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Combined effect of obesity and cardio-metabolic abnormality on the risk of cardiovascular disease: A meta-analysis of prospective cohort studies ☆

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ABSTRACT

Background: Cardiovascular risk is inconsistent in the normal-weight, overweight, and obese individuals due to metabolic abnormality. We aimed to investigate combined effects of obesity and metabolic abnormality on the risk of cardiovascular disease and mortality.
Methods: The MEDLINE, EMBASE, Cochrane library, and references of relevant original articles prior to May 2013 were searched for prospective studies investigating cardiovascular risk and death associated with combined effects of obesity and metabolic syndrome or insulin resistance. Pooled relative risks (RR) and 95% confidence intervals (CI) were calculated using random-effects or fixed-effect models when appropriate.
Results: Fourteen perspective studies with a total of 299,059 participants and 12,125 cases of incident CVD, 2130 cases of CVD death, and 7071 cases of all-cause death were included in the meta-analysis. Compared with healthy normal-weight individuals, metabolically healthy overweight (MHOW) and obese (MHOB) individuals showed increased risk for CVD events, which appeared much stronger during the long-term follow-up period of >15 years, with pooled RR of 1.47 (95% CI 1.37–1.58) in MHOW and 2.00 (95% CI 1.79–2.24) in MHOB. Normal-weight but metabolically abnormal individuals were at increased risk for CVD (pooled RR 1.81, 95% CI 1.56–2.10), CVD-related death (pooled RR 1.55, 95% CI 1.16–2.08), and all-cause death (pooled RR 1.27, 95% CI 1.10–1.47). Metabolically abnormal obese individuals were at the highest risk for CVD and mortality.
Conclusion: Individuals with metabolic abnormality, although at normal-weight, had an increased risk of CVD and mortality. Healthy overweight and obese persons had higher risk, which refuted the notion that metabolically healthy obese phenotype is a benign condition.

1. Introduction

Obesity is a rapidly growing health problem throughout the world with a prevalence of more than 20% in developed countries [1], and confers substantial risk for developing metabolic disorders, type 2 diabetes, and cardiovascular disease (CVD) [2,3]. Body mass index (BMI) has consistently been associated with adverse health outcomes; however, the presence of obesity-related metabolic disturbances varies widely among individuals with similar BMI [4], and the disease risk associated with obesity varies as well [5–7]. Heterogeneity of obesity has remained a challenge in clinical practice given that prevention and treatment of obesity is an enormous medical and socio-economic task.

Ruderman and others [8–10] identified metabolically obese but normal-weight (MANW) individuals who, despite having a normal-weight BMI (<25 kg/m^2), demonstrate a clustering of related metabolic abnormalities typical of obese individuals, including insulin resistance (IR) and increased levels of central adiposity, dyslipidemia, impaired fasting glucose, and hypertension. This clustering of risk factors has been defined as the metabolic syndrome (MetS) [11]. Conversely, metabolically healthy but obese (MHOB) individuals have been described, despite having BMI exceeding 30 kg/m^2, they are relatively insulin sensitive and lack most of the metabolic abnormalities [12–14]. MANW and MHOB individuals are interesting because these phenotypes separate obesity from its usual metabolic consequences.

To date, prospective longitudinal studies have shown inconsistent effects of obesity-metabolic subphenotypes on the risk of developing cardiovascular disease. The concept that obese individuals without metabolic abnormalities (MHOB) are not at high risk of future CVD events is demonstrated in some studies [15–19], but refuted in several recent studies [20–24]. In addition, intervention studies on the effect of weight-loss on metabolic risk factors have also reported controversial results in MHOB individuals [25], although observational

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studies showed that exercise and fitness can attenuate the adverse impact of obesity-metabolic risk on cardiovascular disease and mortality [24].

There is a need to synthesize the results of these studies. We therefore systematically reviewed evidence for the associations of obesity and the presence/absence of metabolic abnormalities with the risk of cardiovascular disease and mortality. In this meta-analysis, we categorized participants into normal-weight, overweight, and obese categories (defined by BMI or waist circumference) and with or without metabolic syndrome (MetS) or insulin resistance to assess the hypothesis that, relative to healthy normal-weight individuals, normal-weight individuals with metabolic abnormality were at intermediate risk (MANW phenotype), obese individuals without metabolic abnormality (MHOB phenotype) were not at remarkably increased risk, and metabolically unhealthy obese individuals were at the highest risk for development of CVD and death.

2. Methods

2.1. Search strategy

We searched for all published prospective studies that described the associations of obesity and the presence/absence of metabolic abnormalities with the risk of incident CVD and all-cause mortality. A systematic literature search was performed using the MEDLINE, EMBASE databases, and Cochrane library and was supplemented through the manual review of reference list of obtained articles up to May 31, 2013. The following terms were used: ((("body mass index" [MeSH Terms] OR ("body" [All Fields] AND "mass" [All Fields] AND "index" [All Fields]) OR "body mass index" [All Fields]) AND versus[All Fields] AND metabolic[All Fields] AND ("syndrome" [MeSH Terms] OR "syndrome" [All Fields])) OR (metabolically[All Fields] AND healthy[All Fields] AND ("obesity" [MeSH Terms] OR "obesity" [All Fields])) OR (metabolically[All Fields] AND benign[All Fields] AND ("obesity" [MeSH Terms] OR "obesity" [All Fields])))) AND (("cardiovascular diseases" [MeSH Terms] OR ("cardiovascular" [All Fields] AND "diseases" [All Fields]) OR "cardiovascular diseases" [All Fields] OR ("cardiovascular" [All Fields] AND "disease" [All Fields]) OR "cardiovascular disease" [All Fields]) OR (all-cause[All Fields] AND ("mortality" [Subheading] OR "mortality" [All Fields] OR "mortality" [MeSH Terms])))). No language restriction was applied for searching and study inclusion. Our systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [26].

2.2. Eligible criteria

Studies were considered eligible for meta-analysis if they met the following criteria: the study had a prospective design; the exposure was obesity and the presence/absence of cardio-metabolic abnormalities; and outcomes were incident coronary heart disease, stroke, or mortality. BMI or waist circumference was used to define normal-weight (BMI < 25 kg/m^2, or waist circumference < 94 cm for men and <80 cm for women), overweight (BMI 25–29.9 kg/m^2, or waist circumference 94–102 cm for men and 80–88 cm for women), and obesity (BMI ≥ 30 kg/m^2 or waist circumference > 102 cm for men and >88 cm for women). Metabolic risk was evaluated by the presence of the cluster of cardio-metabolic abnormalities proposed in the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP ATPIII) [27] or by the presence of insulin resistance [28]. Based on the ATPIII criteria, metabolic syndrome (MetS) was defined as having any 3 or more of the following factors: (1) Elevated blood pressure: systolic/diastolic blood pressure ≥130/85 mmHg or antihypertensive medication use; (2) Elevated triglyceride level: fasting triglyceride level ≥1.69 mmol/L (150 mg/dl); (3) Decreased HDL-C level: HDL-C < 1.04 mmol/L (40 mg/dl) in men or <1.29 mmol/L (50 mg/dl) in women or lipid-lowering medication use; (4) Elevated glucose level: fasting glucose level ≥5.6 mmol/L (100 mg/dl) or antidiabetic medication use; (5) Obesity: waist circumference >88 cm for women and >102 cm for men. Insulin resistance was defined using the homeostasis model assessment (HOMA) [(fasting glucose × fasting insulin)/22.5] [28]. Metabolically healthy but obese (MHOB) phenotype was defined as obesity in the absence of MetS or insulin resistance. We exclude literature reviews, cross-sectional studies, case-control studies, animal studies, and genetic variation studies.

2.3. Data extraction

Data extraction was conducted independently by two authors (J.F. and W.Z.) using a standardized data extraction form. To resolve discrepancies, a third investigator (Y.S.) was consulted. We contacted authors of the original studies in the case of missing data. For each included article, study characteristics were recorded as follows: authors, publication year, country of origin, name of study, study design, features of study population (race/ethnicity, sample size, age, proportion of men, mean BMI and waist circumference, baseline characteristics of participants), duration of the follow-up, definition of study groups, definition of metabolically healthy, ascertainment of outcomes, numbers of incident CVD cases or deaths, and confounding factors that were adjusted for in the multivariable analysis. The participants of the included original studies were categorized into normal-weight, overweight, and obese categories and with or without MetS or insulin resistance to describe obesity subphenotypes as the following: metabolically healthy with normal-weight (MHNW, as the reference group), metabolically abnormal with normal-weight (MANW), metabolically healthy with overweight (MHOW), metabolically abnormal with overweight (MAOW), metabolically healthy with obesity (MHOB), and metabolically abnormal with obesity (MAOB). For each group, we extracted the number of cases/participants, hazard ratios (or relative risk), and 95% confidence intervals (CIs). For studies that reported several multivariable-adjusted HRs, we extracted the effect estimate in every model, and used the most fully adjusted for potential confounders in our meta-analysis.

Accepted standardized quality scores for observational studies are not available. In this analysis, study's quality was assessed by review of study design, including appropriateness and reporting of inclusion and exclusion criteria, assessment of exposure (self-report or measured height and weight), assessment of outcome (self-report or validated medical records), control of confounding (least adjusted, adjusting only for age and/or gender; or adequate adjusted, adjusting for at least one cardiovascular risk factor, such as smoking status, low-density lipoprotein [LDL] cholesterol, alcohol intake, family history of CVD, and physical activity/fitness), and evidence of selection bias. Each of the 5 quality criteria was evaluated and scored on an integer scale (0 or 1, with 1 being better) and summed. Quality scores from 0 to 3 were considered lower quality, and 4 to 5 higher quality.

2.4. Statistical method

We used the multivariable-adjusted hazard ratios or relative risk reported in the original articles. Fixed- and random-effect models were used to calculate the pooled risk estimates and 95% CI for incident CVD and mortality by comparing obesity-metabolic risk subphenotypes to normal-weight individuals with metabolically healthy status. In the fixed-effect model, the pooled RR was obtained by averaging the lnRRs weighted by the inverses of their variances. In the random-effect model, DerSimonian and Laird's method was used to further incorporate between-study heterogeneity [31]. We reported the pooled risk estimates from the random-effects model if the test for heterogeneity was significant. The Cochran Q test and the I^2 statistic were used to examine statistical heterogeneity across studies. I^2 was calculated based on the formula $I^2 = 100\% \times (Q - df)/Q$.

Stratified analyses were performed by meta-regression, examining the statistical significance of the difference in relative risks according to definition of metabolic abnormality (NCEP ATPIII MetS or insulin resistance), gender, mean age and BMI of the study population (continuous), available data on exercise and fitness (Yes/No), duration of follow-up (continuous), publication year (continuous), and number of incident CVD case or deaths (continuous). Sensitivity analyses were performed by omitting 1 study at a time and calculating pooled relative risks for the remainder of the studies.

Potential publication bias was assessed by using visual inspection of a funnel plot [32] and the Egger's regression test [33]. All tests were 2-sided and P value <0.05 was considered statistically significant. All analyses were performed using STATA version 10.1 software (STATA Corp, College Station, Texas, USA).

3. Results

The literature search result was shown in Fig. 1. We identified 14 prospective cohort studies that met our inclusion criteria, in which 8 studies reported results on CVD [15,16,18,19,21–24], 6 studies on CVD mortality [17,21,24,29,30,34], and 9 studies on all-cause mortality [15,17,20,21,24,29,30,34,35] (some reported analyses on more than 1 relevant outcome). The total number of individuals was 299,059 with 12,125 cases of incident CVD, 2130 cases of CVD death, and 7071 cases of all-cause death, with sample sizes ranging from 780 to 119,054 and follow-up durations from 1.3 to 30 years. Characteristics of the included studies were shown in Table 1. Of the 14 studies, 9 were conducted in the United States, 1 in Canada, and 4 in European countries. Study participants were aged from 20 to 83 years, and the mean BMI ranged from 24.9 to 27.4 kg/m^2. A total of 13 studies excluded participants with known pre-existing CVD at baseline, except for the study by Calori et al. [29]. In the assessment of metabolic abnormality, 6 studies used NCEP ATPIII criteria [15,17,19,24,30,34], 2 used insulin resistance criteria [16,29], and 4 studies evaluated the two definitions separately [18,20,21,23], and the other 2 studies defined metabolically healthy as the absence of abnormal glucose, dyslipidemia, and hypertension [22,35]. In the assessment of obesity, 11 studies used BMI categories, 2 studies used waist circumference categories [34,35], and 1 study evaluated the two categories separately [30]. All included studies adjusted for multiple covariates such as age, gender, and other vascular risk factors, 4 of which additionally adjusted for exercise/physical fitness