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Are Metabolically Healthy Overweight/Obese Men at Increased Risk of Sudden Cardiac Death?

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Abstract

Objective: To the association between metabolically healthy overweight/obesity and the risk of sudden cardiac death in middle-aged men.

Participants and Methods: This prospective study was based on a population sample of 2185 men aged 42 to 60 years from the Kuopio Ischaemic Heart Disease Risk Factor Study. Participants were divided into 4 groups on the basis of body mass index and metabolic health status. *Metabolically healthy overweight/obesity* was defined as body mass index 25 kg/m^2 or greater without metabolic abnormalities, and *metabolically unhealthy normal weight* was defined as body mass index less than 25 kg/m^2 with 1 or more metabolic abnormalities.

Results: During a median follow-up of 26 years (interquartile range, 18.7-28.1 years), 240 sudden cardiac deaths (11%) occurred. Compared with metabolically healthy normal weight men, metabolically unhealthy overweight/obese men had a higher risk of sudden cardiac death (hazard ratio, 1.99; 95% CI, 1.03-3.85) after adjusting for potential confounders. However, metabolically healthy overweight/obese men were not at increased risk of sudden cardiac death (hazard ratio, 0.95; 95% CI, 0.40-2.24) as compared with their metabolically healthy normal weight counterparts after adjusting for age, smoking, low-density lipoprotein cholesterol level, high-sensitivity C-reactive protein level, insulin level, history of myocardial infarction, and directly measured peak oxygen uptake.

Conclusion: Our findings indicate that metabolically healthy normal weight men and metabolically healthy overweight/obese men were at comparable risk of sudden cardiac death over a 26-year follow-up period, suggesting that a baseline body mass index of 25 kg/m^2 or greater per se does not adversely affect the risk of sudden cardiac death.

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Although metabolically healthy obese (MHO) individuals appear to be at increased risk of coronary heart disease (CHD), cerebrovascular disease, and heart failure than do their metabolically healthy normal weight (MHNW) counterparts,[1] other studies have reported no association between MHO individuals and cardiovascular events.[2,3] Furthermore, it remains unclear whether differences in body habitus and metabolic health profiles extend to cardiac arrest as a predictable cardiovascular outcome in the general population. Sudden cardiac death (SCD) is a global public health concern, accounting for up to 50% of all cardiovascular deaths. Although obesity has been associated with a higher risk of SCD, the effect of overweight/obesity on the incidence of SCD remains unclear because of inherent confounding variables.[4,5] To further clarify these potential risk modulators, we examined the association between metabolically healthy overweight/obese middle-aged men and the risk of SCD over an extended follow-up period.

PARTICIPANTS AND METHODS

This prospective investigation included participants from the Kuopio Ischaemic Heart Disease Risk Factor Study, which is a prospective population-based long-term study designed to evaluate risk factors for cardiovascular disease (CVD) and related outcomes in a randomly selected sample of men from eastern Finland. Of the original cohort of 3433 men who resided

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in the town of Kuopio or its surrounding rural communities, 198 were excluded for various reasons (eg, serious disease or moved from the area). At baseline, examinations were conducted on 2682 men (82.9% of the eligible population) between March 1, 1984, and December 31, 1989. Participants whose blood markers and anthropometric variables were initially assessed were included in the present analysis (N=2185; age, 42-60 years). The Kuopio Ischaemic Heart Disease Risk Factor Study was approved by the Committee on Research Ethics of the University of Eastern Finland, and all study participants provided written informed consent.

Body mass index (BMI) was calculated as the weight in kilograms divided by the height meters squared. Our cohort did not include any participants who were underweight (BMI<18.5 kg/m^2). Resting blood pressure was measured using a sphygmomanometer and was expressed as the mean value from 6 measurements: 3 while supine, 1 while standing, and 2 while sitting. Blood samples were collected in the morning after a 12-hour overnight fast and analyzed according to standard protocols. Laboratory methods and other assessments are described elsewhere.[6] Peak oxygen uptake as an index of cardiorespiratory fitness was directly measured using a computerized metabolic measurement system during an electrically braked progressive cycle ergometer exercise test to volitional fatigue.

Our study population was divided into 4 groups on the basis of cross-classification of BMI and metabolic health status: MHNW; metabolically unhealthy normal weight (MUNW); metabolically healthy overweight/obese (MHOO); and metabolically unhealthy overweight/obese (MUOO). We used a hybrid definition of metabolically healthy obesity with a modified BMI (original BMI cutoff was ≥30 kg/m^2) as previously suggested.[7] Being *MHOO* was defined as a BMI of 25 kg/m^2 or greater with zero or no metabolic abnormalities or risk factors as signified by the following: systolic blood pressure 130 mm Hg or greater or diastolic blood pressure 85 mm Hg or greater or antihypertensive drug treatment; high-density lipoprotein cholesterol level less than 40 mg/dL (<1.0 mmol/L); serum triglyceride level 150 mg/dL or greater (≥1.7 mmol/L) or treatment of hypertriglyceridemia; and fasting blood glucose level 100 mg/dL or greater (≥5.6 mmol/L) or treatment with hypoglycemic agents. We excluded waist circumference from the definition of metabolically healthy obesity, because most participants met the criteria for a high waist circumference.[7]

Sudden cardiac death was defined as a fatal event that occurred within 1 hour of the onset of symptoms or within 24 hours when autopsy data did not reveal a noncardiac cause of SCD or after a fatal cardiac arrest after successful resuscitation from ventricular tachycardia and/or ventricular fibrillation. The diagnostic classification of events was based on symptoms, electrocardiographic (ECG) findings, cardiac enzyme elevations, autopsy findings (80% of the SCDs), and history of CHD combined with relevant clinical and ECG findings. Data on SCDs were derived from interviews with family members, hospital records, death certificates, autopsy reports, and medicolegal documents. A detailed definition of SCD has been previously described.[6]

We calculated the hazard ratio (HR) and 95% CI using the multivariable Cox proportional hazards model with adjustment for confounding variables to determine the relations of body phenotypes (ie, normal weight and overweight/obese) to the risk of SCD. For multivariable analysis, potential confounding variables (ie, covariates) were selected as variables with statistically significant differences among groups, as shown in Table 1. Statistical significance was set at *P* less than .05, and analyses were conducted using SPSS version 21.0 (IBM Corp.).

RESULTS

Table 1 summarizes the baseline characteristics of the study participants grouped by metabolic health status and body habitus. We found that 193 of the 2185 participants (8.8%) were classified as MHOO. There were significant differences in age, BMI, smoking, history of myocardial infarction, prevalence of diabetes and hypertension, resting systolic and diastolic blood pressures, lipid and lipoprotein profiles, glucose level, insulin level, high-sensitivity C-reactive protein level, and peak oxygen uptake among the 4 groups (*P*<.05).

During a median follow-up of 26 years (interquartile range, 18.7-28.1 years), 240 SCDs (11%) occurred. Compared with

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