment Panel III |
| NHANES | National Health and Nutrition Examination Survey |
| OR | Odds Ratio |
| PAI-1 | Plasminogen Activator Inhibitor |
| SBP | Systolic Blood Pressure |
| SD | Standard Deviation |
| SE | Standard Error |
| TC | Total Cholesterol |
| TG | Triglycerides |
| TNF-∝ | Tumor Necrosis Factor Alpha |
| WC | Waist Circumference |
| WHI | Women Health Initiative |
| WHO | World Health Organization |

# CHAPTER 1

# INTRODUCTION

## 1.1 Background on obesity

Obesity is defined as excessive body fat accumulation, which may impair health [1]. It is best measured in adults using the body mass index cut-off of greater than or equal to 30 kg/m$^2$, and overweight being from 25 to 29.9 kg/m [1]. The world prevalence of obesity and overweight has nearly tripled since 1975 with 1.9 billion adults being overweight and 650 million obese, in 2016. This corresponds to a world prevalence of overweight of 39 % and of obesity of 13 %. There is a mild gender preponderance, with 11% of men being obese and 15% of women [2].

There is also a large regional variability with countries such as Japan, Korea and Italy having a prevalence of less than 10 %, while New Zealand, Mexico, and the United States report a prevalence of more than 30 % [3]. The Middle-East North Africa region and Arab countries are witnessing a rapid rise in obesity rates [4]. In Lebanon, obesity prevalence is intermediate; it was estimated to be 17.4% in children and adolescents, and 28.2% in adults in 2009 [5-7]. However it does follow the world trend of increase in rates [6]. As an example, the estimated rates in 1997 were 14.8% and 19.3% percent, for men and women, respectively, and reached 27.4% and 28.8%, in 2008[6].

Along the same line, Finucane et al estimated the global age-standardized mean BMI in 2008 to be 23.8 kg/m$^2$ (95% CI: 23.6‑24.0) in men with an increase of 0.4 kg/m$^2$ per decade since 1980. Regarding women, the age-standardized mean BMI was

estimated to be 24.1 kg/m$^2$ (95% CI: 23.9‑24.4) with an increase of 0.5 kg/m$^2$ per decade between 1980 and 2008 [8].

Obesity is declared as a disease by most of the organizations worldwide including the National Institutes of Health, the US Food and Drug Administration, the World Health Organization and the World Obesity Federation [9, 10]. Obesity is caused by a constellation of genetic, environmental and behavioral factors. As a complex, obesity is linked to multiple medical conditions, the strongest association being with type 2 diabetes mellitus [11, 12]. It is also associated with dyslipidemia[13], hypertension [14], cardiovascular disease [15], cerebrovascular disease [16], sleep apnea[17] and many cancers [11].

In addition to the increase in cardiovascular risk factors, obese subjects were found to be at increased risk of overall mortality worldwide, in the US, in Europe and in developed countries [18-20]. Having a high body mass index has emerged as a leading, independent risk factor of morbidity, as measured by disability-adjusted life years or DALY, preceded only by hypertension, smoking, ethanol excess, household air pollution, and low fruit intake [21].

However, not all obesity may be associated with adverse health effects. Differentiation between obesity types and their contribution to the different metabolic abnormalities has been raised in literature, and has led to the concept of metabolically healthy obese (MHO). This subset of obese subjects with a favorable metabolic profile represents 10-25% of obesity [22, 23] and is in contradistinction to metabolic syndrome (MetS) which represents a cluster of different metabolic abnormalities including hypertension, diabetes, and dyslipidemia [24]. In the MHO group excessive body fat

accumulation was not associated with metabolic abnormalities observed in unhealthy obese.

### 1.2 Definition of metabolically healthy obese

The definition of healthy obese varied between different studies worldwide. Most studies acknowledge that the definition of MHO includes obese individual (BMI ≥ 30 kg/m$^2$) without the metabolic derangements (Table1) [25]. The most widely used definition of MHO is obese subjects with BMI ≥30 having one or none of the metabolic derangement defined by the updated version of the Adult Treatment Panel III criteria (ATPIII): triglycerides ≥150mg/dl or use of lipid-lowering drugs, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85mmHg or use of antihypertensive drugs, glucose ≥ 100mg/dl or use of medications for diabetes, and HDL-C<40 mg/dl for men and<50mg/dl for women (Table 2). The waist circumference (WC) criterion was not used by some of the studies due to co-linearity with BMI [26-28]. Another metabolic health definition used insulin resistance status expressed by HOMA-IR (Homeostatic model assessment of insulin resistance) such as the definition of Meigs[2] while others have combined the ATPIII criteria with insulin resistance. Wildman et al have used the inflammation marker CRP level to define metabolic health in addition to the combined ATPIII and HOMA-IR score.

The most widely used criteria in the definition of MHO, by descending order and as reviewed by Rey-Lopez et al were blood pressure (83 % of the studies), HDL-Cholesterol (73%), fasting blood sugar and triglycerides (70%), HOMA-IR (40%), diabetes and WC (30%), total cholesterol (13%), CRP and triglycerides/HDL-C (10%), LDL-C (7%) and others (3%). The other factors include WC, fibrinogen, insulin,

HbA1C, uric acid and dyslipidemia diagnosis [29]. Table 2 summarizes the different criteria used to define MHO.

### 1.3 Prevalence of metabolically healthy obese

Although the MHO phenotype was described since 1980, the wide variation in its definition has led to a wide variation in its prevalence. Rey-Lopez et al systematically reviewed cross-sectional and prospective studies worldwide on the prevalence of MHO; thirty different definitions were used to determine MHO groups, the prevalence of MHO (proportion of the overall obese) varied between 6-75 % in all subjects , the lowest prevalence was found in adult Americans age 18-65 years when using the HOMA-IR score and ATPIII criteria [30] while the highest was found in British adults aged ≥20 based on blood pressure, total cholesterol and type 2 diabetes[31].

In addition, this prevalence also varied within the same cohort when using different criteria. From a Switzerland cohort, the prevalence of MHO was estimated to be 25 % in men and 35 % in women using Aguilar-Salinas criteria (Table 2), 3% in men and 11 % in women using Karelis criteria, 32% in men and 43 % in women using Meigs 2 criteria [32].

However, the variation in the prevalence of MHO persisted between different cohorts despite using the same set of criteria. Vliet-Ostaptchouket al harmonized the definition by using two sets of strict and less strict criteria to define MHO (Table 2) in different cohorts from Europe. Although using the same definition, the study found a variable prevalence of MHO in ten different European regions; it was estimated to be 12 % of the obese across all cohorts, highest in men of the Italian CHRIS study (19%) and

women of the UK NCDS study (28.4 %) and lowest in the Finnish cohort (2.3 % in men and 7.3 % in women)[33].

Moreover, the prevalence of MHO may vary according to the characteristics of the population studied, such as age, race, and ethnicity. Rey-Lopez et al found a higher prevalence of MHO in women than in men, and a decreasing prevalence with age regardless of the criteria used [29].

In conclusion the definition used has a great impact on the prevalence of MHO. The prevalence will be high when using less stringent criteria such as HOMA-IR proposed by Meigs et al [34]and will be low when using more stringent criteria combining HOMA-IR with four others metabolic factors as the one proposed by Karelis et al.[35].

In fact, similarly to the MetS definition [28], harmonized criteria are needed to define MHO and subsequently determine its true prevalence.

### 1.4 Predictors and determinants of metabolically healthy obese

It has been suggested that a variety of genetic, dietary and lifestyle factors, contribute to the MHO phenotype. The role of genetic and epigenetic factors is poorly studied in the context of MHO and is worth exploring. While the change in dietary compositions, the sedentary lifestyle and the global urbanization have led to an increase in metabolic abnormalities and the prevalence of obesity, it is important to study their contribution to the MHO phenotype specifically [36]. The following section will be detailing some of the factors that may be different between MHO and MUHO.

### *1.4.1 Dietary factors*

The hypothesis that MHO subjects may have more favorable dietary intake was not observed in all studies. Hankinson et al examined dietary patterns in a multi-ethnic group of 775 obese American adults aged 40–59 years from the International Population Study on Macro/Micronutrients and Blood Pressure (INTERMAP) cohort. MHO definition met all the specific criteria for the study: favorable blood pressure (≤120/≤80 mm Hg) and no medication or special diet for hypertension; no physician diagnosis, medication, or special diet for other metabolic risk factors (i.e., diabetes and dyslipidemia); no prevalent cardiovascular disease prevalence. The prevalence of MHO was 19% similar in men and women [37]. Thirty four food nutrients and fourteen food group variables that were associated with healthy diet composition were compared between MHO and MUHO after stratification by gender. Those items were mainly meat, fish, dairy, eggs, fruits, vegetables and grains [37]. Although total energy intake was non-significantly lower in MHO as compared to unhealthy obese in both genders, there were no significant differences in food groups or nutrients between obesity phenotypes [37]. On the other hand, Manu et al. examined adults participating in the National Health And Nutrition Examination Survey (NHANES) 1999-2004. MHO subjects were defined using both the Meigs2 criteria of insulin resistance and the updated National Cholesterol Education Program Adult Treatment panel III (NCEP ATPIII) criteria. The prevalence of MHO was 4.8 %. There were no significant differences between MHO and metabolically healthy normal weight males in terms of energy intake, diet composition and alcohol consumption, but MHO had less exposure to tobacco while MHO females consumed less fibers [38].

Adherence to specific diets and food pyramid compliance were also examined in the MHO phenotypes. Naja et al. found that subjects with higher adherence to the traditional-Lebanese pattern had higher odds of being metabolically healthy overweight/obese (OR: 1.83, 95% CI: 1.09–3.91) [39]. The proportion of the overweight/obese subjects in this cohort was estimated to be 37%, metabolic health being defined using the ATPIII criteria (Table 2). In parallel, Philips et al investigated dietary factors in the Mitchelstown cohort in Ireland. MHO subjects were defined using five different definitions of metabolic health with prevalence ranging between 2.2 to 11.9%. When using Wildman, Meigs1 and Meigs2 criteria (Table 2), MHO subjects had better compliance with food pyramid components (unadjusted analysis) [40].

Inconsistency in the evidence supporting the role of dietary intake in the shaping of MHO phenotype may be again explained by the wide variety in the definitions of metabolic health used in different studies. It is important to scrutinize dietary content using a standardized and unified definition of MHO, in a specific population.

### *1.4.2 Physical activity*

It is well known that sedentary behaviors and physical inactivity increase the risk of cardio-metabolic diseases, CVD related and all-cause mortality [41, 42]. Conversely, regular exercise and physical activity decrease the risk of abdominal obesity [43], type 2 diabetes [44], cardiovascular events and all-cause mortality [45]. The role of physical activity in the MHO phenotype is not well established. Philips et al examined physical activity duration, intensity and compliance with the Irish physical activity guidelines in the Irish cohort. No difference in any of those parameters were found between MHO and MUHO except for moderate to high level of physical activity

being positively associated with MHO defined by insulin resistance, particularly among those with a high level of activity (OR 2.35, 95% CI 1.28-4.34, p = 0.006, adjusted analysis) relative to those with a low level of physical activity [40]. In addition, Velho et al analyzed different determinants of metabolic health in the CoLaus study in Switzerland. A positive association between MHO and physical activity was found when MHO was defined according to Wildman, Meigs1, Meigs2 and Aguilar Salinas criteria [32]. On the other hand, Manu et al showed no difference between MHO and metabolically healthy normal weight subjects of the 1999-2004 NHANES cohort, in the duration of physical activity and intensity of efforts during physical activity. In this same cohort MHO females were found to be less active than their healthy normal weight counterparts[38].

Despite some inconsistencies in the literature, the above data suggest that the beneficial effects of exercise are observed among obese subjects, and that physical activity may be a predictor of the MHO phenotype.

### *1.4.3 Inflammation*

A chronic low grade inflammatory state is observed in patients with obesity and insulin resistance [46] . Adipocytes and macrophages, through secretion of IL-6 and TNF-α stimulate the liver to produce C-reactive protein (CRP), demonstrating a direct link between adipocytes and the inflammatory marker CRP [47]. In addition, inflammation is associated with the metabolic syndrome and an increase in cardio-metabolic risk [26]. Whether MHO subjects have a better inflammatory status has been proposed as one of the differences between MHO and MUHO phenotypes. Several studies have shown a more favorable inflammatory profile among MHO subjects.

Karelis et al examined 88 obese postmenopausal women and found significantly lower levels of CRP in MHO when compared to MUHO [48]. In addition, Aguilar Salinas have observed a higher adiponectin level (an adipose-specific hormone that has anti-inflammatory and insulin-sensitizing properties) among MHO individuals [49].

On the other hand, Wildman et al compared several inflammatory markers in postmenopausal women of the Women's Health Initiative study at baseline: obese/overweight women with metabolic abnormalities had the highest burden of inflammation (higher CRP, IL-6, TNF-alpha, white blood count, E-selectin, and PAI-1) when compared to healthy non-obese [50]. Despite displaying lower degree of elevation of these inflammatory markers and lower 10-year risk of CVD the MHO group still displayed high levels as compared to healthy non-obese [50].

The lower rates of adiposity-related cardiometabolic abnormalities observed in MHO may be related to the lower inflammatory state and better fat storage capacity as compared to unhealthy obese [51].

### *1.4.4 Other Factors*

Other factors that may differ between the two obese categories were not widely explored worldwide.

It is well known that obesity is associated with lower sleep quality and increased risk of obstructive sleep apnea. Kanagasabai et al assessed sleep habits in a sample of participants from the NHANES 2005-2008 cycle[52]. MHO subjects were not found to have better sleep quality or duration, despite being healthier metabolically and more active physically.

Other obesity related factors that are worth exploring in healthy obese are cortisol level and TSH. Abnormalities in the hypothalamic pituitary axis and cortisol secretion have been linked to obesity and carbohydrate metabolism [53, 54]. In addition, the low cortisol binding globulin (CBG) levels observed in obesity is thought to be the culprit in fat accumulation through a better accessibility of cortisol by peripheral tissues [55]. To date, no studies have examined the cortisol secretion and action in healthy obese. Manco et al have shown decrease in CBG and increase in free cortisol after weight loss from bilio-pancreatic diversion in morbidly obese subjects [56]. This observation highlighted the complexity of this topic, emphasizing the need for future studies to assess the possible differences in cortisol metabolism between healthy and unhealthy obese. On the other hand, the pituitary thyroid axis was not examined in MHO group. It was previously observed that a higher TSH value in young euthyroid women was associated with metabolic syndrome components including waist circumference, blood pressure and triglycerides [57]. Subsequently, exploring TSH difference between MHO and MUHO is also a research question of interest.

Beside TSH and cortisol, it is well known that obese subjects display lower levels of vitamin D when compared to the general population [58]. In addition, some studies have observed higher levels of vitamin D in MHO when compared to MUHO [59]. The reason behind this difference is complex and relates to a constellation of phenomena including sequestration of vitamin D in fat tissues, altered metabolism and decreased intestinal absorption[60].

Our study will be exploring whether the above mentioned factors do differ between obese MHO and MUHO, and non-obese subjects.

### 1.5 Cardiovascular outcomes of metabolically healthy obese

Although it is well established that MetS is associated with increased cardiovascular morbidity [61] and mortality [62], studies have shown mixed results regarding the cardiovascular outcomes of MHO [22]. Hamer et al reported the association of MHO with the risk of mortality in large representative cohorts from Scotland and England. A total of 22,203 men and women [aged 54.1 years (SD ±12.7), 45.2% men] without known history of CVD at baseline were examined. MHO were not at elevated risk of CVD when compared to healthy non-obese, while MUHO were at increased all-cause mortality when compared to MHO or healthy [63].Similarly, Calori et al examined a sample from the Cremona Study, Italy. All-cause mortality adjusted for age and sex was higher in the obese insulin-resistant subjects (HOMA-IR ≥ 2.5) when compared to healthy non-obese, while insulin sensitive obese (HOMA-IR <2.5) participants were not at increased all-cause, cancer, and CVD mortality when compared to healthy non-obese subjects [64].

In contrast, analyses of the U.S. NHANES III data have shown increased all-cause mortality in obese subjects without the metabolic factors[30]. The U.S. findings were replicated by a Swedish cohort that has shown increased cardiovascular events risk and mortality in obese subjects without metabolic syndrome as compared to normal non obese [65].

One possible explanation for the inconsistencies observed in the above studies could be in the different definition used for MHO among the different cohorts, as well as differences among the populations studied. Despite that, Hinnouho et al. documented an increased risk of mortality in MHO using different definitions of metabolic health, by using the ATPIII criteria or insulin sensitivity index as compared to metabolically

normal or healthy subjects being defined as non-obese with one or no metabolic abnormality.

On the other hand, to better explore cardiovascular risk of MHO, surrogate markers of CVD can be explored in cross-sectional studies. In addition to cholesterol and CRP, microalbumin/creatinine ratio has been declared as a new CVD marker [66]. High ratios were observed in obese subjects and in patients with MetS [67, 68]. It is important to explore any difference in microalbumin/creatinine ratio between the two subcategories of obese subjects.

### 1.6 Metabolically healthy obese in Lebanon

Only few studies conducted in Lebanon in limited age groups, explored the prevalence of MHO or metabolic syndrome [7, 69].

The prevalence of metabolically healthy obese and overweight in Lebanon by Naja et al study was found to be 37.2 % [39]. The prevalence of MetS in the Lebanese adult population was calculated from a representative sample of 499 subjects (43% men and 57% women) from 23 health care centers distributed over the six Lebanese districts in 2008 [7]. Using the IDF criteria of metabolic syndrome [28], MetS prevalence was found to be 31.2% in the overall sample, 38.6% in men and 25.8% in women [7].

Because of the wide variability in prevalence of MHO reported worldwide, and because there is a lack of reports on MHO and little on MetS in Lebanon, it would be important to determine the prevalence in a community-based sample with well-defined criteria and population. In addition, because of the possibly different health implications than MUHO, it would be important to assess which factors may be associated with MHO, as compared to MUHO and to healthy non obese. We have sought to determine

the different health associations and risk factors among three groups of patients, whom would in theory, have increasing health morbidity by definition. These would be healthy, normal weight individuals, MHO and MUHO. We have additionally sought to determine the prevalence of the latter three groups in a random sample of the Lebanese population residing in the Greater Beirut Area.

Our study will help policy makers locally in planning, as well as raising awareness on the possible risk factors of obesity and accordingly further devise strategies which would aid in decreasing obesity and/or its associated metabolic comorbidities.

### 1.7 Thesis Objectives

The objectives of the present study are:

(1) To determine the prevalence of healthy non obese individuals, metabolically healthy obese (MHO) and unhealthy obese MUHO in the Greater Beirut area

(2) To assess differentials between the two groups of MHO and MUHO and explore associations with socio-demographic characteristics, lifestyle factors and the traditional (such as cholesterol, LDL and NON-HDL levels ) and non-traditional risk factors (such as CRP, insulin, C-peptide, the HOMA-IR score, microalbumin/creatinine ratio, cortisol, TSH and Vitamin D) linked to metabolic health

(3) To assess differentials between MHO and healthy non obese subjects and compare them with respect to the above mentioned factors.

# CHAPTER 2

# METHODS

## 2.1 General description of the study

The present study will involve secondary data analysis. The original dataset was collected using a cross-sectional study design, involving a representative sample of 501 adults aged >18 years with 64 % women and 36% men, residing in the Greater Beirut area. The mean age of the population was 45 ±15 years old. The study was conducted between February and June 2014 using multistage probability sampling for participant selection. The primary aim was to measure Bisphenol A level (BPA), a chemical found mainly in carbonated plastics, identify its predictors and explore any link to metabolic disorders among Lebanese population: BPA being an endocrine disruptor known to be linked to metabolic abnormalities. The original study protocol was approved by the IRB at the American University of Beirut.

## 2.2 Sampling

A random sample of the Lebanese population residing in Beirut and its suburbs was selected based on area probability and multistage cluster sampling. More specifically, the districts (clusters) were selected, within each neighborhood, and then households were selected based on a systematic random sample according to the estimated number of buildings in the neighborhood. Finally, the primary respondents within each household were those whose birthdays occurred most recently. Recruitment was carried out by trained personnel. Subjects who agreed to participate were informed about the study objectives and methods before they signed informed consent forms.

Transportation for the subjects was provided to and from the study site. Subjects were brought in groups of 8 to 10 per day, in the morning during weekdays only. Subjects were instructed to bring all their medications with them. The site visit was composed of three parts: the first one is a face to face interview by trained personnel to collect demographics and socio-economic factors, lifestyle factors, medical history and food frequency questionnaires. The second part is the anthropometric measures, and the third one is the blood withdrawal after 10 hours of fasting.

### 2.3 Definition of the outcome variables

Table 3 illustrates the definition of the two major outcomes, obesity and metabolic health. Obesity was defined as BMI ≥30 kg/$m^2$ and metabolic health was defined as per the ATPIII definitions of metabolic health characterized by the presence of obesity in addition to two or more of the four components of metabolic syndrome namely, elevated triglycerides ≥ 150 mg/dl, low HDL <40mg/dl in males and <50 mg/dl in females, elevated blood pressure ≥ 130 systolic or ≥ 85 diastolic or elevated fasting glucose ≥ 100mg/dl. Both outcomes were examined as dichotomous variables (yes/no) and hence study subjects were classified into four mutually exclusive groups, as detailed below.

#### *2.3.1 Metabolically healthy obese (MHO)*

Subjects with BMI ≥ 30 Kg/$m^2$ and having one or none of the four other components of metabolic syndrome were labeled as metabolically healthy obese (MHO).

### *2.3.2 Metabolically unhealthy obese (MUHO)*

Subjects with BMI ≥ 30 Kg/$m^2$ having two or more of the above mentioned metabolic factors were labeled MUHO.

### *2.3.3 Healthy:*

Healthy non obese are subjects with BMI <30 Kg/$m^2$ with one or no component of metabolic abnormality.

## 2.4 Definition of the independent variables and covariates

### *2.4.1 Demographics and anthropometrics*

We will be using demographics and anthropometric measures originally collected using a detailed questionnaire such as: age, gender, education (primary, secondary, and university), income per family divided by categories <1000$ or>1000$, calculated crowding index (defined as the total number of co-residents per household, excluding the newborn infant, divided by the total number of rooms excluding kitchen and bathrooms), smoking (none or current), coffee drinking (none or current),alcohol intake (none or current) and macronutrients intake.

Physical activity was collected using the short version of the International Physical Activity Questionnaire (IPAQ) [70]. Sleep habits were collected using the Berlin questionnaire[71].

Weight and height were taken using a calibrated scale, waist circumference (WC) using a standardized method [72].

Body composition was obtained using a bioimpedance analyzer (Body Composition Analyzer, Inbody 230, Inbody, Seoul, South Korea). Sitting blood pressure

was measured twice at 10 minute interval using a digital sphygmanometer, the mean value was considered.

### *2.4.2 Medical history*

Medical history was collected for the presence of diabetes, hypertension, coronary artery disease, and cancer history.

The presence of diabetes was defined as history of diabetes and/ or either FPG ≥126 mg/dL, or HbA1c ≥6.5%. The presence of hypertension was defined as history of hypertension or taking medicine for blood pressure or abnormal mean blood pressure (SBP ≥ 130or DBP ≥ 80).

### *2.4.3 Laboratory workup*

The laboratory and urine data used to determine risk factors are: creatinine level measured by the Jaffe rate method (Cobas 6000, Roche); cholesterol, LDL, HDL, triglycerides and CRP measured using Vitros 350 analyzer (Ortho Clinical Diagnostics, Johnson & Johnson, New Brunswick, NJ);fasting glucose(FPG) measured by the enzymatic method (Cobas 6000, Roche, Basel, Switzerland), glycosylated haemoglobin (HbA1C) measured by high-performance liquid chromatography (Bio-Rad, Hercules, CA); insulin and cortisol levels measured by radioimmunoassay (Cisbio), C peptide measured by electrochemiluminescence immunoassay (Cisbio), TSH measured by electrochemiluminescence immunoassay (Cobas), 25(OH) vitamin D measured by electrochemiluminescence immunoassay (ECLIA, Cobas e 411, Roche);urine microalbumin/creatinine ratio by immunoturbidimetry (Cobas 6000, Roche). The

HOMA-IR score for insulin resistance was calculated by HOMA2 score calculator version 2.2.3, diabetes trial Unit University of Oxford.

Non-HDL variable was computed as total cholesterol – LDL levels.

**2.5 Statistical analysis**

The analysis was done using the Statistical Package for Social Sciences (SPSS, version 22, IBM Corp, Armonk, NY).

A descriptive analysis was carried out to determine the prevalence of healthy non-obese, MHO and MUHO.

We documented demographics, anthropometrics, medical history and laboratory data as means ± SD for continuous variables and number and frequencies for categorical variables.

For bivariate analyses, analysis was done in two steps, MHO versus healthy and the MHO versus MUHO.

T-test was used to compare means of 2 continuous variables, Chi square test to compare percentages for categorical variables in both groups MHO vs. MUHO and MHO vs. healthy. The association of each of the characteristics of study participants was assessed using simple logistic regression analysis. Results in the univariate analysis were presented as OR with 95 % CI for categorical variables and beta coefficient ± standard error (SE) for continuous variables. A p-value $<0.05$ was considered significant.

To adjust for potentially confounding variables, binary logistic regression analyses were carried out with the factors included being age, gender, crowding index and the variables with clinical significance.

Results will be presented by the odds ratio (OR) and 95% confidence interval (CI).

To account for missing data, we imputed the mean for missing data in the HOMA-IR score.

# CHAPTER 3

# RESULTS

## 3.1 Prevalence of the different outcome variables

The total sample was composed of 501 participants with female predominance (64.3 %), the mean age was 45.4 ± 15 years, and the mean BMI was 29.4 ± 5.9 kg /m2. Overall, obese and metabolically unhealthy subjects constituted respectively 41.5% and 75.2% of the total sample. The prevalence of MHO was 8% (95% CI: 5.8-10.7%; n=40) (Table 4); 4.5% (95% CI: 1.9-8.6%) among males and 9.9 % (95% CI: 6.9-13.7%) among females. The MHO group composed 19 % of all the obese subjects. The prevalence of MUHO was 33.5% (95% CI: 29.4-37.9%; n=168), 29.5% (95% CI: 23.0-36.9%) among males and 35.5 % (95% CI: 30.5-41.2) among females. The prevalence of healthy non-obese was 16.4% (13.2-19.9%; n= 82), 16.8% (95% CI: 11.6-23.1 %) among males, 16.1% (95% CI: 16.1-12.3%) among females (figure 1). The rest of the cohort was labeled as unhealthy non obese representing 41.7 % (95% CI: 37.4%-46.2%; n= 209) and is not a group of interest for this study.

The rest of the analysis will be comparing MHO to MUHO and MHO to healthy participants.

## 3.2 Univariate analysis

Table 5 presents the general characteristics of the three groups, in regards to demographic components, socio-economic and lifestyle elements and sleep pattern. Results did not show significant differences between the study groups by gender, family income and education. However, MHO participants were significantly younger than

MUHO subjects (45.5±12.9 v/s. 51.1 ±14.0years, respectively; p-value: 0.02), but did not differ in age from healthy non-obese (45.5±12.9 v/s. 40.8 ±15.4 years, respectively; p-value: 0.10). Both the healthy and MUHO groups were significantly more likely to include single subjects when compared to the MHO group [OR = 3.83, 95% CI (1.35-10.84) and OR= 3.5, 95% CI (1.30-9.420 respectively]. The crowding index was statistically significantly higher in the MHO group vs. MUHO (1.83 ±1.24 vs. 1.47 ±0.89, respectively; p-value: 0.04) but did not differ between MHO and healthy groups (1.83 ±1.24 vs. 1.58 ±0.9, respectively; p-value: 0.22). None of the lifestyle factors (cigarette smoking, waterpipe smoking, alcohol intake, coffee drinking and levels of physical activity) differed when comparing MHO and MUHO or MHO and healthy). The Berlin Score was lowest in the healthy group and was significantly different when compared with the MHO group (0.45±0.68 vs. 1.76±0.71, p-value <0.001). There was no significant difference in the Score between the MUHO and MHO groups. Similar results were obtained when the variable was treated as dichotomous. The proportions of patients with high risk to develop obstructive sleep apnea were similar in the MUHO vs. MHO groups [53.6% vs. 60.6% respectively; p-value = 0.47, OR=0.75, 95% CI (0.35-1.63)] while it was significantly lower in the healthy when compared to MHO [7.9% vs. 60.6%; p-value: <0.001, OR = 0.06; 95% CI (0.20-0.17)].

Table 6 and Figure 1 summarize the factors included in the definition of the three groups. As expected, the mean BMI was not statistically different between MHO and MUHO groups (33.8 ± 3.48 vs. 34.6 ±4.69 kg/m2 respectively, p-value: 0.30) but was significantly lower in the healthy group when compared to the MHO group (25.36 ±3.1 kg/m2 vs. 33.8 ± 3.48respectively, p value< 0.001). There was significantly lower fasting plasma glucose (FPG) level in the MHO group as compared to MUHO (100 ±12

mg/dl vs. 126 ±53 mg/dl; p-value: 0.006) and significantly higher FPG in MHO vs. healthy (100 ±12 vs. 95 ±7 mg/dl respectively; p-value: 0.032). The glycosylated hemoglobin results were parallel to the FPG results in the case of MHO compared to the MUHO (5.57% ±0.4% vs. 6.5% ±0.7 % respectively; p-value: 0.001) and when MHO was compared with the healthy (5.57% ±0.4% vs. 5.36% ±0.4 % respectively; p-value: 0.007).Triglycerides levels were significantly lower in MHO as compared to MUHO (114 ± 41vs. 178 ±139 mg/dl; p-value: <0.001) and higher in MHO as compared to healthy with borderline significance (114 ± 41vs. 97 ±47 mg/dl respectively; p-value: 0.053). The HDL level was significantly higher in MHO vs. MUHO (55 ±13 vs. 47 ±14 mg/dl respectively; p-value: 0.001) and similar to the HDL of the healthy group (55 ±13 vs. 51 ±15 mg/dl respectively; p-value: 0.092).

Mean systolic blood pressure was significantly lower in the MHO group as compared to the MUHO group (116 ±12 vs. 131 ±18 mm/Hg respectively; p-value: <0.001) and did not differ in the MHO vs. healthy (116 ±12 vs. 113 ±14 mm/Hg respectively; p-value: 0.154). The mean diastolic blood pressure results paralleled the systolic ones; it was significantly lower in the MHO vs. MUHO group (73±8 vs. 79 ±10 mm/Hg respectively; p-value: <0.001) but similar in the MHO and healthy (73±8 vs. 71 ±9 mm/Hg respectively; p-value: 0.33).

The Odds of having hypertension was 5 times higher for the subjects in the MUHO group as compared to MHO group [OR: 5.54, 95%CI (2.66-11.52) p value <0.001] while it wasn't significantly different for healthy subjects as compared to MHO [OR: 0.82, 95%CI (0.38-1.78)].Similarly the Odds of having diabetes was 6.5 times higher in the participants of the MUHO group as compared to MHO [OR: 6.5, 95% CI

(1.92-22)] while it wasn't significantly different in healthy vs. MHO [OR: 0.15 (0.02-1.51)].

Table 7 and Figure 2 show differences between the groups in the obesity related factors. The mean body fat did not statistically differ between MHO and MUHO (37.37 ±8.21 vs. 39.06 ±9.05 kg respectively ; p-value: 0.28) but was significantly higher in the MHO compared to the healthy (37.37 ±8.21 vs. 21.6 ±7.3 kg; p-value :< 0.001); while the mean muscle mass was not different across both compressions (MHO vs. MUHO: 26.46 ±5.66 vs. 27.72 ±6.50 kg respectively; p-value: 0.26; and MHO vs. healthy: 26.46 ±5.66 vs. 24.7 ±5.7 kg respectively; p-value: 0.12). The mean waist circumference was significantly lower in the MHO group as compared to MUHO (102.71 ±10.3 vs. 108.5 ±14.7 cm respectively; p-value: 0.02) and significantly higher than that of the healthy non-obese group (102.71 ±10.3 vs. 87.6 ±8.8 cm respectively; p-value: <0.001). When stratifying the mean waist circumference by gender, it was lower in the MHO group when comparing to the MUHO group without statistical significance (101.7 ±11.0 vs 107.0 ±16.3 cm in females; p-value: 0.08 and 106.9 ±5.7 vs. 111.9 ±9.6 cm in males;p-value:0.15 ) but remained significantly higher in the MHO group than the healthy group in both genders (101.7 ±11.0 vs 86.6 ±8.0 cm in females; p-value: <0.001 and 106.9 ±5.7 vs. 89.4 ±10.14 cm in males; p-value:0.004).

The macronutrients intake (including total calories, calories from carbohydrates and calories from fat), stratified by gender, did not statistically differ when comparing MHO to MUHO or to healthy individuals.

Table 8 and Figures 3 and 4 present the findings for the non-traditional risk factors linked to metabolic health. MHO group had significantly higher level of CRP when compared to the healthy group (12.6 ±6.5 vs. 9.1 ±6.5 respectively; p-value: 0.02)

and significantly lower when compared to MUHO group (12.6 ±6.5 vs. 16.04 ±12.56, respectively; p-value: 0.01).

In addition, MHO group had similar microalbumin/creatinine ratio when compared to the healthy group (7 ±16 vs. 20 ±125 mg/g respectively; p-value: 0.64) and non-significantly lower ratio when compared to MUHO (7 ±16 vs. 78 ±324 mg/g respectively; p-value: 0.21). On the other hand, in regards to the insulin resistance markers, MHO group had significantly higher fasting insulin level as compared to healthy (29.73 ±9.6 vs. 22.66 ±8.9 µIU/mL respectively; p-value: 0.002) and non-significantly lower insulin level when compared to MUHO (29.73 ±9.6 vs. 33.88 ±13.3 µIU/mL respectively; p-value: 0.11) . Similarly, MHO group had significantly higher C-peptide level when compared to healthy individuals (3.41 ±1.64 vs. 2.71 ±0.96 ng/dl respectively; p-value: 0.01) and non-significantly lower levels when compared to MUHO (3.41 ±1.64 vs. 3.63 ± 1.45 ng/dl respectively; p-value: 0.41). In parallel, MHO group had significantly higher HOMA score when compared to healthy individuals (3.79 ±1.23 vs. 2.89 ±1.09 respectively; p-value: 0.001) and significantly lower score when compared to MUHO (3.79 ±1.23 vs. 4.5 ±1.72 respectively; p-value: 0.03).There was no significant difference between the three groups in the other laboratory tests such as TSH, cortisol, 25-(OH)-vitamin D and creatinine levels.

Table 9 shows the results of the associations with the traditional and other risk factors. Except for CAD which was significantly lower in the MHO as compared to MUHO (OR:0.79, 95% CI =0.74-0.85; p-value: 0.03), there was no significant difference between the two groups in any the remaining variables considered, including total cholesterol, LDL, non-HDL levels, family history of CAD and cancer. Furthermore, and except for cholesterol, which showed significantly higher levels in the

MHO as compared to healthy (192 ±42 vs. 175 ±37 mg/dl respectively; p-value: 0.03), findings did not show any significant difference between MHO and the healthy groups in any of the remaining levels.

### 3.3 Multivariate adjusted analysis

Table 10 represents the results of the multivariate regression analysis including age, gender, and crowding index in addition to the covariates that showed statistical significance in the bivariate analyses (marital status, CRP, HOMA-IR score, cholesterol levels). The Berlin questionnaire score and CAD were excluded from the multivariate analysis due to the small sample size that affected the robustness of the final model.

Other variables, while showing significant results at the bivariate level, were also excluded from the final model due to co-linearity with the definition of the dependent variables. It is to be noted that there was around 20 % missing data in the HOMA-IR score. Two models were examined, one comparing healthy to MHO subjects and the other comparing the MUHO to the MHO subjects.

As shown in Table 10, marital status associated significantly in both models, with the healthy and the MUHO subjects being significantly more likely to include single subjects compared with MHO [adjusted OR=5.30, 95% CI (1.21-23.04), p-value:0.02; and adjusted OR=3.97; 95% CI (1.21-13.05), p-value:0.02, respectively), after adjusting for age, gender, crowding index, HOMA-IR score, CRP and cholesterol level. Findings also showed that for each one unit increment in the HOMA-IR score, the odds of being healthy decreases by 61 % after adjusting for the other factors [Adjusted OR= 0.39(95% CI (0.24- 0.64); p-value <0.001]. When comparing MUHO to MHO, for

each one year increment in age the Odds of being MUHO increases by 4 % [Adjusted OR=1.04, 95% CI (1.01-1.08); p-value: 0.004] after adjusting for gender, marital status, crowding index, HOMA-IR score, CRP and cholesterol level.

# CHAPTER 4

# DISCUSSION

## 4.1 Review and discussion of findings

In the study at hand, we were able to show that the MHO phenotype, despite having normal criteria of metabolic health defined by the ATPIII criteria, still displays high levels of abdominal obesity, insulin resistance expressed by the HOMA-IR score and inflammation as measured by the surrogate marker CRP, when compared to healthy non-obese population. The degree of abdominal obesity, insulin resistance and inflammation was less than that observed in the MUHO group. Subsequently our study have put the MHO phenotype at an intermediate state of metabolic health between being healthy non-obese and unhealthy obese.

In addition, several epidemiological studies have shown that CRP is an independent predictor of CVD events [73], thus MHO subjects could not be protected from the cardiovascular morbidity and mortality despite being metabolically healthy. Subsequently it may be of great importance to measure insulin level and CRP in metabolically healthy obese subjects to further classify their cardiovascular risk.

The prevalence of obese subjects having BMI $\geq$ 30 kg/m$^2$ in our cohort was 41.5%. The prevalence of MHO was 8 %, MHO representing 19.2 % of the overall obese individuals.

Worldwide, the prevalence of MHO ranged from 6-75% of the obese population [29]. When using the same criteria to define metabolic health as our cohort, the prevalence of MHO in our study was similar to that of populations from the Far-East. In China the overall prevalence of MHO (with BMI cutoff to define obesity >25 kg/m$^2$

according to the 2000 World Health Organization Asian Pacific Guideline) was 8.2 % representing 29% of the overweight and obese [74]. In South India, MHO prevalence was 13.3 % representing 47 % of the obese [75], in Korea; it was 15.2% representing 18% of the obese subjects [76].

In contrast, MHO prevalence in Lebanon was higher than that in Europe, possibly explained by the lower incidence of obesity per se in the European countries. In Italy, in a population based survey to determine the prevalence of diabetes in Cremona, Calori et al estimated the prevalence of insulin sensitive obese (obese with BMI ≥30 kg/m$^2$ and HOMA-IR score < 2.5) to be 2.1% of the overall population (n= 43, the overall population n=2011) and 11 % of the obese population with BMI ≥30 kg/m$^2$ (n= 43, the obese population n=380) [64]. In Spain, the prevalence of MHO was estimated from a longitudinal cohort in South Spain at baseline and at 6 years of follow up. MHO was defined using the WHO criteria for metabolic health (not having known diabetes or unknown diabetes discovered during the OGTT, FPG <110 mg/dL, BMI ≥30 kg/m$^2$, Triglycerides < 150 mg/dL, HDL-C > 40 mg/dL in men and HDL-C >50 mg/dL in women, HOMA-IR < 90th percentile of the frequency distribution of baseline and 6-year follow-up studies, and Blood pressure < 140/90 mm Hg or not receiving antihypertensive treatment) [77]. The estimated prevalence of MHO was found to be 3% and to 3.7% after 6 years of follow up. In this same cohort, using less strict criteria and excluding blood pressure and HDL-C from the definition, the prevalence decreased slightly from 14.7% at baseline to 13.6% at 6 years of follow up [77].

In another study from Spain, a Mediterranean random cohort of 2270 participants, the prevalence of MHO using the same criteria as our study was estimated to be 2.2 % of the overall sample and 9.6% of the obese population [78]. Lopez-Garcia

et al estimated the prevalence of MHO from a large cross-sectional study representing the non-institutionalized Spanish population using 2 additional criteria than our study (refer to Wildman et al criteria in Table 1). The prevalence was estimated to be 6.5 % (n=754/11450) of the Spanish cohort and 28.9% of the obese (754/ 2602) [79].

In the US, the prevalence of MHO using the Wildman criteria was estimated to be 9.7 % of the NHANES 1999-2004 population and 31.7% of the obese subjects [80]. Another study by Durward et al, explored the prevalence of MHO in the NHANES III database using three different sets of criteria [81]. When using the same criteria as our study, the prevalence of MHO was 11.7 % of the overall population of 4373 adult participants, and 44.2% of the obese (n=1160 obese). However, it decreased to 5.2 % of the overall population and 19.7% of the obese when using the HOMA-IR criteria (healthy: HOMA-IR<2.5) versus 2.3 % of the overall population and 8.5 % of the obese when combining both ATP III and HOMA-IR criteria [81]. The higher prevalence of MHO as compared to our study may be related to differences in the population, the NHANES being larger and more population representative, which likely included younger adults than in our study. The other possible explanation is that obesity rates I general are higher in the US, which may affect both MHO and MUHO rates.

Additionally, the wide heterogeneity of the prevalence can be explained by the fact some studies used the insulin resistance criteria alone (HOMA score), other used the metabolic syndrome criteria and others the combined criteria of insulin resistance and metabolic factors. In addition, this prevalence varied in the same population when using different definitions of metabolic health. This heterogeneity urges the need to harmonize the definition of metabolically healthy obese worldwide to be able to determine the true prevalence.

On the other hand, the determinants of healthy obesity are not widely studied. In our cohort the adjusted analysis showed the positive predictors of MHO to be younger age, while the negative predictors were higher CRP and insulin resistance as compared to healthy non-obese. In addition, subjects with MHO were more likely to be married.

Higher age was related to less probability of MHO and higher probability of MUHO. This finding was duplicated by several studies and this can be explained by the difficulty to maintain metabolic health with age. Prospective studies such as the Pizarra study by Soriguer et al showed that MHO subject were at risk of developing diabetes at 6 and 11 years of follow up [77]. Wolffenbuttel et al observed a decrease in the prevalence of MHO with increasing age in Europe [33]. This hypothesis was also supported by the higher prevalence of metabolic syndrome components in post-menopausal woman as compared to premenopausal woman [82]. The observed findings suggest MHO to be a dynamic concept that may change with time.

MHO subjects in our study were more likely to be married as compared to MUHO or healthy. When stratifying by gender and adjusting for age, the effect of marital status only persisted for females (Table 12), where MHO women were more likely to be married than healthy or MUHO women. Of note is that the proportion of females in the cohort was higher than males (64% vs. 36% respectively). In addition, most of the women presenting to the site of the study were married (75% in the healthy group, 91% in the MHO group and 63 % in the MUHO group). These higher percentages may lead to a selection bias where more married women stay at home and are more likely to present to the study site. In addition, the observation that MHO women were more likely to be married may be explained by the hypothesis that they may eat healthier and cook at home, as compared to single women whether in the

MUHO or healthy group. This observation was not reported in previous studies and would need to be confirmed in subsequent ones. However, healthier dietary patterns did show a positive association with MHO in one study from Lebanon by Naja et al [39], which will be detailed at the end of the section.

Another significant observation in our study was the HOMA-IR score. The Odds of being MHO increase with every unit increase in the HOMA-IR score when comparing MHO to healthy, and decreases when comparing MHO to MUHO in the adjusted analysis. This observation makes MHO subjects insulin resistant despite being healthy. In the literature, a strong co-linearity exists between BMI and HOMA-IR score and Studies have shown mixed results concerning the insulin resistant status in the MHO phenotype.

Several studies have used the HOMA-IR score in the definition of MHO either alone or combined with metabolic health factors. It may be important to include HOMA-IR in the definition of MHO but the inclusion will pose several concerns. There are different methodologies to measure insulin levels (subsequently affecting HOMA-IR score) and the method needs to be standardized before using it as an essential criteria to define MHO. In addition, different cutoff values have been used to define the insulin resistance state (using the $90^{th}$ percentile, $75^{th}$ percentile or fixed numbers such as 1.95 or 2.5 (Table 2)). The aforementioned concerns render the inclusion of HOMA-IR in the definition of MHO a challenge. In summary, our observation suggests that obesity represents a state of higher insulin resistance, even among the ‘metabolically healthy’ and the quantification of the resistance is essential before labeling the obese as healthy or insulin sensitive.

In parallel to HOMA-IR score, the factors associated with obesity including waist circumference and total body fat were the lowest in the healthy group and the highest in the MUHO group, leaving MHO to be an intermediate state in the body composition and anthropometric factors between the healthy non-obese and the MUHO. Nevertheless, the excess weight of the MHO subjects, regardless of the metabolic derangements, put them at high risk of obesity associated diseases such as osteoarthritis, chronic pain, pulmonary disease, some types of cancer [11] and heart failure [83]. In our study, MHO group was found to be at a significantly higher risk of developing sleep apnea assessed by Berlin questionnaire as compared to the healthy group. This observation is mainly due to higher BMI and the effect persisted even after adjusting for the other significant findings in our study (age, marital status, HOMA-IR, CRP, data not shown).

On the other hand, our study found CRP to be a predictor of MHO. The odds of being MHO increases with CRP increase when compared to healthy non obese individuals. Although sharing similar criteria of metabolic health, MHO subjects had higher level of this inflammatory marker when compared to non-obese subjects.

Inflammation is a key mechanism in the pathophysiology of obesity. The latter is characterized by chronic inflammation, leading to a low inflammatory state with increase in serum concentrations of CRP [84], IL-6, IL-8, monocyte chemotactic protein (MCP)-1, and TNF-α; all found to be increased with elevated insulin resistance[85, 86]. In addition, the adipose tissue inflammation leads to an increase in other inflammatory mediators such as amyloid A, resistin, leptin, and adiponectin [87]. It was speculated that MHO individuals, despite being obese, have lower levels of inflammation [88], higher adipogenic capacity and adiponectin levels known to increase the metabolic

adipose tissue flexibility [49] . This mechanism leads to increased lipid storage, lower waist circumference, lower inflammatory state and less visceral abdominal tissue accumulation in MHO subjects [51]. The aforementioned pathophysiology may be behind the lower risk of the development of metabolic syndrome and cardiovascular risk in MHO population. In our study, CRP level was not included in the definition of MHO, and we showed a significant elevation of this inflammatory marker in the MHO group when compared to healthy but to a lower extent than that in the MUHO group.

More importantly, the non-traditional risk factors for the development of cardiovascular disease are more related to inflammation and insulin resistance [47]. The CRP and HOMA-IR score represent respectively their surrogate markers. Both being elevated in our cohort, may put our MHO population at higher risk of developing CVD as compared to healthy population. Subsequently it may be essential to include them in the definition of MHO along with hypertension, dyslipidemia and diabetes components.

To further investigate the possible causality behind the difference in MHO and MUHO, dietary factors represented by macronutrients intake were included in our study. We could not show any difference in the macronutrients intake between the three groups studied.

Hankinson et al examined 83 different nutrient variables in the US population and could not show any difference in intake between MHO and MUHO [37]. Naja et al examined dietary patterns in a cohort of adult Lebanese. Subjects with higher adherence to the Traditional-Lebanese pattern ( a variant of the Mediterranean diet including fruits, vegetables, olive oils, dairy products, olive oil and traditional sweets) had higher odds of being metabolically healthy overweight or obese (OR: 1.83, 95% CI: 1.09–3.91)[39].

Variations in the dietary patterns may be an essential difference between MHO and MUHO and need to be further investigated in future studies.

Another predictor of healthy obesity observed in literature is the physical fitness mainly represented by the level of physical activity. Although we did not find any difference in the level of exercise between the groups, some studies have shown that higher level of exercise is associated with MHO; Velho et al positively linked physical activity to higher MHO diagnosis [32] a finding that can be explained by physical activity positively affecting metabolic abnormalities in obese subjects despite high BMI [89, 90]. In contrary, Philips et al did not show difference in any physical activity level or engagement between healthy and unhealthy obese despite using five different sets of criterion to define metabolic health [40]. In our cohort, half of the subjects were sedentary with a low level of physical activity across all groups (ranging from 43-55%) which may have prevented us from any discrimination between the three groups should, small differences exist.

**4.2 Limitations and strengths**

The current study has several limitations. One limitation of our study is mainly due to its cross sectional nature, which limits interpretation of the results and does not allow inference about causality. Another limitation is the small sample size observed in some of the variables in the MHO group.

In addition, the overall sample had high levels of obese subjects and high level of intermediate to low socioeconomic status, which may have affected the representativeness of the sample and may have overestimated the prevalence of MHO and MUHO, despite the rigorous sampling methodology. In addition, our population

included subjects from greater Beirut area where almost 40% of the Lebanese population resides, subsequently generalizability to the whole Lebanese population maybe questionable.

One final limitation is the missing data in the insulin levels and subsequently HOMA-IR score and Berlin questionnaire score, that was dealt with as described in our methods above.

This study also has strengths: we only used one definition of metabolic health, with clearly defined covariates, study groups, and measurements, all of which would render the study findings of high quality and reliable, despite the above-mentioned limitations.

Therefore, this study fills an important knowledge gap in the prevalence and predictors of MHO in the Lebanese population. In addition our study clarified more the profile of MHO subjects being less healthy than previously thought.

### 4.3 Conclusion and recommendations

Our study placed MHO defined by ATP III definition of metabolic health in between being healthy non obese and unhealthy obese. Despite sharing same criteria of metabolic health as healthy non obese, MHO had higher levels of inflammation and insulin resistance.

Our observations suggest that a more unified and harmonized definition of MHO is needed. We propose that in addition to the traditional diabetes, hypertension and dyslipidemia factors, to add waist circumference, the insulin resistance (HOMA-IR) and inflammation (CRP) as essential components of the definition, to better assess the cardiovascular risks of MHO.

**Figure 1. Factors included in the definition of the outcome variables**

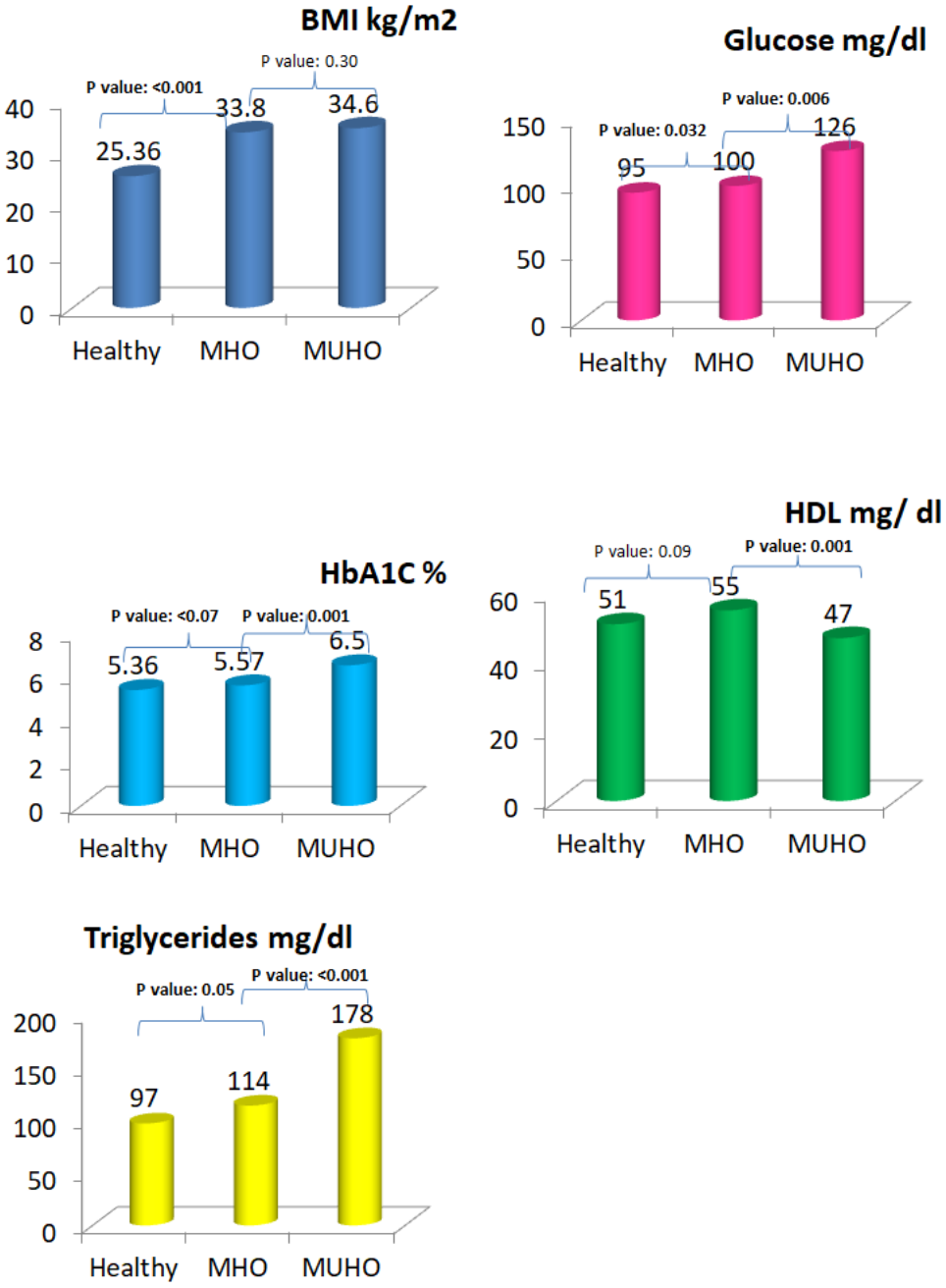
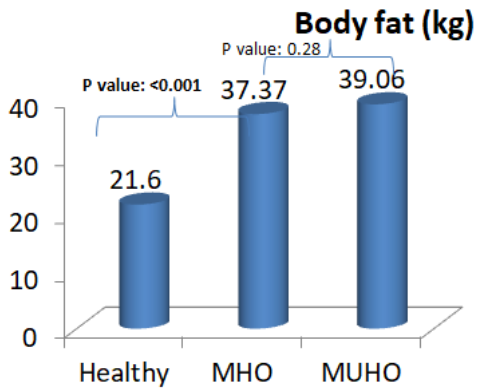
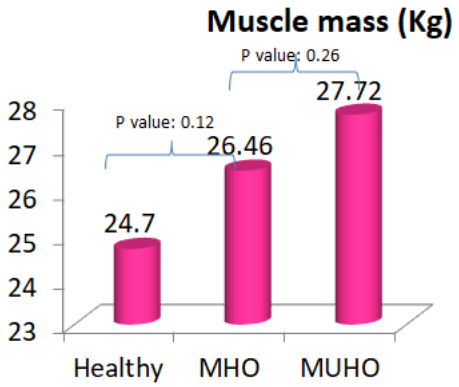


**Figure 2. Obesity related factors**



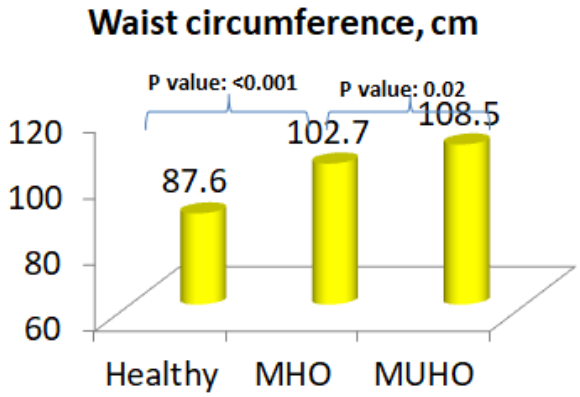



**Figure 3. Non-traditional risk factors, insulin resistance:**

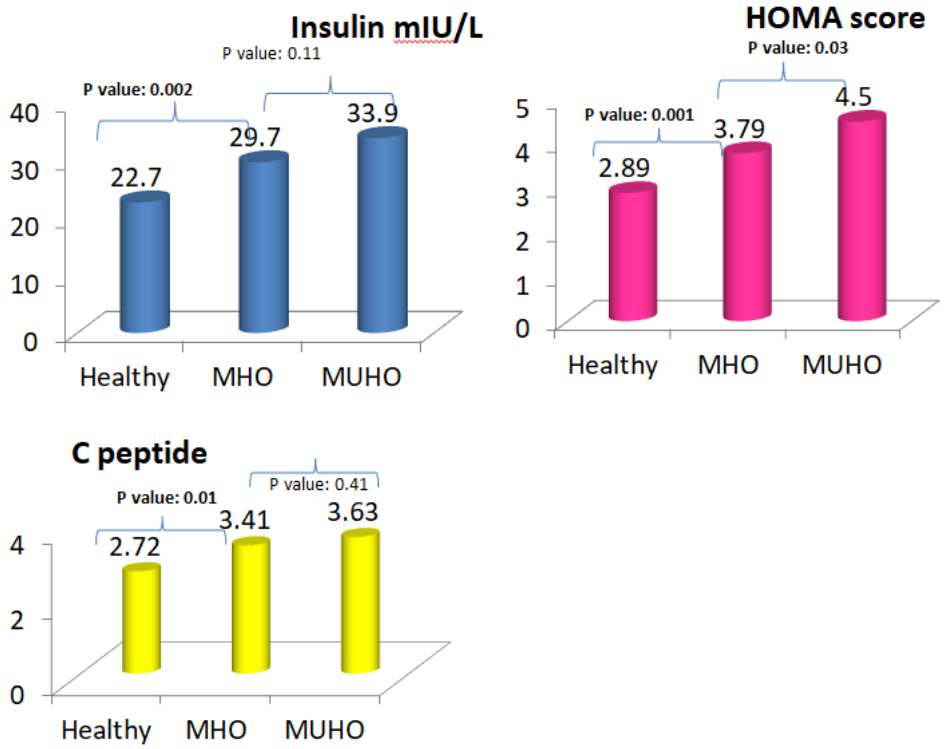



**Figure 4. Non-traditional risk factors, inflammation**

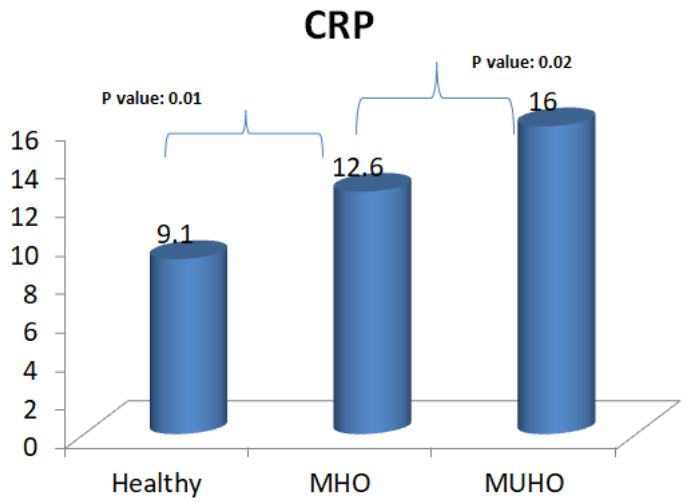


**Table 1. The different categories of BMI and metabolic health**

| | | BMI | |
|---|---|---|---|
| | | **Non-obese <30** | **Obese ≥ 30** |
| **Metabolic health** | **Healthy** | Healthy<br>Non-obese | Metabolically<br>healthy obese<br>**MHO** |
| | **Unhealthy** | Unhealthy<br>Non-obese | Metabolically<br>unhealthy obese<br>**MUHO** |

**Table 2. Different definitions of metabolic health**

| Criteria | Aguilar-Salinas 2008 [49] | Karelis 2004[35] | Meigs1 [34] | Meigs2 [34] | Wildman et al 2008 [80] | Lynch et al 2009[91] | NCEPATP III (2005 version)[27] | Vliet-Ostaptchouk et al 2014[33] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Strict criteria | Less strict criteria |
| **Blood pressure mmHG** | SBP <140 and DBP <90 or no treatment | - | SBP ≥130 or DBP ≥85 or treatment | - | SBP ≥130 or DBP ≥85 or treatment | SBP ≤130 or DBP ≤85 And no treatment | SBP >130 and/or DBP >85 | SBP ≥130 or DBP ≥85 or treatment | SBP ≥140 or DBP ≥90 or treatment |
| **TG, mg/dl** | - | ≤150 | ≥150 | - | ≥150 | - | ≥150 | | |
| **HDL-C, mg/dl** | ≥40 | ≥50 and no treatment | <40 (M) <50 (F) | - | <40 (M) <50 (F) or treatment | - | <40 (M) <50 (F) | <40 (M) <50 (F) or treatment | <40 (M) <50 (F) or treatment |
| **LDL-C, md/dl** | - | ≤100 and no treatment | | - | - | - | - | - | - |
| **Total-C, mg/dl** | | ≥201 | | - | - | - | - | - | - |
| **TG/HDL ratio** | | | | | | ≤1.65 (M) ≤1.32 (F) and no treatment | | - | - |
| **FPG mg/dl** | < 126 and no treatment | - | ≥100 or treatment | - | ≥100 or treatment | ≤100 and treatment | ≥100 or treatment | ≥110 or Non fasting ≥126 or treatment | ≥126 or Non fasting ≥140 or treatment |
| **HOMA-IR score** | - | ≤1.95 | | <75th percentile | >90$^{th}$ percentile | - | - | - | - |
| **Waist circumference** | - | - | Waist>102 cm M Waist >88 cm F | - | | - | Waist>102 cm (M) Waist >88 cm (F) | - | - |

| Criteria continued | Aguilar-Salinas 2008 [49] | Karelis 2004[35] | Meigs1 [34] | Meigs2 [34] | Wildman et al 2008 [80] | Lynch et al 2009[91] | NCEPATP III (2005 version)[27] | Vliet-Ostaptchouk et al 2014[33] | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Strict criteria | Less strict criteria |
| **Other** | - | - | | - | CRP >90th percentile | no history of cardiovascular, respiratory, or metabolic diseases | - | Diagnosis of CVD YES | Diagnosis of CVD YES |
| **MH criteria** | All of the above | ≥4 of the above | <3 of the above | All of the above | <2 of the above | All of the above | <3 of the above | None of the above | None of the above |
| **Population n %male** | Mexico, n=716 26.4% male | Canadian, obese postmenopausal women n=156 0% male | US, n=2902 45% male | US, n=2902 45% male | US, n=5440 45% male | Dublin, n=126 Obese 34.2% | - | 10 European cohorts, n=163517 NAv | 10 European cohorts, n=163517 NAv |
| **Prevalence of MHO: overall % among obese** | 23.9% 36.4% | NA 12.3% | 8.1% 37% | 11.8% 44.3% | 9.7% 31.7% | NA 20% | | 2.1% 12% | Data NAv |

F: female, M: male, MH: metabolic health, NA: not applicable, NAv: not available

**Table 3. Definitions of the outcome variables**

| | | BMI | |
|---|---|---|---|
| | | **Non-obese <30** | **Obese ≥ 30** |
| **Metabolic health** | **Healthy** | **Healthy**<br>**BMI < 30 having one or none :**<br>i. elevated triglycerides ≥ 150 mg/dl<br>ii. low HDL <40mg/dl in males and <50 mg/dl in females<br>iii. Elevated blood pressure ≥ 130 systolic or ≥ 85 diastolic<br>iv. Elevated fasting glucose ≥ 100mg/dl | **MHO:**<br>**BMI ≥ 30 having one or none :**<br>i. elevated triglycerides ≥ 150 mg/dl<br>ii. low HDL <40mg/dl in males and <50 mg/dl in females<br>iii. Elevated blood pressure ≥ 130 systolic or ≥ 85 diastolic<br>iv. Elevated fasting glucose ≥ 100mg/dl |
| | **Unhealthy** | **Unhealthy**<br>**Non-obese** | **MUHO**<br>**BMI ≥ 30 having two or more:**<br>i. elevated triglycerides ≥ 150 mg/dl<br>ii. low HDL <40mg/dl in males and <50 mg/dl in females<br>iii. Elevated blood pressure ≥ 130 systolic or ≥ 85 diastolic<br>iv. Elevated fasting glucose ≥ 100mg/dl) |

**Table 4. Prevalence of the different outcome variables**

| | | BMI | |
|---|---|---|---|
| | | **Non-obese <30** | **Obese ≥ 30** |
| **Metabolic health** | **Healthy** | **Healthy**<br>N=82<br>16.4%<br>(95% CI: 13.2-19.9%) | **MHO**<br>N= 40<br>8 %<br>(95% CI: 5.8-10.7%) |
| | **Unhealthy** | **Unhealthy**<br>**Non-obese**<br>N= 209<br>41.7 % (95% CI 37.4 %- 46.2%) | **MUHO**<br>N= 168<br>33.5% (95 % CI 29.4%-37.9%) |

**Table 5. General characteristics of the study sample**

| | | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Healthy n=82** | **MHO n=40** | **MUHO n=168** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** |
| **Demographic** | **Age (years)** | mean (±sd) | 40.8(±15.4) | 45.5(±12.9) | 51.1 (±14.0) | 0.10 | -0.02 ± 0.01 | **0.02** | 1.03 (1.00-1.06) |
| | **Gender** | Male<br>Female | 30 (36.6)<br>52 (63.4) | 8(20.0%)<br>32 (80.0%) | 53(31.5%)<br>115(68.5%) | 0.063 | REF<br>0.43 (0.18-1.06) | 0.15 | REF<br>0.54 (0.23 -1.26) |
| **Socioeconomic** | **Income per family** | < 1000$<br>≥1000 | 49(66.2%)<br>25(33.8%) | 25(71.4%)<br>10 (28.6) | 126 81.3%)<br>29 (18.7%) | 0.59 | REF<br>1.28 (0.53-3.07) | 0.19 | REF<br>0.58 (0.25-1.33) |
| | **Highest education** | Primary<br>Secondary<br>University | 26 (31.7)<br>35 (42.7)<br>21 25.6%) | 16 (40%)<br>21 (52.5%)<br>3 (7.5%) | 77 (46.1%)<br>69 (41.3%)<br>21 (12.6%) | 0.061 | REF<br>1.03 (0.45-2.34)<br>4.3(1.10-16.79) | 0.38 | REF<br>0.68 (0.33-.41)<br>1.46 (0.39-.47) |
| | **Marital Status** | Married<br>Single | 53 (64.3%)<br>29 (35.4%) | 35 (87.5%)<br>5 (12.5%) | 112(66.7%)<br>56 (33.3%) | **0.008** | REF<br>3.83 (1.35-10.84) | **0.009** | REF<br>3.5 (1.30-9.42) |
| | **Crowding index*** | mean (±sd) | 1.58 (±0.9) | 1.83 (±1.24) | 1.47 (±0.89) | 0.22 | -0.23 ± 0.18 | 0.04 | -0.34 ± 0.17 |
| **Lifestyle** | **Cigarette smoking** | No<br>Yes | 44 (53.7%)<br>38 (46.3%) | 24 (60.0%)<br>16 (40.0%) | 110(65.5%)<br>58 (34.5%) | 0.51 | REF<br>1.30 (0.60-2.79) | 0.52 | REF<br>0.79 (0.39-1.61) |
| | | | | | | | | | |

| | Table 5 continued | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Healthy n=82** | **MHO n=40** | **MUHO n=168** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** |
| | **Waterpipesmoking** | No<br>Yes | 53 (64.6%)<br>29 (35.4 %) | 26 (65.0%)<br>14 (35.0) | 131 (78.0%)<br>37 (22.0%) | 0.97 | REF<br>1.02 (0.46-2.24) | 0.09 | REF<br>0.53 (0.25-1.11) |
| | **Alcohol intake** | No<br>Yes | 61 (74.4%)<br>21 (25.6) | 34 (85.0%)<br>6 (15.0%) | 150 (89.3%)<br>18 (10.7%) | 0.19 | 1.95 (0.72-5.30) | 0.45 | REF<br>0.68 (0.25-1.84) |
| | **Coffee drinking** | No<br>Yes | 15 (18.3%)<br>67(81.7%) | 9 (22.5%)<br>31(77.5%) | 25 (14.9%)<br>143(85.1%) | 0.58 | 1.30(0.51-3.29) | 0.24 | REF<br>1.66 (0.71-3.91) |
| | **Physical activity** | No<br>Yes | 12 (14.6%)<br>70 (85.4%) | 6 (15.0%)<br>34 (85.0%) | 32 (19.0%)<br>136 81.0%) | 0.96 | 1.03 (0.36-2.98) | 0.55 | REF<br>0.75 (0.29-1.94) |
| | | Low<br>Moderate<br>High | 36(44%)<br>27(32.9%)<br>19(23.1%) | 17(42.5%)<br>16 (40.0%)<br>7 (17.5%) | 92 (54.8%)<br>50 (29.8%)<br>26 (15.4%) | 0.67 | REF<br>0.78 (0.28-2.21)<br>0.62 (0.21-1.80) | 0.35 | REF<br>0.58 (0.30-1.24)<br>0.45 (0.26-1.83) |
| **Sleep habits** | **Berlin questionnaire score** | **mean (±sd)** | 0.45 (±0.68) | 1.76 (±0.71) | 1.66 (±0.70) | **<0.001** | -2.2 ± 0.4 | 0.49 | -0.19 ± 0.27 |
| | | Low risk<br>High risk | 70 (92.1%)<br>6 (7.9%) | 13 (39,4%)<br>20 (60.6%) | 65 (46.4%)<br>75 (53.6%) | **<0.001** | 0.06 (0.20-0.17) | 0.47 | 0.75 (0.35-1.63) |

**Table 6. Factors included in the definition of the outcome variables**

| | | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Healthy n=82** | **MHO n=40** | **MUHO n=168** | **P value** | **OR (95% CI** | **P value** | **OR (95% CI)** |
| | **BMI (kg/m$^2$)** | mean (±sd) | **25.36 (±3.1)** | **33.8 (±3.48)** | **34.6 (±4.69)** | **<0.001** | - | 0.30 | - |
| | **Glucose (mg/dl)** | mean (±sd) | 95 (±7) | 100 (±12) | 126 (±53) | **0.032** | - | **0.006** | - |
| | **HbA1C (%)** | % (±sd) | 5.36 (±0.4) | 5.57 (±0.4) | 6.5 (±0.7) | **0.007** | - | **0.001** | - |
| | **Triglycerides (mg/dl)** | mean (±sd) | 97 (±47) | 114 (±41) | 178 (±139) | 0.053 | - | **<0.001** | - |
| | **HDL (mg/dl)** | mean (±sd) | 51 (± 15) | 55 (±13) | 47 (±14) | 0.092 | - | **0.001** | - |
| | **Systolic blood pressure (mm Hg)** | mean (±sd) | 113 (±14) | 116(±12) | 131 (±18) | 0.154 | - | **<0.001** | - |
| | **Diastolic blood pressure(mm Hg)** | mean (±sd) | 71 (±9) | 73 (±8) | 79 (±10) | 0.327 | - | **<0.001** | - |
| | **Hypertension** | No<br>Yes | 51 (62.2)<br>31(37.8%) | 23 (57.5)<br>17 (42.5) | 33(19.6%)<br>135(80.4%) | 0.61 | 0.82 (0.38-1.78) | **<0.001** | 5.54 (2.66-11.52) |
| | **Diabetes** | No<br>Yes | 81 (98.8%)<br>1 (1.2%) | 37(92.5%)<br>3 (7.5%) | 110(65.5%)<br>58 (34.5%) | 0.07 | 0.15 (0.02-1.51) | **0.001** | 6.5 (1.92-22) |

**Table 7. Obesity related factors**

| | | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|---|
| | | | **Healthy n=82** | **MHO n=40** | **MUHO n=168** | **P value** | **Beta coefficient ± SE** | **P value** | **Beta coefficient ± SE** |
| | **Body fat (kg)** | mean (±sd) | 21.6 (±7.3) | 37.37 (±8.21) | 39.06 (±9.05) | **<0.001** | -0.3 ± 0.07 | 0.28 | 0.023 ± 0.021 |
| | **Muscle mass (kg)** | mean (±sd) | 24.7 (±5.7) | 26.46 (±5.66) | 27.72 (±6.50) | 0.12 | -0.05 ± 0.03 | 0.26 | 0.03 ± 0.03 |
| | **Waist circumference, cm** | mean (±sd) | 87.6 (±8.8) | 102.71 (±10.3) | 108.5 (±14.7) | **<0.001** | -0.21 ± 0.04 | **0.02** | 0.04 ± 0.02 |
| | **Waist circumference, female (cm)** | mean (±sd) | 86.6 (±8.0) | 101.7 (±11.0) | 107.0 (±16.3) | **<0.001** | -0.24 ± 0.05 | 0.08 | 0.03 ± 0.02 |
| | **Waist circumference, male (cm)** | mean (±sd) | 89.4 (±10.14) | 106.9(±5.7) | 111.9 (±9.6) | **0.004** | -0.33 ± 0.11 | 0.15 | 0.08 ± 0.06 |
| Nutritional intake | **Total calories (male)** | mean (±sd) | 4019 (±1648) | 4241 (±2356) | 4774 (±2639) | 0.74 | - | 0.60 | - |
| | **Total calories (female)** | mean (±sd) | 2482(±1176) | 2706 (±1085) | 2576 (±1349) | 0.33 | - | 0.65 | - |
| | **Calories from carbohydrates (male)** | mean (±sd) | 490 (±192) | 459 (±140) | 579 (±391) | 0.66 | - | 0.40 | - |
| | **Calories from carbohydrates (female)** | mean (±sd) | 321 (±172) | 330 (±158) | 324 (±155) | 0.80 | - | 0.88 | - |
| | **Calories from fat (male)** | mean (±sd) | 166 (±81) | 144 (±78) | 194 (±96) | 0.49 | - | 0.19 | - |
| | **Calories from fat (female)** | mean (±sd) | 101 (±58) | 119 (±50) | 104 (±64) | 0.11 | - | 0.25 | - |

**Table 8. Non-Traditional risk factors**

| | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|
| | | **Healthy n= 82** | **MHO n=40** | **MUHO n=168** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** |
| **CRP (mg/dl)** | mean (±sd) | 9.1 (±6.5) | 12.6 (±6.5) | 16.0(±12.6) | **0.01** | -0.08 ± 0.03 | **0.02** | 0.04 ± 0.02 |
| **Microalbumin/creatinine ratio** | mean (±sd) | 20 (±125) | 7 (±16) | 78 (±324) | 0.64 | 0.003 ± 0.007 | 0.21 | 0.01±0.01 |
| **Insulin (mIU/mL)** | mean (±sd) | 22.7 (±8.9) | 29.7 (±9.6) | 33.9 (± 13.3) | **0.002** | -0.08 ± 0.03 | 0.11 | 0.03 ± 0.02 |
| **HOMA-IR score** | mean (±sd) | 2.89 (±1.09) | 3.79 (±1.23) | 4.5 (±1.72) | **0.001** | -0.69 ± 0.22 | **0.03** | 0.30 ± 0.14 |
| **C peptide (g/dl)** | mean (±sd) | 2.72 (±0.96) | 3.41 (±1.64) | 3.63 (± 1.45) | **0.01** | -0.46 ± 0.18 | 0.41 | 0.11 ± 0.13 |
| **Creatinine (mg/dl)** | mean (±sd) | 0.73 (±0.20) | 0.72 (±0.20) | 0.76 (±0.23) | 0.80 | 0.26 ± 0.99 | 0.35 | 0.84 ± 0.90 |
| **TSH (µIU/mL)** | mean (±sd) | 1.9 (± 1.8) | 2.2 (±2.4) | 2.4 (±4.4) | 0.51 | -0.06 ± 0.09 | 0.77 | 0.02± 0.06 |
| **Cortisol (µg/dL)** | mean (±sd) | 18.4 (±10.5) | 15.9 (±8.1) | 18.0 (±14.0) | 0.19 | 0.03 ± 0.02 | 0.39 | 0.02±0.02 |
| **25 (OH) vitamin D (ng/dL)** | mean (±sd) | 15.9 (±9.7) | 16.6 (±13) | 15.9 (±9.7) | 0.77 | -0.01 ± 0.02 | 0.71 | -0.01±0.02 |

**Table 9. Traditional and other risk factors**

| | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|
| | | **Healthy n= 82** | **MHO n=40** | **MUHO n=168** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** | **P value** | **OR (95% CI) Or Beta coefficient ± SE** |
| **Cholesterol (mg/dl)** | mean (±sd) | 175 (±37) | 192 (±42) | 195 (±48) | **0.03** | -0.01 ± 0.00 | 0.69 | 0.002 ± 0.004 |
| **LDL (md/dl)** | mean (±sd) | 103 (±31) | 113 (±39) | 115 (±42) | 0.14 | -0.01 ± 0.01 | 0.81 | 0.001 ± 0.004 |
| **Non HDL (mg/dl)** | mean (±sd) | 124 (±34) | 136 (±41) | 148 (±49) | 0.10 | -0.01 ± 0.00 | 0.16 | 0.006 ± 0.004 |
| **Coronary Artery disease (CAD)** | **No**<br>**Yes** | 79 (96.3%)<br>3 (3.7%) | 40 (100%)<br>0 (0%) | 150 (89.9%)<br>18 (10.1%) | 0.22 | 0.66(0.58-0.75) | **0.03** | 0.79 (0.73-0.85) |
| **Family history of CAD** | **No**<br>**Yes** | 57(69.5%)<br>25(30.5%) | 21(52.5%)<br>19(47.5%) | 98 (58.3%)<br>70 (41.7%) | 0.07 | 0.49 (0.22-1.06) | 0.50 | 0.79 (0.40-1.58) |
| **Cancer** | **No**<br>**Yes** | 81 (98.8%)<br>1 (1.2%) | 39 (97.5%)<br>1 (2.5%) | 163 (97%)<br>5 (3%) | 0.6 | 0.48 (0.03-7.9) | 0.87 | 1.20 (0.14-10.53) |

**Table 10. Multivariate regression analysis**

| | **MHO v/s Healthy** | | **MHO v/s MUHO** | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR (95% CI)** | **P value** | **Adjusted OR (95% CI)** | **P value** |
| Age years | 1.01 (0.97-1.05) | 0.73 | **1.04 (1.01-1.08)** | **0.02** |
| Gender | 0.60 (0.16 -2.20) | 0.44 | 0.42 (0.14-1.25) | 0.12 |
| Marital status | 5.30 (1.21-23.04) | **0.02** | **3.97 (1.21-13.05)** | **0.02** |
| Crowding index | 0.71 (0.44-1.13) | 0.15 | 0.72 (0.46-1.13) | 0.15 |
| HOMA-IR score | 0.39 (0.24-0.64) | **<0.001** | 1.22 (0.89- 1.67) | 0.22 |
| CRP | 0.94 (0.88-1.02) | 0.13 | 1.06 (0.99-1.13) | 0.08 |
| Total Cholesterol (by 10 units) | 0.99 (0.98- 1.01) | 0.38 | 1.03 (0.94-1.14) | 0.52 |

**Table 11. Multivariate analysis with missing data managed***

| | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|
| **Factors** | **Adjusted OR (95% CI)** | **P value** | **Adjusted OR (95% CI)** | **P value** |
| Age | 1.00 (0.97- 1.04) | 0.81 | **1.04 (1.01-1.07)** | **0.03** |
| Gender | 0.67 (0.22-1.98) | 0.47 | 0.50 (0.20-1.19) | 0.11 |
| Marital status | **4.95 (1.27- 19.29)** | **0.02** | **4.13 (1.44-11.85)** | **0.008** |
| Crowding index | 0.73 (0.46 - 1.15) | 0.17 | 0.81 (0.53-1.18) | 0.29 |
| HOMA-IR score corrected | **0.33 (0.20 -0.55)** | **<0.001** | **1.35 (1.00 - 1.82)** | **0.048** |
| CRP | **0.93(0.86-0.99)** | **0.03** | 1.04 (0.99-1.10) | 0.11 |
| Total Cholesterol (by 10 units) | 0.88 (0.0.77 -1.01) | 0.07 | 1.01 (0.93-1.09) | 0.90 |

*After imputing the mean for HOM-IR score

**Table 12. Sensitivity analysis, marital status stratified by gender***

| | | | | | MHO v/s Healthy | | MHO v/s MUHO | |
|---|---|---|---|---|---|---|---|---|
| | | **Healthy n= 82** | **MHO n= 40** | **MUHO n= 168** | **Adjusted OR (95% CI)** | **P-value** | **Adjusted OR (95% CI)** | **P-value** |
| **Marital Status** | Married n (%)<br>Single n (%) | 53 (64.3%)<br>29 (34.5%) | 35 (87.5%)<br>5 (12.5%) | 112(66.7%)<br>56 (33.3%) | **3.36 (1.11- 10.16)** | **0.03** | **4.05 (1.44- 11.36)** | **0.008** |
| **Marital status Male** | Married n (%)<br>Single n (%) | 14 (46.7%)<br>16 (53.3 %) | 6(75%)<br>2 (25%) | 40 (75.5%)<br>13 (24.5%) | 3.37 (0.22- 52.9) | 0.39 | 1.10 (0.16- 7.56) | 0.92 |
| **Marital status female** | Married n (%)<br>Single n (%) | 39(75%)<br>13 (25%) | 29 (90.6%)<br>3 (9.4 %) | 72 (62.6%)<br>43 (37.4%) | 3.08 (0.80- 11.9) | 0.1 | **5.72 (1.58- 20.7)** | **0.08** |

*above analysis is adjusted for age

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