Are Metabolically Normal but Obese Individuals at Lower Risk for All-Cause Mortality?

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OBJECTIVE — The clinical relevance of the metabolically normal but obese phenotype for mortality risk is unclear. This study examines the risk for all-cause mortality in metabolically normal and abnormal obese (MNOB and MAOB, respectively) individuals.

RESEARCH DESIGN AND METHODS — The sample included 6,011 men and women from the Third National Health and Nutrition Examination Survey (NHANES III) with public-access mortality data linkage (follow-up = 8.7 ± 0.2 years; 292 deaths). Metabolically abnormal was defined as insulin resistance (IR) or two or more metabolic syndrome (MetSyn) criteria (excluding waist).

RESULTS — A total of 30% of obese subjects had IR, and 38.4% had two or more MetSyn factors, whereas only 6.0% (or 1.6% of the whole population) were free from both IR and all MetSyn factors. By MetSyn factors or IR alone, MNOB subjects (hazard ratio $[HR]_{MetSyn}$ 2.80 [1.18–6.65]; HR_{IR} 2.58 [1.00–6.65]) and MAOB subjects (HR_{MetSyn} 2.74 [1.46–5.15]; HR_{IR} 3.09 [1.55–6.15]) had similar elevations in mortality risk compared with metabolically normal, normal weight subjects.

CONCLUSIONS — Although a rare phenotype, obesity, even in the absence of overt metabolic aberrations, is associated with increased all-cause mortality risk.

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Recent interest has focused on a unique subgroup of obese individuals who are "metabolically normal" (MNOB) despite increased adiposity (1–4). The interpretation of some of these studies is that MNOB subjects are not at increased risk for morbidity and mortality and that obesity treatment is therefore unnecessary. This is in clear contrast with the current U.S. obesity treatment guidelines that suggest that obese individuals should be treated for their obesity, regardless of their cardiovascular (CVD) risk status (5).

The purpose of this study is to examine all-cause mortality risk in "metabolically normal obese" and "metabolically abnormal obese" (MAOB) phenotypes.

RESEARCH DESIGN AND METHODS

— A sample of 6,011 adults (age 18–65 years) from the Third National Health and Nutrition Examination Survey (NHANES III) Public Access Mortality Linkage was used. Age, sex, income, ethnicity, smoking status, exercise frequency, dietary fat (>30%), alcohol intake, intentions to lose weight over the last year (yes/no), and self-reported body weight 10 years prior were assessed by questionnaire. BMI cutoffs for normal weight (18.5–25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2) were used. To increase the sample size (n = 6,011 vs. 3,320), participants with fasting data (≥6 vs. ≥8 h) for at least three of the four MetSyn criteria were included.

Metabolic abnormalities were defined as follows (6,7): *1*) triglycerides ≥1.69 mmol/l or medications; *2*) systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or medications; *3*) glucose ≥5.6 mmol/l or medications; *4*) HDL cholesterol <1.04 mmol/l for men and <1.29 mmol/l for women; and *5*) homeostasis model assessment (HOMA) ≥2.5 (n = 4,602).

Metabolically normal was defined using three separate definitions: *1*) insulin sensitive by HOMA; *2*) one or fewer MetSyn criteria; or *3*) absence of all MetSyn criteria and IR.

Statistical analysis

Cox regression was used to assess risk for all-cause mortality, adjusting for age, sex, income, smoking status, ethnicity, and alcohol. Because of small cell sizes, mortality analyses were limited to metabolically normal definitions 1 and 2. Analyses were performed using SAS version 9.1 or SUDDAN 10.0, weighted to be representative of the U.S. population.

RESULTS

— Within the sample, 25.6% of participants were free from all MetSyn factors and IR, wherein MNOB represented 1.3% of the population and 6.0% of the obese. The proportion of obese who were MNOB by IR alone (30.2%) or had ≤1 MetSyn factor (38.4%) was considerably higher than those with no MetSyn factors (9.4%).

During the 8.7 ± 0.2 year follow-up, there were 292 (5%) deaths. As defined by MetSyn factors, MNOB (hazard ratio [HR] 2.80 [1.18–6.65]) and MAOB (HR 2.74 [1.46–5.15]) were associated with increased mortality risk compared with MNNW (referent) (Figure 1). All IR BMI categories and MNOB were associated with increased mortality risk (MNOB: HR 2.58 [1.00–6.65]; metabolically abnormal normal weight: HR 2.26 [1.19–4.42]; metabolically abnormal overweight: HR 2.44 [1.34–4.42]; MAOB: HR 3.09 [1.55–6.15]).

Regardless of definition, MAOB subjects had a higher BMI and waist than MNOB subjects ($P < 0.05$) but reported similar dietary fat, alcohol consumption, and weight loss intentions ($P > 0.10$). Exercise frequency was significantly lower in IR obese but not by MetSyn factors. MAOB subjects by MetSyn factors, but not IR, were older (7.5 years) and heavier (7.7 kg) 10 years ago.

CONCLUSIONS

— This analysis suggests that a truly metabolically normal obese individual is a rare phenotype, ac-

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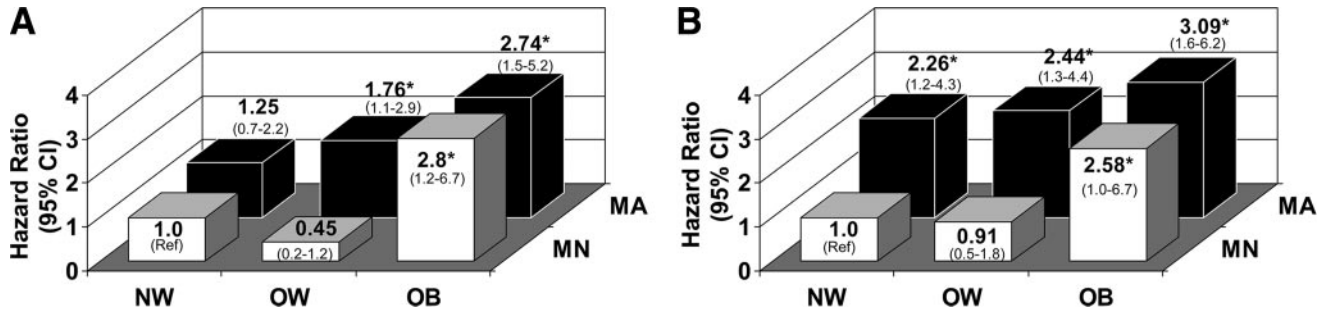

Figure 1—*Relative risk of all-cause mortality by BMI category and metabolic status as defined by MetSyn factors* (A) *and insulin resistance* (B) *criteria. *HR significantly different from MNNW referent* ($P < 0.05$). *Data are adjusted for age, sex, income, ethnicity, smoking status, and alcohol consumption. Metabolically normal (MN) was defined as one or less MetSyn risk factor or HOMA <2.5. MA, metabolically abnormal; NW, normal weight; OB, obese; OW, overweight.*

counting for 1.3% of the U.S. population. Moreover, obese individuals are at higher risk of mortality than their nonobese counterparts, regardless of whether they present with insulin resistance or a clustering of metabolic risk factors.

Previous studies report MNOB subjects to be 11–40% of obese subjects (1,3), whereas we report MNOB subjects to be 6.0–38.4% of obese subjects depending on the definition. We used a more stringent definition with lower clinical cutoffs and a HOMA cutoff of 2.5 that is associated with clamp-measured IR (7) as opposed to an arbitrary 90th percentile cutoff of 5.13. Despite our stricter definition, the true prevalence of MNOB may in fact be lower than the 6.0% that we report, since individuals in negative energy balance typically display metabolic profiles that are better than expected for their level of obesity (8). Because over two-thirds of obese individuals are attempting to lose weight (9), some MNOB subjects may be in negative energy balance. Nevertheless, reported intentions to lose weight were not different between MNOB and MAOB subjects.

The name "metabolically normal" implies MNOB subjects are not at an elevated health risk. For example, Brochu et al. (1) identified a subgroup of MNOB postmenopausal women who were insulin sensitive and questioned the medical urgency to treat these women as they were "metabolically normal." The notion that some obese individuals may not require obesity treatment is in contrast to current U.S. obesity treatment algorithms (5) that recommend overweight individuals with two or more CVD risk factors and *all* obese individuals regardless of their risk profile should be treated. The algorithm defines CVD risk using nonmetabolic (age, smoking, and personal/family CVD history) and metabolic (LDL, HDL, hypertension, and glucose) factors. Although important, many of the nonmetabolic CVD factors cannot be altered. Thus, examination of modifiable metabolic factors may be more clinically relevant and useful.

That MAOB subjects were older and more obese currently and 10 years prior may imply that MNOB subjects have not had sufficiently high levels of obesity, or adequate time for metabolic abnormalities to develop as a consequence of their obesity (10). Alternatively, increased mortality risk could be mediated through both metabolic and nonmetabolic consequences. Obese individuals are more likely to die from traumatic incidences (11) and have cancer diagnosed at more advanced stages than their normal weight counterparts (12). Further, weight bias by some health professionals results in greater reluctance to provide health care—a problem that is compounded by the fact that obese individuals are more likely to avoid seeking health care (13). Regardless of the reasons why MNOB and MAOB subjects are at similarly elevated mortality risk, these findings reinforce the importance of obesity reduction in *all* obese individuals.

In summary, obesity in the absence of metabolic abnormalities is a rare condition. Further, obesity is associated with an increased risk for all-cause mortality, regardless of whether the obese patients present with insulin resistance or a clustering of metabolic risk factors. As such, weight management should continue to be a target for reducing morbidity and mortality in all obese individuals.

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The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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