Metabolically Healthy Versus Unhealthy Obese Phenotypes and Risk of Hypertension Incidence; A Case–Cohort Analysis

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Abstract

Background

Although obesity contributes in increasing the risk of hypertension, it is not known the effect of obesity based on metabolic status on the incidence of hypertension. This study was aimed to determine association between obesity phenotypes including metabolically unhealthy obesity (MUO) and metabolically healthy obesity (MHO) and risk of hypertension incidence.

Methods

We conducted a case-cohort study on 6,747 adults 35–65 aged from Ravansar non-communicable diseases (RaNCD) study. Obesity was defined body mass index > 30 kg/m$^2$ and metabolically unhealthy was considered at least two metabolic disorders based on the International Diabetes Federation criteria. Obesity phenotypes were categorized four groups including MUO, MHO, metabolically unhealthy non obesity (MUNO), and metabolically healthy non obesity (MHNO). Cox proportional hazards regression models were applied to analyze associations with hypertension incidence.

Results

The incidence of hypertension was one case per 1000 person-months (393/391162). The MHO (HR: 1.37; 95% CI: 1.03–1.86) and MUO phenotype (HR: 2.44; 95% CI: 1.81–3.29) was linearly associated with higher hypertension risk compared to MHNO. In addition, MUNO phenotype was significantly associated with risk of hypertension incidence (HR: 1.65; 95% CI: 1.29–2.14).

Conclusions

Both metabolically healthy and unhealthy obesity was elevated risk of hypertension incidence, however, this increase in metabolically unhealthy phenotypes was higher.

Background

Hypertension is one of the strongest modifiable risk factors for cardiovascular disease (CVDs) which its prevalence is increasing especially in low- and middle-income countries [1, 2]. In addition to CVDs, hypertension is involved in the pathogenesis of stroke, cerebral hemorrhage, subarachnoid hemorrhage, renal failure, and macrovascular disease [3, 4]. Reports indicate that a quarter of men and a fifth of women have hypertension, and hypertension is responsible for approximately 45% of deaths from the CVDs [5, 6]. Results of data from World Health Organization and United Nations Development Program for 182 countries showed that the prevalence of hypertension was 13–41% [5].

Many factors contribute to hypertension, including sedentary lifestyle, kidney disease, diabetes, obesity, high salt intake and processed foods [7, 8]. Among these factors, obesity is contributed in the development of CVDs, type 2 diabetes, cancer, inflammatory diseases, and hypertension [9–11]. Evidence suggests that obesity, with its pro-inflammatory effects and oxidative stress, causes insulin resistance, dyslipidemia, and other metabolic disorders in which is considered metabolically unhealthy obesity (MUO) [12, 13]. Nevertheless, some people with obesity have metabolically healthy status, in which are described metabolically healthy obesity (MHO) phenotype [12]. Additionally metabolically unhealthy non obesity (MUNO) phenotypes are at risk of type 2 diabetes, CVDs, fatty liver, and mortality [13, 14].
Reports indicate that obesity is associated with a risk of developing hypertension. Since a study has not yet examined the types of obesity phenotypes based on the metabolic status of individuals, the present study was conducted with the aim of metabolically healthy versus unhealthy obese phenotypes and risk of hypertension incidence in the Ravansar non-communicable diseases (RaNCD) cohort study.

Methods

Study design and setting

We conducted a case-cohort study nested in the RaNCD cohort. The RaNCD study which is a first cohort study on Kurdish population, on aged 35–65 years living in Ravansar city, Kermanshah province, Western-Iran which started in October 2014. The RaNCD cohort study is a component of the PERSIAN (Prospective Epidemiological Research Studies in Iran) mega cohort study that was approved by the Ethics Committees in the Ministry of Health and Medical Education, the Digestive Diseases Research Institute, Tehran University of Medical Sciences, Iran. The details of this study were described in previous studies [15, 16]. In this study, all recruitment phase participants included, which was surveyed from October 2014 to January 2017 and followed until January 2021 (n = 4764 men and 5258 women). The RaNCD cohort study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (No: KUMS.REC.1394.318).

Participants

Among the RaNCD participants, 3300 of them were not included in the study for the following reasons: 1) participants with CVDs (n = 1709), type 2 diabetes (n = 870), hypertension (n = 1579), cancer (n = 83), and thyroid diseases (n = 763); 2) pregnant women (n = 138); 3) energy intake less than 800 Kcal/day or more than 4200 Kcal/day (n = 737). After excluding participants with missing data, overall, 6747 participants were included into this study.

Measurements

This current study was obtained demographic data including age, sex, smoking status, and physical activity, as well as, medical history, medication, anthropometric indices, blood pressure, and biochemical analysis.

Anthropometry

All participants’ height were measured by the automatic stadiometer BSM 370 (Biospace Co., Seoul, Korea) with a precision of 0.1 cm in standing position without shoes. InBody 770 device (Inbody Co, Seoul, Korea) was applied to measure the weight and body fat mass (BFM) of participants with the least clothing and without shoes. To determine obesity, body mass index (BMI) was calculated by dividing weight in kilogram to square height in meter$^2$, after that BMI more than 30 kg/m$^2$ as obesity. Waist circumference (WC) was measured using non-stretched and flexible tape in standing position at the level of the iliac crest.

Blood pressure

In RaNCD cohort study, conventional sphygmanomanometry and auscultation of the Korotkoff sounds was used to measure systolic and diastolic blood pressure (SBP and DBP) in sitting position after at least 4–5 minutes of rest. The blood pressure measuring was conducted two times with 10 minutes interval and the mean of them was calculated and reported as the final blood pressure [15].

Biochemical analysis

25 cc blood samples were collected from all RaNCD participants. The serum and whole blood samples were subdivided and were stored at -80°C the RaNCD cohort laboratory until analysis. Serum fasting blood sugar (FBS) was measured by
glucose oxidase method. Total cholesterol (TC), high-density lipoproteins (HDL), triglyceride (TG) and low-density lipoproteins (LDL) concentration were measured by enzymatic kits (Pars Azmun, Iran) [15].

**Obesity phenotypes**

We defined MUO presence of BMI > 30 kg/m\(^2\) and at least two metabolic disorder according to the International Diabetes Federation (IDF) statement [17] as follow: HDL < 40 mg/dl in men and < 50 mg/dl in women; increased TG > 150 mg/dl; SBP > 130 mmHg or DBP > 80 mmHg or antihypertensive medication; and FBS > 100 mg/dl or medication for diabetes. Also, MHO was defined BMI > 30 kg/m\(^2\) and having at most one metabolic disorder mentioned in the previous sentences, as well as, MUNO phenotype was considered presence of BMI < 30 kg/m\(^2\) and at least two metabolic disorder. In addition, MHNO participants were related to healthy participants without obesity and metabolic disorder.

**Outcome measurement hypertension incidence**

The hypertension was defined by codes I10 of the International classification of diseases Tenth Edition (ICD-10), which included SBP/DBP ≥ 140/90 mmHg and/or using anti-hypertensive medications in the time interval between baseline (first phase of Ravansar cohort which has been conducted from 2014) and hypertension diagnosis (from 2015 to 2021), which the overall duration of the follow-up was 391162 person-months.

**Statistical analysis**

Statistical analysis was performed using Stata, version 14 (Stata Corp, College Station, TX). Mean ± standard deviation (SD) and frequency percent was used to report baseline characteristics of studied participants. To compare results of baseline characteristics among different obesity phenotypes, one-way analysis of variance (ANOVA) was used for continuous variables, and a Chi-square test was used for categorical variables.

Incidence rate (IR) calculated based on 1000 person/months Cox proportional hazards regression model were used to calculate hazard ratios (HRs) stratified by obesity phenotypes, with hypertension as the event and the time interval between baseline (first phase of RaNCD cohort) and hypertension diagnosis as the time covariate. The models of adjusted for confounding variables including age, sex, physical activity, smoking and energy intake, and reported as HR with 95% confidence interval (CI).

**Results**

A total of 6,747 participants were analyzed in this study as sub-cohort and 393 incidence cases were also in the sub-cohort. The incidence rate of hypertension was one cases per 1000 person-months (393/391162, male: 150/188718, female: 243/202443) during a mean follow-up of 57.74 months (Minimum: 0.27, Maximum: 73.30). In addition, the new case of hypertension was significantly higher in female than male (6.84% vs. 4.63%, P < 0.001). (Table 1)
| Variables       | Total (n = 6747) | MHNO (n = 3965) | MHO (n = 1036) | MUNO (n = 1204) | MUO (n = 542) |
|-----------------|------------------|-----------------|---------------|-----------------|---------------|
| Age (year)      | 45.77 ± 7.76*    | 45.67 ± 7.97    | 44.99 ± 7.04  | 46.76 ± 7.88    | 45.86 ± 7.02  | < 0.001       |
| Weight (kg)     | 71.87 ± 13.42    | 66.49 ± 11.02   | 84.54 ± 10.83 | 71.76 ± 10.11   | 87.12 ± 12.25 | < 0.001       |
| WC (cm)         | 96.26 ± 10.36    | 92.03 ± 8.64    | 106.89 ± 8.23 | 95.94 ± 7.01    | 107.54 ± 8.81 | < 0.001       |
| BMI (kg/m²)     | 27.01 ± 4.67     | 24.73 ± 3.34    | 33.11 ± 2.93  | 26.45 ± 2.45    | 33.33 ± 3.28  | < 0.001       |
| BFM (kg)        | 24.27 ± 9.41     | 19.76 ± 6.61    | 36.38 ± 6.78  | 22.41 ± 5.25    | 36.24 ± 7.61  | < 0.001       |
| SBP (mmHg)      | 103.55 ± 12.42   | 101.62 ± 11.83  | 104.10 ± 11.31| 107.16 ± 13.07  | 108.59 ± 13.83| < 0.001       |
| DBP (mmHg)      | 67.44 ± 7.82     | 66.37 ± 7.36    | 67.76 ± 7.51  | 69.44 ± 8.28    | 70.18 ± 8.95  | < 0.001       |
| FBS (mg/dl)     | 89.92 ± 9.49     | 87.91 ± 8.03    | 88.96 ± 8.08  | 94.36 ± 11.29   | 96.58 ± 11.04 | < 0.001       |
| TC (mg/dl)      | 184.01 ± 36.79   | 180.03 ± 37.31  | 186.74 ± 33.72| 190.40 ± 36.80  | 193.68 ± 34.36| < 0.001       |
| TG (mg/dl)      | 130.01 ± 73.75   | 101.75 ± 46.35  | 114.06 ± 47.34| 205.82 ± 87.54  | 198.37 ± 83.06| < 0.001       |
| HDL (mg/dl)     | 46.83 ± 11.41    | 49.67 ± 11.21   | 49.82 ± 10.55 | 38.04 ± 7.45    | 39.85 ± 8.31  | < 0.001       |
| LDL (mg/dl)     | 101.26 ± 24.90   | 98.66 ± 25.16   | 102.64 ± 22.76| 105.89 ± 25.49  | 107.33 ± 22.79| < 0.001       |
| PA (MET hour/ day) | 41.08 ± 8.15   | 41.90 ± 8.78    | 39.71 ± 6.19  | 40.37 ± 7.78    | 39.32 ± 6.55  | < 0.001       |
| Current smoking (%) | 11.9          | 20.7          | 9.4          | 23.1          | 14.1         | < 0.001       |
| Hypertension incidence | 5.79     | 4.4          | 6.2          | 7.7          | 10.9        | < 0.001       |

*Mean ± SD

**P-values were obtained one-way ANOVA and Chi square.

MHNO: metabolically healthy non-obese; MHO: metabolically healthy obese; MUNO: metabolically unhealthy non-obese; MUO: metabolically unhealthy obese; WC: waist circumference; BMI: body mass index; BFM: body fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; PA: physical activity.

The prevalence of MHO, MUNO, and MUO were 15.3, 17.4, and 8.03%, respectively. The mean of physical activity in MHNO was significantly higher than other three obesity phenotypes (MHO, MUNO, and MUO) in both men and women. Table 2 are presented baseline characteristics of studied participants based on the different types of obesity phenotypes.
The risk increased in MHO phenotype compared to MHNO (HR: 1.41; 95% CI: 1.05–1.88) in model I, which remained significant after adjustment for age, sex, physical activity and smoking (HR: 1.37; 95% CI: 1.03–1.86). The risk increased

### Table 2
Baseline characteristics of studied participants based on the different types of obesity phenotypes

| Variables    | Men (n = 3217) | Women (n = 3530) |
|--------------|----------------|------------------|
|              | MHNO (n = 2094) | MHO (n = 246) | MUNO (n = 692) | MUO (n = 185) | P** | MHO (n = 1871) | MUNO (n = 512) | MUO (n = 357) | P** |
|---------------|----------------|----------------|----------------|---------------|-----|----------------|----------------|---------------|-----|
| Age (year)    | 45.95 ± 7.88*  | 45.13 ± 7.09   | 45.96 ± 7.40   | 44.98 ± 7.01  | 0.174 | 45.35 ± 8.06   | 44.94 ± 7.03   | 47.84 ± 8.37   | 46.31 ± 6.99 | <   |
| Weight (kg)   | 71.01 ± 10.74  | 94.50 ± 9.53   | 76.69 ± 8.93   | 95.74 ± 10.33 | <   | 61.44 ± 8.94   | 81.44 ± 9.22   | 65.11 ± 7.47   | 82.65 ± 10.70 | <   |
| WC (cm)       | 92.49 ± 8.30   | 107.53 ± 7.70  | 96.14 ± 6.87   | 106.97 ± 7.71 | <   | 91.51 ± 8.97   | 106.68 ± 8.39  | 95.66 ± 7.20   | 107.83 ± 9.32 | <   |
| BMI (kg/m²)   | 24.36 ± 3.40   | 32.42 ± 2.30   | 26.26 ± 2.52   | 32.37 ± 2.29  | <   | 25.15 ± 3.22   | 33.32 ± 3.07   | 26.70 ± 2.34   | 33.82 ± 3.60  | <   |
| BFM (kg)      | 17.74 ± 6.24   | 33.77 ± 6.69   | 20.91 ± 5.01   | 33.54 ± 7.17  | <   | 22.31 ± 6.18   | 37.32 ± 4.77   | 24.71 ± 7.41   | 37.90 ± 7.41  | <   |
| SBP (mmHg)    | 103.59 ± 11.53 | 108.20 ± 11.10 | 107.77 ± 12.22 | 110.03 ± 12.87 | <   | 99.41 ± 11.77 | 102.83 ± 11.08 | 106.33 ± 14.11 | 107.84 ± 14.26 | <   |
| DBP (mmHg)    | 67.31 ± 7.50   | 70.30 ± 7.65   | 69.98 ± 8.00   | 71.25 ± 8.77  | <   | 65.32 ± 7.05   | 66.97 ± 7.29   | 68.72 ± 8.60   | 69.62 ± 9.00  | <   |
| FBS (mg/dl)   | 88.32 ± 8.14   | 89.74 ± 8.57   | 93.71 ± 10.90  | 95.53 ± 9.94  | <   | 87.45 ± 7.88   | 88.72 ± 7.91   | 95.25 ± 11.74  | 97.12 ± 11.55 | <   |
| TC (mg/dl)    | 178.53 ± 36.02 | 187.56 ± 35.36 | 185.02 ± 33.58 | 188.54 ± 30.04 | <   | 181.72 ± 38.64 | 186.49 ± 33.22 | 197.68 ± 39.64 | 196.34 ± 36.15 | <   |
| TG (mg/dl)    | 108.41 ± 51.12 | 134.62 ± 67.99 | 216.65 ± 89.80 | 220.14 ± 86.05 | <   | 94.28 ± 39.00 | 107.65 ± 36.49 | 191.19 ± 82.24 | 187.09 ± 79.27 | <   |
| HDL (mg/dl)   | 46.37 ± 9.98   | 44.71 ± 8.98   | 35.24 ± 5.92   | 35.29 ± 5.74  | <   | 53.39 ± 11.35 | 51.41 ± 10.50 | 41.82 ± 7.64   | 42.22 ± 8.46  | <   |
| LDL (mg/dl)   | 99.23 ± 24.50  | 106.41 ± 23.50 | 103.03 ± 22.89 | 105.91 ± 20.73 | <   | 98.03 ± 25.87 | 101.46 ± 22.42 | 109.77 ± 28.19 | 108.08 ± 23.78 | <   |
| PA (MET hour/day) | 43.70 ± 10.87 | 41.59 ± 9.87 | 41.31 ± 9.59 | 40.09 ± 9.78 | <   | 39.89 ± 4.84 | 39.12 ± 4.30 | 39.10 ± 3.92 | 38.93 ± 3.91 | <   |
| Current smoking (%) | 35.9 | 30.7 | 34.8 | 35.3 | 0.462 | 3.7 | 2.8 | 7.1 | 3.1 | 0.001 |
| Hypertension incidence | 4 | 6.5 | 5.1 | 8.1 | 0.029 | 4.9 | 6.1 | 11.3 | 12.3 | < 0.001 |

*Mean ± SD

**P-values were obtained one-way ANOVA and Chi square.

MHNO: metabolically healthy non-obese; MHO: metabolically healthy obese; MUNO: metabolically unhealthy non-obese; MUO: metabolically unhealthy obese; WC: waist circumference; BMI: body mass index; BFM: body fat mass; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TC: total cholesterol; TG: triglyceride; HDL: high density lipoprotein; LDL: low density lipoprotein; PA: physical activity.
in MUO phenotype compared to MHNO (HR: 2.44; 95% CI: 1.81–3.29) after adjust sex and age, which remained significant after adjustment for age, sex, physical activity and smoking (HR: 2.40; 95% CI: 1.77, 3.26). (Table 3)

Table 3
Hazard ratio of incident hypertension according to obesity phenotypes

| Obesity phenotypes | N     | % (N) of cases | Hazard ratio (95% CI) |
|-------------------|-------|----------------|----------------------|
|                   |       |                | Model I              | Model II            | Model III             |
| MHNO              | 3965  | 4.4 (175)      | Ref.                 | Ref.                | Ref.                  |
| MHO               | 1036  | 6.2 (64)       | 1.41 (1.05, 1.88)    | 1.37 (1.02, 1.83)   | 1.37 (1.03,1.86)      |
| MUNO              | 1204  | 7.7 (93)       | 1.68 (1.31, 2.16)    | 1.64 (1.27, 2.11)   | 1.65 (1.29, 2.14)     |
| MUO               | 542   | 10.9 (59)      | 2.44 (1.81, 3.29)    | 2.36 (1.75, 3.20)   | 2.40 (1.77, 3.26)     |

**Model 1**: Adjusted for age and sex; **Model 2**: Adjusted for age, sex and physical activity; **Model 3**: Adjusted for age, sex, physical activity and smoking

MHNO, metabolically healthy non-obese; MHO, metabolically healthy obese; MUNO, metabolically unhealthy non-obese; MUO, metabolically unhealthy obese

In addition, risk of hypertension significantly increased in MUNO phenotype compared to MHNO in all adjusted models (HR: 1.65; 95% CI: 1.29–2.14). The cumulative hazard curves show the incidence of hypertension has increased by approximately 7% in MUO phenotype over 70 months; and this increase was more than other phenotypes in over time (Fig. 1).

**Discussion**

Our results shows both phenotypes obesity MHO and MUO increase to develop risk of the hypertension compared to MHNO phenotype. Furthermore, MUNO phenotype was associated with higher risk of hypertension incidence compared to MHNO phenotype. Overall, the MUO phenotype increased risk of hypertension incidence more than other phenotypes in the follow-up study time. The obesity epidemic is growing and increases the risk of chronic non-communicable diseases leading to increased health system costs [18]. Epidemiological studies highlight the persistent link between obesity and hypertension, and the presence of obesity increases the risk of developing hypertension [8, 19]. Since there are different phenotypes of obesity based on the metabolic status, to best our knowledge, we examined the association between obesity phenotypes and risk of hypertension incidence.

The results of Whitehall II cohort study by Hinnouho et al. [20] on 5269 participants indicated that both obesity phenotypes, MHO and MUO lead to increased risk of mortality after seventeen years following. Another prospective study by Fingeret et al. [21] after 10.9 years follow up was not seen any difference between MHO and MUO in hypertension incidence (odds ratio (OR): 1.3, CI 95%: 0.8–2.09). Yuan et al. [22] showed that MHO had no association with arterial stiffness developing (OR: 0.99; CI 95%: 0.61–1.6), while MUO and MUNO phenotypes lead to significantly progressed arterial stiffness (OR: 4.56; CI 95%: 2.60–8) and (OR: 5.05; CI 95%: 3.12–8.19), respectively.

In current study we observed that MUO and MUNO increase the risk of hypertension incidence more than MHO. Also, BFM and WC of the participants were higher in all three groups than MHNO phenotype. Obesity, especially the high excess visceral fat distribution is increased inflammatory cytokines and endothelial disorders in which stimulate several mechanisms contribute to hypertension [18, 23]. High excess adipose tissue increases the production of pro-inflammatory factors such as leptin, tumor necrosis factor-α, interleukin-6, and resistin in which develops various metabolic diseases [24]. High calorie intake and increase in adipocytes stimulate α and β adrenergic receptors, thereby
increasing the activity of the sympathetic nervous system [25]. Obesity activates the renin-angiotensin nervous system and the sympathetic nervous system, which leads to increased sodium reabsorption and arterial blood pressure [26, 27]. On the other hand, increasing adipose tissue leads to decreased adiponectin production and increased insulin resistance [28, 29]. Therefore, chronic hyperinsulinemia in obese people causes vascular vasoconstrictor and also increases urinary sodium reabsorption and is involved in the pathogenesis of hypertension [30]. Also, increased circulating leptin levels in response to increased adipose tissue lead to impaired nitric oxide synthesis and ultimately vascular endothelial dysfunction [18]. Therefore, obesity increases the production of adipose tissue, causing the production of pro-inflammatory cytokines, which play an important role in the pathogenesis of hypertension by disrupting the metabolic status.

**Strength And Limits**

The present prospective study follows for the first time the Kurdish population and examines the types of obesity based on metabolic status and risk of hypertension incidence. In this study, we also applied appropriate exclusion criteria, such as people who did not have normal calorie intake. However, this study had its limitations. First, the follow-up period seems to have been short. Second, the hypertension incidence was small for the study groups, and we could not assess the relationship between hypertension incidence and obesity phenotypes based on the sex, although it was adjusted for sex.

**Conclusion**

In conclusion, present study stated that both of MHO and MUO phenotypes lead to rise hypertension incidence compared to MHNO phenotype, as well as, MUNO phenotype can increase hypertension incidence. However, MUO and MUNO phenotypes increase the risk of hypertension incidence more than MHO compared to MHNO phenotype. For protecting from hypertension maintaining normal weight and controlling central obesity as well as visceral fat is highly recommended.

**Declarations**

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**Compliance with ethical standards**

**Ethics approval and consent to participate:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethics Committee of Kermanshah University of Medical Sciences (ethics approval number: KUMS.REC.1394.318).

**Informed consent:** Written informed consent was obtained from each studied subject after explaining the purpose of the study. The right of subjects to withdraw from the study at any time and subject’s information is reserved and will not be
published.

Consent for publication: Not applicable

Availability of data and materials: Data will be available upon request from the corresponding author.

Competing interests: All authors have no conflict of interest.

Authors' contributions: F, Njafi, B, Hamzeh, S, Moradi and Y, Pasdar equally contributed to the conception and design of the research; F, Njafi, B, Hamzeh, E, Shakiba and Y, Pasdar contributed to data collection; S, Moradi, Y, Pasdar and M, Darbandi contributed to the acquisition and analysis of the data; S, Moradi, Y, Pasdar and M, Darbandi contributed to the interpretation of the data; and S, Moradi, Y, Pasdar and M, Darbandi contributed to draft the manuscript. All authors are in agreement with the manuscript and declare that the content has not been published elsewhere.

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**Figures**
Figure 1

Cumulative hazard curves for the incidence of hypertension in over time according to obesity phenotypes