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Lessons from the trials

Is there an increased cardiovascular risk in metabolically healthy obese individuals? Lessons from the HUNT (Nord-Trøndelag Health) study

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ABSTRACT
Obesity and metabolic syndrome frequently co-exist and are major health problems worldwide. Prior research has questioned whether obesity without cardiometabolic abnormalities "metabolically healthy obesity" (MHO), has adverse effects on overall cardiovascular disease risk (CVD). The association between MHO and the first development of acute myocardial infarction and heart failure (HF) was evaluated in the second HUNT (Nord-Trøndelag Health).

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INTRODUCTION

Atherosclerosis, obesity, and metabolic syndrome are closely linked and constitute, arguably, the most menacing three conditions to modern society.[1] Obesity adversely affects almost all of the major cardiovascular risk factors, including blood pressure, dyslipidemia and insulin sensitivity leading to metabolic syndrome and type-2 diabetes mellitus. It is not surprising that obesity increases the risk of almost of all cardiovascular disorders including hypertension, coronary artery disease, heart failure, atrial fibrillation and peripheral arterial disease. However, previous research has questioned whether obesity without cardiometabolic abnormalities "metabolically healthy obesity" (MHO) has adverse effects on overall cardiovascular risk.[2] Using data from the second HUNT (Nord-Trøndelag health) study Mørkedal B, et al attempts to evaluate this association.[3]

THE STUDY

Inhabitants 20 years of age and older in Nord-Trøndelag County in Norway were invited to participate in the second HUNT from August 1995 to June 1997. Of the 93,898 individuals eligible to participate, 64,726 (69%) accepted the invitation, and attended a clinical examination conducted by trained nurses. Exclusion criteria were; missing information on body-mass index (BMI) or history of acute myocardial infarction (AMI), heart failure (HF) or cerebral stroke at baseline. Thus 61,299 participants (28,255 men and 33,044 women) were included in the main analyses of BMI and metabolic health with risk of AMI and HF. Furthermore, 21,796 of participants had information about their BMI from prior analysis; the tuberculosis screening (conducted between 1966 and 1969) and from HUNT-1 (conducted between 1984 and 1986). Thus, for the latter proportion of participants, BMI measurements' were available approximately 10 and 30 years before baseline for the present study.

The investigators used a modified definition of metabolic health as described by the International Diabetes Federation. Participants were categorized as metabolically unhealthy if they had elevated waist circumference (>94 cm for men, >80 cm for women) or BMI ≥ 30 kg/m2 in addition to 2 or more of the following criteria: elevated nonfasting triglycerides (≥ 1.7 mmol/l), reduced high-density lipoprotein cholesterol (<1.03 mmol/l for men, <1.29 mmol/l form women), elevated blood pressure ($\geq 130/85$ mmHg) or use of blood pressure medication, elevated nonfasting glucose (≥ 11.1 mmol/l), or diabetes diagnosis. Patients were subdivided into three categories according to their BMI; 25 $<$ kg/m2 (normal), 25 to 29.9 kg/m2 (overweight) and ≥ 30 kg/m2 (obese) and metabolically healthy or unhealthy.

The investigators also performed sub-analysis using 6 categories of BMI (underweight <18.5 kg/m2, normal weight 18.3-24.9 kg/m2, overweight 25-29.9 kg/m2, class I obese 30-34.9 kg/m2, class II obese 35-39.9, and class III obese $\geq$ 40 kg/m2). A separate analysis was also made for the duration of obesity among participants whom previous BMI measurements had been conducted. In this analysis, the participants were divided into 5 categories: long-term normal weight; long-term overweight; long-term obese; recent development of obesity; and variable body mass (any other combination of BMI categories). Analysis of abdominal obesity (waist-hip ratio >0.9 for men and >0.85 for women) instead of BMI and outcome was also made. Endpoints: first AMI or for HF.

RESULTS

Among the overall participants, 10,059 (16.4%) were classified as obese and 15,576 (25.4%) were classified as metabolically unhealthy. Among the obese, the proportion of metabolically healthy (MHO) was 26.4%. Obese and metabolically healthy participants were more likely to be women younger, and unmarried compared with obese and metabolically unhealthy participants (MUO).

Acute myocardial infarction (AMI)

During a median follow-up of 12.2 years, 2,547 participants had a first AMI. The age- and sex-adjusted HR among obese men and women who were metabolically healthy was 1.0 (95% CI: 0.8-1.2) compared with normal weight and metabolically healthy participants. The corresponding HR for obese and metabolically unhealthy men and women was 1.7 (95%: 1.5-1.9). Furthermore, the risk of AMI was consistently higher among metabolically unhealthy participants across the range of BMI, including the severe obese, compared with metabolically healthy participants. Neither long-term obesity nor recently developed obesity was associated with substantial risk for AMI among metabolically healthy participants.

Heart failure (HF)

During a median follow-up of 12.3 years 1,201 participants developed HF. There was a stronger risk of HF associated with long-term obesity, regardless of metabolic status, compared with normal-weight and metabolically healthy participants. There was also a higher risk of HF among metabolically healthy participants who had recently developed obesity. The results of using abdominal waist circumference were similar to those obtained in he primary analyses using BMI.

DISCUSSION

The investigators concluded that the metabolic status and not obesity was the main determinant risk of AMI. In contrast, the risk of HF was similarly increased in MHO and MUO participants compared with normal-weight participants with healthy metabolic status, suggesting that metabolic health may not play a central role for these associations. The results of using abdominal waist circumference were similar to those obtained in he primary analyses using BMI for AMI & HF. This increased risk of HF has been explained in an accompanying editorial by the fact that increased adiposity increases total blood volume, stroke volume, cardiac output and cardiac work leading to significant abnormalities on both the right and left sides of the heart.[2] The complexity of the association between obesity and cardiovascular diseases is further complicated by the current understanding of the various physiologic functions of adiposity. Adipose tissue in addition to its role in thermogenesis and energy storage, it is a complex endocrine organ and is believed to have a role in the evolution of human brain as well as in myocardial regeneration and repair.[4]

The findings of the current study are *not* concordant with a recently published meta-analysis[5] as well as a number of recent studies[6,7] (see Table 1). A meta-analysis by Kramer et al[5], which included 8 previously published studies, demonstrated a significant association between being overweight and cardiovascular events. The Whitehall II study[6], an ongoing prospective cohort study,

Table 1. Comparison between studies evaluating the association between metabolic syndrome and cardiovascular disease.

Author/year	No of Individuals	Follow-up (Years)	Findings/Conclusion
Kramer CK/2013 (metanalysis)[5]	66,556		Metabolically healthy obese individuals (relative risk [RR], 1.24; 95% CI, 1.02 to 1.55) had increased risk for events compared with metabolically healthy normal-weight individuals when only studies with 10 or more years of follow-up were considered. All metabolically unhealthy groups had a similarly elevated risk: normal weight (RR, 3.14; CI, 2.36 to 3.93), overweight (RR, 2.70; CI, 2.08 to 3.30), and obese (RR, 2.65; CI, 2.18 to 3.12).
Mørkedal B/ 2014[3]	61,299	12.2	In relation to AMI, obesity without metabolic abnormalities did not confer substantial excess risk (HR = 1.0, 95% CI:0.8–1.2), not even for severe or long-lasting obesity. For HF metabolically healthy obesity was associated with increased risk (HR: 1.7, 95% CI: 1.3–2.3), particularly for long-lasting or severe obesity.
Hinnouho GM/ 2014[6]	7,122	17.4	MHO was at increased risk for CVD (HR = 1.97, 95% CI: 1.38–2.8) and type 2 diabetes (HR = 3.25, 95% CI: 2.32–4.54) when compared to metabolically healthy normal weight individuals. There was excess risk in MUO compared with MHO for type 2 diabetes (HR = 1.98, 95% CI: 1.39–2.83) but not CVD (HR = 1.23, 95% CI: 0.81–1.87).
Chang Y/ 2014[7]	14,828 metabolically healthy	No	MHO individuals had a higher prevalence of coronary calcification than those with normal weight. In multivariable adjusted models, the CAC score ratio comparing MHO to normal weight participants was 2.26 (95% CI 1.48–3.43). In mediation analyses, further adjustment for metabolic risk factors markedly attenuated this association, which was no longer statistically significant (CAC score ratio 1.24, 95% CI 0. 79–1.96). The study suggests that label of metabolically healthy for obese subjects may be an artifact of the cut-off levels used in the definition of metabolic health.

included 7122 participants aged 39-63 years who were enrolled between 1991 and 1993 and followed up for 17.4 years. Cardiovascular diseases risk was comparable between metabolically healthy and unhealthy obese participants, although the risk of type-2 diabetes was lower among MHO compared to MUO.

Another recent study from Korea by Chang and colleagues[7], which involved 14,828 metabolically healthy individuals who took part in a comprehensive regional health-screening program compared coronary calcium scores (CAC) between MHO versus metabolically normal weight participants. Across a series of analyses adjusting for potential confounding variables, the MHO group had a significantly greater prevalence of coronary atherosclerosis compared with the metabolically normal weight group. However following additional adjustment of metabolic risk factors and LDL-C levels, this difference no longer remained significant. The authors concluded obesity even among metabolically healthy individuals is associated with greater prevalence of subclinical CAD. Furthermore, this association appears to be determined by components of metabolic parameters that fell below specific threshold levels. Rush Puri, MD in an accompanying editorial[8] suggested that it is probably time to dispel the concept of metabolically healthy obesity. Finally, the interaction between obesity / metabolic syndrome and cardiovascular risk is further complicated by the dietary "habit" in the community, for example in Norway there is higher consumption of fish which may play a protective role when compared to that in the Middle East, where the high consumption of red meat needs to be studied.

In conclusion, even with these recent studies including that of HUNT-2[3], the association between metabolically healthy obesity cardiovascular disease risks (specifically coronary artery disease) remains controversial and needs further study.

WHAT WE HAVE LEARNED?

Obesity and metabolic syndrome are major public health problems. The incidence of obesity-related metabolic disturbances varies widely among obese individuals. Whether MHO is associated with reduced risk of cardiovascular disease is controversial.

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