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ORIGINAL INVESTIGATIONS

Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women

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ABSTRACT

BACKGROUND Previous studies have been unclear about the cardiovascular risks for metabolically healthy obese individuals.

OBJECTIVES This study examined the associations among metabolically healthy obese individuals and 4 different presentations of incident cardiovascular disease in a contemporary population.

METHODS We used linked electronic health records (1995 to 2015) in The Health Improvement Network (THIN) to assemble a cohort of 3.5 million individuals, 18 years of age or older and initially free of cardiovascular disease. We created body size phenotypes defined by body mass index categories (underweight, normal weight, overweight, and obesity) and 3 metabolic abnormalities (diabetes, hypertension, and hyperlipidemia). The primary endpoints were the first record of 1 of 4 cardiovascular presentations (coronary heart disease [CHD], cerebrovascular disease, heart failure, and peripheral vascular disease).

RESULTS During a mean follow-up of 5.4 years, obese individuals with no metabolic abnormalities had a higher risk of CHD (multivariate-adjusted hazard ratio [HR]: 1.49; 95% confidence interval [CI]: 1.45 to 1.54), cerebrovascular disease (HR: 1.07; 95% CI: 1.04 to 1.11), and heart failure (HR: 1.96; 95% CI: 1.86 to 2.06) compared with normal weight individuals with 0 metabolic abnormalities. Risk of CHD, cerebrovascular disease, and heart failure in normal weight, overweight, and obese individuals increased with increasing number of metabolic abnormalities.

CONCLUSIONS Metabolically healthy obese individuals had a higher risk of coronary heart disease, cerebrovascular disease, and heart failure than normal weight metabolically healthy individuals. Even individuals who are normal weight can have metabolic abnormalities and similar risks for cardiovascular disease events. (J Am Coll Cardiol 2017;70:1429–37)
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Obesity, an established risk factor for cardiovascular disease (CVD) (1) has been increasing globally over the past 40 years (2). Metabolic abnormalities such as hypertension, dyslipidemia, and dysglycemia are known to mediate its effects (3); however, the clustering of obesity-related metabolic abnormalities varies widely among obese individuals. A subset of obese individuals without obesity-related metabolic abnormalities are often referred to as being "metabolically healthy obese" (MHO) (4–8).

Three meta-analyses (9–11) have demonstrated that, compared with metabolically healthy normal weight individuals, obese individuals are at

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ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CHD = coronary heart disease

CVD = cardiovascular disease

MHO = metabolically healthy obese

PVD = peripheral vascular disease

increased risk for CVD events. Whether MHO is associated with excess risk of CVD remains a subject of debate because of important limitations to the evidence base. The main limitation is the inconsistent definition of metabolic health across studies. Previous studies have also not compared the association of MHO and a wide range of CVD events such as cerebrovascular disease, heart failure, and peripheral vascular disease (PVD). Additionally, potential confounders have been inconsistently controlled for across studies, and there are a limited number of studies that have examined other metabolically defined body size phenotypes.

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We sought to address these limitations in a large contemporary cohort based on linked electronic health records, which combine routine information about diagnoses, risk factors, and medication use with future CVD events. Our objective was to examine associations among body size phenotypes (underweight, normal weight, overweight, and obese) with or without metabolic abnormalities (diabetes, hypertension, hyperlipidemia) and incident coronary heart disease (angina, ischemic heart disease, myocardial infarction), cerebrovascular disease (transient ischemic attack, ischemic stroke, hemorrhagic stroke), heart failure, and PVD. We tested the hypothesis that compared with metabolically healthy (i.e., no metabolic abnormalities) normal weight individuals, MHO individuals are at increased risk for CVD events.

METHODS

STUDY DESIGN AND SETTING. We undertook a cohort study with prospectively collected data from The Health Improvement Network (THIN) database, which contains computerized primary care records from primary care physicians who use the Vision IT system and have agreed at the practice level to participate (covering 6.2% of the U.K. population) (12). THIN captures diagnoses, prescriptions, and tests from primary care, and referrals to specialists, hospital admissions, and diagnoses made in secondary care, which are typically reported back to the primary care physician. The database contains records of lifestyle (e.g., smoking status) and anthropometric measurements (e.g., height, weight); these measurements could be recorded at patient registration, opportunistically during care, or as deemed clinically relevant by the primary care physicians. THIN data are representative of the U.K. population (13), and comparisons to external statistics and other independent studies have shown that both the clinical diagnostic and prescribing information are well recorded and accurate (13,14). Data collection began in January 1995, and we used all data to September 2015. For this study, THIN's independent Scientific Review Committee granted approval in August 2016 (scientific review committee reference number: 16THIN078).

PARTICIPANTS. We included all persons in THIN 18 years of age and older with body mass index (BMI) data. Patients were only eligible to take part once their primary care physicians had implemented the Vision IT system. Study entry began 12 months after registration to minimize the chance that CVD events recorded after registration reflected pre-existing or historical disease. We assigned the first BMI record from the registration date or the first one recorded after the Vision IT system was initiated. Individuals with any record of CVD events before study entry were excluded.

EXPOSURE. BMI was defined as kg/m^2 at study entry. We defined individuals as having diabetes and hypertension by coded diagnoses (READ codes) recorded in THIN at study entry (Online Table 1). We defined individuals as having hyperlipidemia on the basis of whether individuals had specific prescription records of lipid-lowering agents. Individuals who developed diabetes, hypertension, or hyperlipidemia during follow-up were analyzed according to their baseline status of no diabetes, hypertension, or hyperlipidemia.

Body size phenotypes were defined using World Health Organization criteria as follows: underweight (BMI of <18.5 kg/m^2), normal weight (BMI of 18 kg/m^2 to <25 kg/m^2), overweight (BMI of 25 kg/m^2 to <30 kg/m^2), and obese (BMI of ≥ 30 kg/m^2). The 3 metabolic abnormalities were summed to create a metabolic abnormalities score (0, 1, 2, and 3). Persons were divided into 14 body size phenotypes: underweight with 0 metabolic abnormalities; underweight with 1 or more metabolic abnormalities; normal weight with 0 metabolic abnormalities; normal weight with 1 metabolic abnormality; normal weight with 2 metabolic abnormalities; normal weight with 3 metabolic abnormalities; overweight with 0 metabolic abnormalities; overweight with 1 metabolic abnormality; overweight with 2 metabolic abnormalities; overweight with 3 metabolic abnormalities; obese with 0 metabolic abnormalities; obese with 1 metabolic abnormality; obese with 2 metabolic abnormalities; and obese with 3 metabolic abnormalities.

OUTCOMES. The endpoints were the first record of one of the following 4 presentations of CVD: coronary heart disease (angina, ischemic heart disease,

myocardial infarction); cerebrovascular disease (transient ischemic attack, ischemic stroke, hemorrhagic stroke); heart failure; and PVD. Any events occurring after the first CVD presentation were ignored. Endpoint definitions are described in Online Table 2.

COVARIATES. Participant's age, sex, self-reported smoking status, and social deprivation were included in models. Data recorded at study entry were used to classify participants as never smokers, ex-smokers, or current smokers. Social deprivation was included as quintiles of the index of multiple deprivation (15), a score calculated for each participant's neighborhood on the basis of indices such as income, education, and employment.

STATISTICAL ANALYSIS. Of the 4,091,344 individuals ≥18 years of age in the THIN database without a history of CVD, we excluded persons with missing data for sex (128,458 of 4.09 million subjects [3.1%]), BMI (161,699 of 4.09 million subjects [4.0%]), smoking (53,262 of 4.09 million subjects [1.3%]), and social deprivation (252,148 of 4.09 million subjects [6.2%]). After these exclusions, there remained a final sample of 3,495,777 participants (85.4% of the eligible sample). Those excluded due to missing information were less likely to be male (41.4% vs. 43.1%; $p < 0.001$), younger (41.1 years of age vs. 44.7 years of age; $p < 0.001$), have a lower BMI (25.9 kg/m^2 vs. 26.4 kg/m^2; $p < 0.001$), more likely to belong to the most deprived quintile (14.5% vs. 14.0%; $p < 0.001$), and more likely to be current smokers (25.1% vs. 24.6%; $p < 0.001$).

Follow-up was censored at the occurrence of first CVD endpoint, death, de-registration from the practice, or the last data collection for the practice, whichever occurred first. We used Cox proportional hazard models to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for associations between each body size phenotype with or without metabolic abnormalities and CVD events. We adjusted for age at BMI record, sex, self-reported smoking, and social deprivation. We assessed the proportional hazards assumption by visually checking the Kaplan-Meier curves and tested it using Schoenfeld residuals. Using subgroup analyses, we stratified associations by sex and age (<65 years of age and ≥65 years of age). The cutoff at 65 years of age was chosen because this is commonly used to designate an individual as an older person (16). Using sensitivity analyses, we defined metabolic status by diagnostic or prescription code as well as by laboratory or physical measurement; adjusted analyses for hormone replacement therapy and oral contraceptives, respectively; and excluded patients with type 1 diabetes. Residual confounding by cigarette smoking has been suggested as a possible explanation for inconsistent associations between obesity and PVD (17). Excess risk for CVD events associated with low BMI can also be associated with smoking-related diseases (such as chronic obstructive pulmonary disease [COPD] and lung cancer). Therefore, using sensitivity analyses, we examined body size phenotypes with or without metabolic abnormalities and CVD events only among individuals who reported never smoking cigarettes.

RESULTS

Among 3,495,777 individuals, 2.7% were classified as underweight with no metabolic abnormalities, 37.7% were classified as normal weight with no metabolic abnormalities, 25.7% were classified as overweight with no metabolic abnormalities, and 14.8% were classified as obese with no metabolic abnormalities (Online Table 3). The prevalence of 3 metabolic abnormalities was rare regardless of the weight category, with underweight individuals having the lowest percentage (0%) (Online Table 3). Metabolically healthy obese individuals were more likely to be younger, male, current smokers, and socioeconomically deprived compared with metabolically unhealthy obese individuals (**Table 1**).

There were 154,051 deaths (4.4%) and 1,182,658 patients (30.8%) who transferred out of their general practice. Over a mean 5.4 years' follow-up, there were 165,302 initial CVD presentations: 61,546 (37.2%) developed CHD; 54,705 (33.1%) developed cerebrovascular disease; 25,254 (15.3%) developed heart failure; and 23,797 (14.4%) developed PVD. Incidence rates of CVD events by body size phenotype and metabolic status are shown in Online Tables 4 to 7. Among initially metabolically healthy overweight individuals, approximately 1.9% developed diabetes, 9.4% developed hyperlipidemia, and 7.2% developed hypertension. Among individuals who were initially MHO, approximately 5.6% developed diabetes, 11.5% developed hyperlipidemia, and 10.5% developed hypertension.

Figure 1 depicts the associations between the 14 body size phenotypes with or without metabolic abnormalities and CVD events (CHD, cerebrovascular disease, heart failure, and PVD) with the normal weight 0 metabolic abnormalities group as the reference.

CORONARY HEART DISEASE. Individuals who were overweight with 0 metabolic abnormalities (HR: 1.30; 95% CI: 1.27 to 1.34) and obese with 0 metabolic abnormalities (HR: 1.49; 95% CI: 1.45 to 1.54), had an increased risk of coronary heart disease compared to

TABLE 1 Baseline Characteristics of the Study Population by Body Size and Metabolic Health Status

	Underweight	Normal Weight	Overweight	Metabolically Healthy and Obese*	Metabolically Unhealthy and Obese†
Age, yrs	38.0 ± 20.3	41.3 ± 17.6	47.7 ± 16.6	42.6 ± 13.8	58.6 ± 12.6
Sex					
Males	24,753 (26.3)	547,600 (37.0)	603,492 (52.1)	301,974 (58.4)	114,196 (46.6)
Females	69,276 (73.7)	932,626 (63.0)	555,324 (47.9)	215,470 (41.6)	131,066 (53.4)
Smoking status					
Never smoker	51,614 (54.9)	842,573 (56.9)	637,442 (55.0)	284,510 (55.0)	133,878 (54.6)
Ex-smoker	10,075 (10.7)	235,766 (15.9)	257,903 (22.3)	109,051 (21.1)	73,015 (29.8)
Current smoker	32,340 (34.4)	401,887 (27.2)	263,471 (22.7)	123,883 (23.9)	38,369 (15.6)
Social deprivation quintile					
1 Least deprived	16,736 (17.8)	352,906 (23.8)	295,984 (25.5)	110,089 (21.3)	54,712 (22.3)
2	16,119 (17.1)	303,729 (20.5)	256,192 (22.1)	104,285 (20.2)	52,844 (21.6)
3	20,083 (21.4)	318,076 (21.5)	248,836 (21.5)	114,512 (22.1)	53,628 (21.9)
4	22,583 (24.0)	293,845 (19.9)	212,177 (18.3)	108,679 (21.0)	49,278 (20.1)
5 Most deprived	18,508 (19.7)	211,670 (14.3)	145,627 (12.6)	79,879 (15.4)	34,800 (14.2)
BMI, kg/m^2	17.4 ± 1.0	22.3 ± 1.7	27.2 ± 1.4	34.4 ± 4.5	34.9 ± 4.8

Values are mean ± SD or n (%). *Obese with 0 metabolic abnormalities. †Obese with 1 or more metabolic abnormalities.
BMI = body mass index.

normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (Figure 1). Risk of coronary heart disease in the normal weight, overweight, and obese groups increased with the increased number of metabolic abnormalities (Figure 1).

CEREBROVASCULAR DISEASE. Individuals who were underweight (HR: 1.31; 95% CI: 1.23 to 1.40) and obese with 0 metabolic abnormalities (HR: 1.07; 95% CI: 1.04 to 1.11) had an increased risk of cerebrovascular disease compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (Figure 1). Risk of cerebrovascular disease in the normal weight, overweight, and obese groups increased with the increased number of metabolic abnormalities (Figure 1).

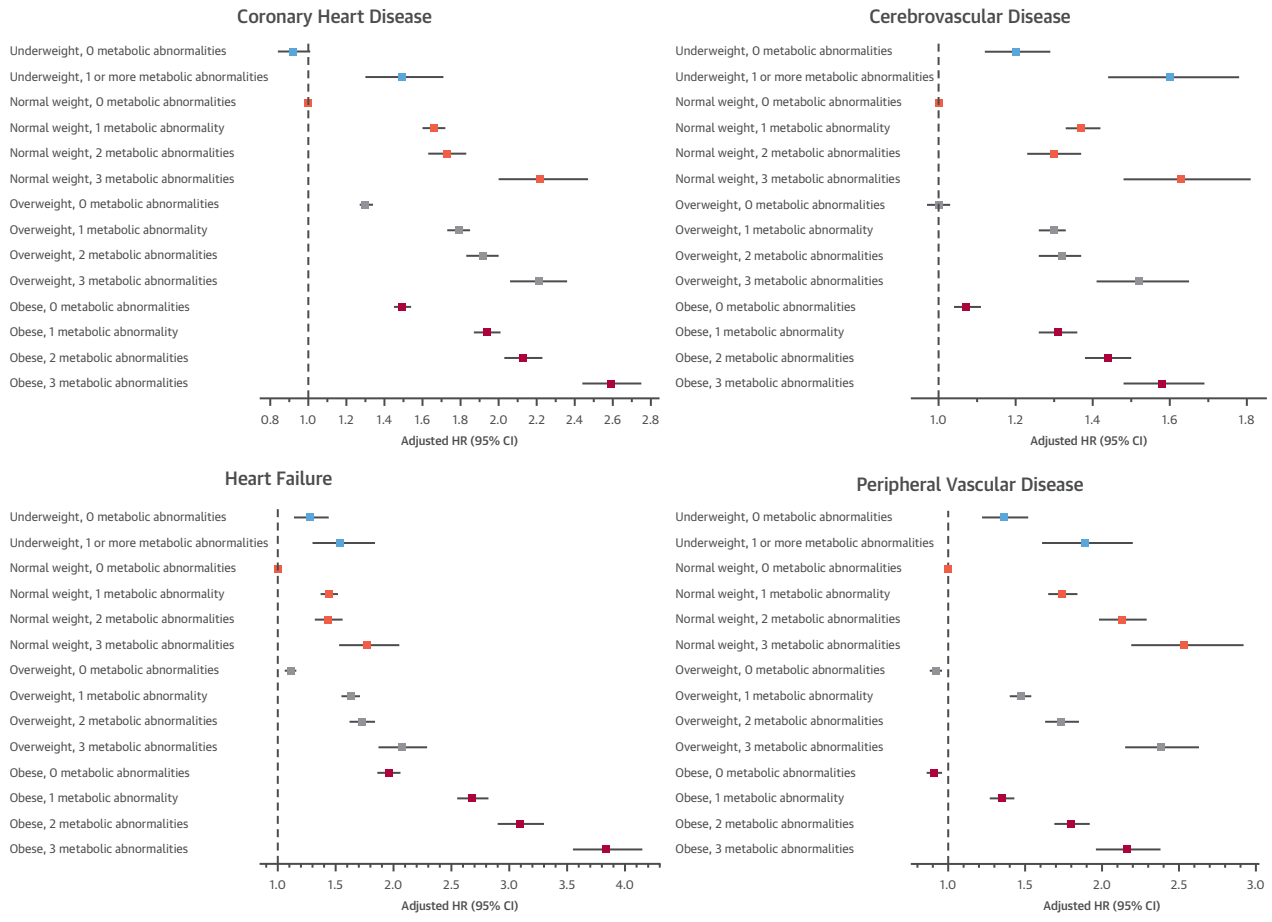
HEART FAILURE. Individuals who were underweight (HR: 1.36; 95% CI: 1.23 to 1.51), overweight with 0 metabolic abnormalities (HR: 1.11; 95% CI: 1.06 to 1.16) and obese with 0 metabolic abnormalities (HR: 1.96; 95% CI: 1.86 to 2.06) had an increased risk of heart failure compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (Figure 1). Risk of heart failure in the normal weight, overweight, and obese groups increased with the increased number of metabolic abnormalities (Figure 1).

PERIPHERAL VASCULAR DISEASE. Individuals who were underweight had an increased risk of PVD (HR: 1.49; 95% CI: 1.36 to 1.63), compared to normal weight individuals with no metabolic abnormalities after adjustment for potential confounders (Figure 1). Individuals who were overweight with 0 metabolic abnormalities (adjusted HR: 0.92; 95% CI: 0.88 to 0.96) and obese with 0 metabolic abnormalities (adjusted HR: 0.91; 95% CI: 0.86 to 0.96) had a decreased risk of PVD compared to normal weight individuals with no metabolic abnormalities (Figure 1). Risk of PVD in the normal weight, overweight, and obese groups increased with the increased number of metabolic abnormalities (Figure 1).

SUBGROUP ANALYSES. We undertook several subgroup analyses (Online Tables 8 to 15). There was some evidence that the risk of cerebrovascular disease in overweight and obese individuals without metabolic abnormalities, heart failure in overweight individuals without metabolic abnormalities, differed significantly by sex. Females had stronger positive associations with cerebrovascular disease and heart failure than males. There was some evidence that the risk of CHD, cerebrovascular disease, heart failure, and PVD in overweight and obese individuals without metabolic abnormalities differed significantly by age. Individuals <65 years of age had significantly stronger positive associations with CHD, cerebrovascular disease, heart failure, and PVD than individuals ≥65 years of age. Among overweight and obese individuals without metabolic abnormalities, age-stratified analyses revealed significant positive associations with PVD.

SENSITIVITY ANALYSES. When metabolic status was derived from diagnostic codes or prescription records as well as laboratory and physical measurements,

FIGURE 1 Association Between Body Size Phenotypes and Metabolic Status and Cardiovascular Disease Events in 3.5 Million UK Adults



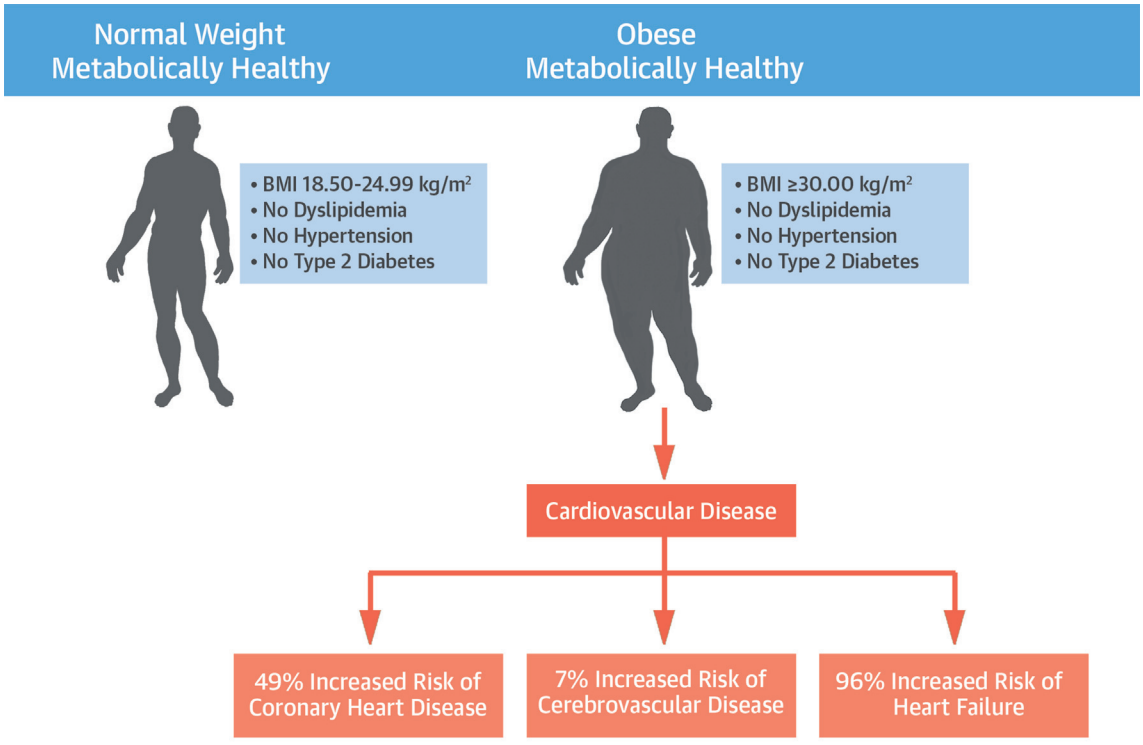
Analyses adjusted for age, sex, smoking status, and social deprivation. The reference category is normal weight, 0 metabolic abnormalities. BMI = body mass index.

the magnitude of associations between the body size phenotypes and metabolic status with CHD, cerebrovascular disease, heart failure, and PVD were generally larger (Online Tables 9, 11, 13, and 15). For metabolically healthy overweight or obese groups, the negative association with PVD became nonsignificant (Online Table 15). Further adjustment for hormone replacement therapy or oral contraceptives did not significantly change the estimates (Online Tables 9 and 11). Exclusion of participants with type 1 diabetes did not significantly alter the results (Online Tables 9, 11, 13, and 15). In analyses restricted to individuals who reported they never smoked cigarettes, individuals who were obese with no metabolic abnormalities had a significantly stronger positive association with PVD (Online Table 15). For individuals who were underweight with no metabolic abnormalities, we repeated analyses only in those who reported they never smoked cigarettes. This did not significantly alter the results, with the exception that the positive association with cerebrovascular disease became nonsignificant (Online Table 15).

DISCUSSION

In this study of approximately 3.5 million individuals, accruing 165,302 CVD events during 5.4 years' average follow-up, we showed that individuals who are obese and classified as metabolically healthy (either no metabolic abnormalities, 1 or 2) are still at an increased risk for CHD, cerebrovascular disease, and heart failure compared with individuals who are normal weight with no metabolic risk factors (**Central Illustration**). These associations were not dependent on participants' sex. Approximately, 1 in 10 individuals who were normal weight had metabolic abnormalities and had increased risks for CHD, cerebrovascular disease, heart failure, and PVD compared

CENTRAL ILLUSTRATION Metabolically Healthy Obese and Incident Cardiovascular Disease



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to normal weight individuals without metabolic abnormalities.

Although 3 meta-analyses (9-11) have assessed the risks of CVD for the MHO phenotype, each of these analyses had limitations. The meta-analysis by Kramer et al. (10) demonstrated that MHO individuals had increased risk for CVD events compared with metabolically healthy normal weight individuals. However, their findings were controversial. The meta-analysis roughly merged CVD events and all-cause mortality to calculate the pooled risk estimates for MHO individuals. Another limitation of the meta-analysis was the fact that it did not adequately adjust for important baseline factors, including age and sex. Similarly, in the meta-analysis by Fan et al. (11), they did not differentiate between CVD events and all-cause death events but merged them to calculate the pooled risk estimate. In our study, we examined MHO with the incidence of specific CVD events (i.e., CHD, cerebrovascular disease, heart failure, and PVD) based on validated electronic health records (18-20). We were also able to adjust for important baseline factors including age, sex, smoking status, and socioeconomic deprivation. Recently, Zheng et al. (9) conducted a meta-analysis that attempted to examine the association between MHO and CVD events in only studies using the strictest definition for metabolic health (absence of all metabolic abnormalities). They found an insignificant association between MHO and CVD events; however, only 2 studies provided data, and as such, the statistical power was limited in its detection of significant associations. In our study, we had unprecedented statistical power to examine obese individuals classified by the number of metabolic abnormalities, potentially reflecting several definitions of the "metabolically healthy" phenotype in relation to a range of CVD events.

Being metabolically unhealthy, regardless of BMI, generally conferred increased risk of CVD events, and normal weight status did not necessarily indicate metabolic health. Some individuals with normal weight have previously been reported to have elevated metabolic abnormalities (21,22). In the United States, the Preventive Services Task Force currently recommends that clinicians in primary care

settings use overweight and obesity as the main criteria to screen adults for abnormal blood glucose concentration as part of cardiovascular risk assessment (23). This could result in the failure to identify metabolic abnormalities in many patients. Early detection and management of normal weight individuals with metabolic abnormalities may therefore be beneficial in the prevention of CVD events. We found that underweight individuals had an increased risk of cerebrovascular disease, heart failure, and PVD. The impact of underweight on CVD events has not been adequately studied, with most previous research not evaluating underweight individuals separately from normal weight individuals (3,24). Excess risk for CVD events associated with low BMI may be related to smoking-related diseases such as COPD and lung cancer. To minimize this possibility in sensitivity analyses, we only examined the association between underweight with no metabolic abnormalities and CVD events restricted to individuals who never reported smoking cigarettes. The results were unchanged from the main results with the exception that underweight individuals with no metabolic abnormalities now had a nonsignificant risk for cerebrovascular disease.

Our finding that obesity was associated with a lower risk of PVD was surprising, considering that it may influence the atherosclerotic process (25). Previous studies of the association between obesity and PVD have been inconsistent (17). In the Israeli Ischemic Heart Disease Project (26), those with new-onset intermittent claudication had a higher BMI than those who remained symptom free. Other large population-based studies, however, have failed to demonstrate that obesity increases risk for PVD (27–29), with some studies even reporting a reduction in risk for PVD (30–32). In the Framingham study cohort, relative weight was found to be inversely associated with intermittent claudication (31). One potential explanation for this is residual confounding by cigarette smoking (cigarette smoking is strongly associated with both PVD and lower BMI) (17). In sensitivity analyses restricted to individuals who were obese with no metabolic abnormalities and reported never smoking cigarettes, risk for PVD was increased compared to normal weight individuals with no metabolic abnormalities.

To the best of our knowledge, this is the largest prospective study of the association between body size phenotypes with or without metabolic abnormalities (including MHO) and a range of incident CVD events with unprecedented precision and power. Dividing our participants into 4 BMI groups according to the classification provided by World Health Organization gave us the possibility of a more granular analysis of the CVD risk in the different body size phenotypes.

STUDY LIMITATIONS. BMI has many advantages as a surrogate of body fat, such as simplicity and reproducibility (33), but we are unable to distinguish differences between high percentage of body fat and preserved or increased lean mass, particularly in participants with a BMI of <30 kg/m^2. Even though patients registered in THIN are representative of the general U.K. adult population (13), persons with a BMI measurement may not necessarily be representative of the general population. Body mass index data, if not recorded at registration, tends to be opportunistically recorded (i.e., recorded when the patient is attending for other reasons or when the matter is of direct clinical importance). We limited this possibility by only using the first BMI recorded from the registration date (because the values would have probably been recorded for administrative and not health reasons). Our findings are drawn from baseline measurements of BMI and metabolic abnormalities. Considering the difficulty in losing weight, it is more likely that individuals transition to higher weight (i.e., normal weight/overweight to obese) categories than transition to lower weight categories (i.e., obese to overweight/normal weight) (10). Thus, the potential misclassification effect of changes in weight over time was probably conservative. In our study, a small proportion of individuals who were initially metabolically healthy overweight or obese did progress to metabolically unhealthy overweight or obesity. Therefore, due to changes in metabolic abnormalities, a degree of misclassification did occur. We did not have access to appropriate data for diet or physical activity and therefore could not examine, for example, whether physical activity could modify the association between MHO and incident CVD. Patients were defined as having diabetes or hypertension by using diagnostic codes, and hyperlipidemia was defined using prescription codes. Given that a proportion of individuals with metabolic abnormalities may be undiagnosed in the U.K. (34,35), we used available measurements of HbA1c concentration, blood pressure, and serum lipids to minimize misclassification error. Additionally, given that improvement of glycemia, blood pressure, or lipid control obtained through treatment can prevent CVD events in the long term, we may therefore expect that patients with optimally treated and controlled conditions would have a reduced risk of developing a CVD events compared to those whose conditions were uncontrolled, and therefore, our HR estimates would be conservative. The proportion of participants

who transferred out of their practice was high (30.8%). However, the difference between the proportion of participants who were obese with no metabolic abnormalities transferring out of their practice and those who remained in their practice was small (13.0% vs. 16.0%, respectively) and therefore less likely to bias the HRs substantially.

Taking into consideration the genetic heterogeneity related to obesity (36), it is plausible to assume that a distinct, benign phenotype in terms of CVD risk may be present. Of the body size phenotypes, MHO has been the most commonly examined phenotype (37), and it has been suggested that the concept of MHO may be important in the stratification of individuals in the clinical treatment of obesity (37). Some researchers have called for a shift in the public health focus away from markers of adiposity, such as BMI (38), and have suggested that health providers prescribing weight loss interventions may be misusing time and resources (39). Our study robustly challenges the assertion that MHO is a benign condition and adds to the evidence base that MHO is a high-risk state for future CVD events.

CONCLUSIONS

Individuals who are obese with no metabolic abnormalities are at higher risk of coronary heart disease, cerebrovascular disease, and heart failure than normal weight metabolically healthy persons. Clinicians need to be aware that individuals who would otherwise be considered non-obese, based on a normal BMI, can have metabolic abnormalities, and therefore also be at high risk for CVD events.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Even when they have no metabolic abnormalities, men and women who are obese are at increased risk of coronary heart disease, cerebrovascular disease, and heart failure compared to people of normal weight with no metabolic abnormalities. Men and women who are normal weight can have metabolic abnormalities and be at high risk of cardiovascular disease events.

TRANSLATIONAL OUTLOOK: Prospective trials are needed to assess the effect of weight loss on cardiovascular risk among metabolically healthy obese individuals.

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KEY WORDS cerebrovascular disease, coronary heart disease, heart failure, obesity, overweight, phenotype, weight

APPENDIX For supplemental tables, please see the online version of this article.