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# Abdominal obesity phenotypes and risk of cardiovascular disease in a decade of follow-up: The Tehran Lipid and Glucose Study

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ABSTRACT

**Objective**: Obesity is a heterogeneous condition and risk of related health outcomes in different obesity phenotypes is a controversial subject. In this study, we aimed to evaluate the risk of cardiovascular disease (CVD) in different abdominal obesity phenotypes during a decade-long follow-up. **Methods**: In this large population-based cohort, 7122 participants (42.7% men), aged ≥30 years, from the Tehran Lipid and Glucose Study (TLGS) were enrolled. Abdominal obesity was defined using national waist circumference cut-off points of ≥89 cm for men and ≥91 cm for women. Metabolic health was defined as ≤1 components of metabolic syndrome (excluding waist circumference), using the Joint Interim Statement (JIS) definition. **Results**: At baseline, 3745 individuals (52.7%) were abdominal obese and 23.5% ($n = 881$) of these were categorized as "metabolically healthy abdominal obese" (MHAO). A total of 638 CVD events occurred during a median follow-up of 10 years (1999–2011). "Metabolically healthy non-abdominal obese" was considered as the reference group. After adjustment for various variables, MHAO individuals were at increased risk for CVD events compared with the reference group (HR: 1.64, CI: 1.09–2.47). Both the metabolically unhealthy phenotypes (with and without abdominal obesity) were also at increased risk. We also observed the same pattern using insulin resistance data for categorizing abdominal obesity phenotypes. **Conclusion**: Abdominal obesity and presence of metabolic derangements are both important risk factors for future CVD. MHAO may not be a benign condition regarding future CVD events, which highlights the importance of prevention and treatment of abdominal obesity, even in the absence of metabolic derangements.



## 1. Introduction

Along with the epidemic of obesity and abdominal obesity, concomitant metabolic derangements pose obese individuals at greater risk for future morbidity and mortality [1,2]. A combination of obesity and metabolic components leads to evolvement of different obesity phenotypes that may have different risks for future health outcomes such as cardiovascular disease (CVD), type-2 diabetes, and all-cause mortality [3,4]. In this regard, "metabolically healthy obesity" (MHO) is in the center of attention and inconsistencies exist on the benign nature of this obesity phenotype [5]. While many studies suggest that MHO is a relatively benign condition in comparison to metabolically unhealthy phenotypes [1,2,6], other studies show that this might not be the case and in longer follow-ups the so-called "benign obesity" is not that benign after all, when compared to metabolically healthy non-obese subjects [4,7–9].

Although no uniform definition for MHO exists, about one-fifth to one-third of obese individuals are estimated to have MHO-like phenotypes highlighting the importance of this condition [5]. Using different criteria for defining both obesity and metabolic health may be a source of inconsistency in different studies, as well as the length of follow-ups, and also the specific outcomes of interest [4,10]. The choice of an appropriate anthropometric index for defining obesity is one obstacle in characterizing MHO individuals;

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although most studies in this field use body mass index (BMI), recently some have also used abdominal obesity measures like waist circumference (WC) for this purpose [11,12]. In fact, increased health risks in the "metabolically healthy obese" and also the "metabolically unhealthy non-obese" observed in some studies, may be in part due to increased waist circumference or higher abdominal obesity rates in these groups. Evidence shows that increased BMI and WC are both strongly associated with morbidity and mortality in the long-term, but some suggest that abdominal obesity measures may better predict CVD and other health outcomes in comparison with BMI [13–15]. On the other hand, visceral adiposity and insulin resistance may be the driving force for other metabolic derangements and may precede the evolvement of metabolic syndrome [16]; hence using abdominal obesity measures (e.g. WC) is a reasonable approach that provides deeper insight into the nature of different obesity phenotypes.

Given the aforementioned inconsistencies, we used WC and metabolic syndrome components, and also insulin resistance, to categorize abdominal obesity phenotypes in a population-based prospective cohort study in Iran and compared incident CVD in the "healthy" and "unhealthy" abdominal obesity phenotypes over a 10-year follow-up.

## 2. Materials and methods

### 2.1. Participants

The Tehran Lipid and Glucose Study (TLGS) is an ongoing prospective, population-based study being conducted to determine the risk factors for non-communicable diseases among a representative Tehranian urban population [17]. In the TLGS, 15,005 Participants, aged ≥3 years, were selected by a multistage cluster random sampling method. Details of the study protocol are available elsewhere [17]. For the current study, 9754 participants, aged ≥30 years, which entered the study during phases I and II (1999–2001, and 2002–2005, respectively) were selected. Based on the original TLGS study protocol, those with chronic and debilitating conditions at baseline (e.g. cancers, chronic renal or hepatic disease, etc.) were not recruited in the TLGS. After exclusion of those who were pregnant ($n = 42$), had history of cardiovascular disease (CVD) at baseline ($n = 526$), those with BMI<18.5 kg/m$^2$ ($n = 140$), and those who had missing values for anthropometric or metabolic data ($n = 1924$), 7122 participants were selected for categorization of phenotypes and analyses of the follow-up data until 2011 (median follow-up of 10 years). Of these participants, 692 (9.7%) had no further follow-up data and the final analysis were performed on 6430 participants with complete data (Fig. 1).

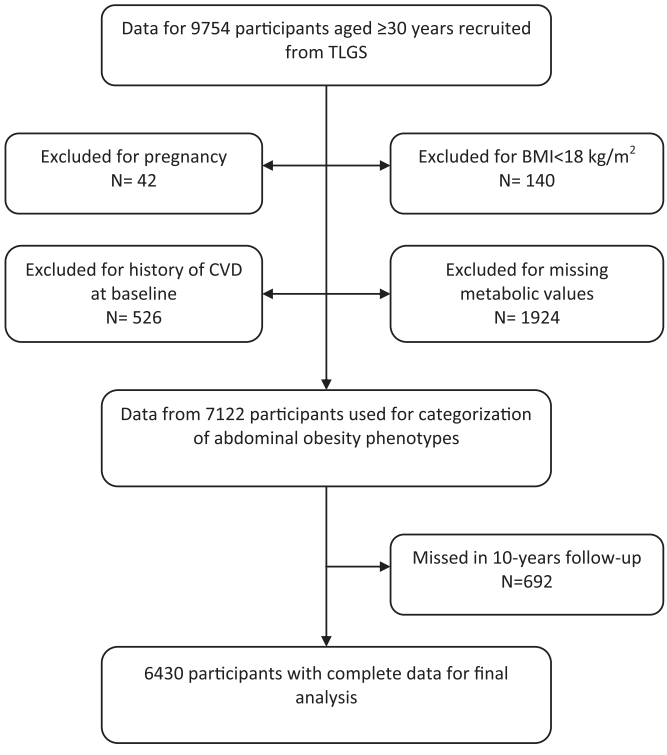


**Fig. 1.** Diagram showing the inclusion and exclusion process for sample selection.

### 2.2. Measurements

At baseline, trained personnel interviewed all participants using pretested questionnaires to collect information on age, gender, education, medical history of CVD, medication use, smoking habit, physical examination results, and family history of premature coronary artery disease (CAD).

Weight was measured with participants minimally clothed without shoes, using digital scales and recorded to the nearest 100 g. Height was measured with participants in a standing position without shoes, using a tape meter, with the shoulders in a normal state. BMI was calculated as weight in kilograms divided by height in meters squared. WC was measured at the level of the umbilicus using an un-stretched tape meter, without any pressure to the body surface, and was recorded to the nearest 0.1 cm. All measurements were taken by the same person. To measure blood pressure, participants were first asked to rest for 15 min, when a qualified physician took the systolic blood pressure (SBP) and diastolic blood pressure (DBP) twice in a seated position, after one initial measurement for determining the peak inflation level using a standard mercury sphygmomanometer. The mean of the two measurements was considered to be the participant's blood pressure.

Blood samples were drawn from all the study participants after 12–14 h overnight fasting, and all blood samples analyses were undertaken at the TLGS research laboratory on the day of blood collection, using selectra 2 auto-analyzer (Vital Scientific, Spankeren, the Netherlands). Fasting blood sugar (FBS) was measured by the enzymatic colorimetric method using glucose oxidase. For lipid measurements, total cholesterol (TC) and triglyceride (TG) levels were assayed by relevant kits (Pars Azmoun, Tehran, Iran) using enzymatic colorimetric tests with cholesterol esterase and cholesterol oxidase, and glycerol phosphate oxidase, respectively. High-density lipoprotein cholesterol (HDL-C) was measured with phosphotungstic acid. All samples were analyzed when internal quality control met the acceptable criteria. Inter- and intra-assay coefficients of variations at baseline were 2.2% for serum glucose, 2.0% and 0.5% for HDL-C and 1.6% and 0.6% for TG, respectively. Details of all measurement methods are available elsewhere [17].

### 2.3. Definitions

To define metabolically unhealthy, we used the criteria proposed by the Joint Interim Statement (JIS) [18] as follows: (1) FBS ≥100 mg/dl (5.6 mmol/l) or 2-h blood glucose ≥140 mg/dl (7.8 mmol/l) or drug treatment; (2) fasting TGs ≥150 mg/dl (1.7 mmol/l) or drug treatment; (3) fasting HDL-C <50 mg/dl (1.29 mmol/l) in women and <40 mg/dl (1.03 mmol/l) in men or drug treatment; (4) raised blood pressure defined as SBP ≥130 mmHg, DBP ≥85 mmHg or antihypertensive drug treatment. Subjects with ≤1 of the JIS components were considered as