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

Running Head: Metabolic Profile, Obesity and Mortality Risk

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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).

Research Design and Methods: The sample included 6,011 men and women from NHANES III with public-access mortality data linkage (follow-up = 8.7±0.2 years; 292 deaths). MA was defined as insulin resistance (IR) or ≥2 metabolic syndrome (MetS) criteria (excluding waist).

Results: Thirty percent of obese were IR, and 38.4% had ≥2 MetS factors, whereas only 6.0% (or 1.6% of the whole population) were free from both IR and all MetS factors. By MetS factors or IR alone, MNOB [HR_{MetS}=2.80(1.18-6.65); HR_{IR}=2.58(1.00-6.65)] and MAOB [HR_{MetS}=2.74(1.46-5.15); HR_{IR}=3.09(1.55-6.15)] had similar elevations in mortality risk compared to MNNW.

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

**METHODS**

A sample of 6,011 adults (age: 18 to 65 years) from 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 cut-offs for normal weight (NW: 18.5 to 25 kg.m\(^{-2}\)), overweight (OW: 25 to 29.9 kg.m\(^{-2}\)), and obese (OB: ≥30 kg.m\(^{-2}\)), were used. To increase the sample size (n=6,011 vs. 3,320), participants with fasting data (>6 vs. >8 hours) for at least 3 of the 4 metabolic MetS criteria were included. Metabolic abnormalities were defined as (6, 7):

1. Triglycerides ≥1.69 mM or medications
2. Systolic blood pressure (BP) ≥130 mmHg, diastolic BP ≥85 mmHg or medications
3. Glucose ≥5.6 mM or medications
4. High-density lipoprotein cholesterol (HDL-C) <1.04 mM (men), HDL-C <1.29 mM (women)
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 less MetS criteria, or
3. Absence of all MetS criteria and IR

**Statistical Analyses**: Cox regression was used to assess risk for all-cause mortality, adjusting for age, sex, income, smoking status, ethnicity and alcohol. Due to small cell sizes, mortality analyses were limited to MN definitions #1 and 2. Analyses were performed using SAS v9.1 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 MetS factors and IR, wherein MNOB represented 1.3% of population, and 6.0% of obese. The proportion of obese who were MNOB by IR alone (30.2%) or ≤1 MetS factors (38.4%) was considerably higher than with no MetS factors (9.4%).

During the 8.7±0.2y follow-up there were 292 (5%) deaths. As defined by MetS factors, MNOB [HR=2.80(1.18-6.65)] and MAOB [HR=2.74(1.46-5.15)] were associated with increased mortality risk compared to MNNW (referent) (Figure). All IR BMI categories and MNOB were associated with increased mortality risk [MNOB: HR=2.58(1.00-6.65); MANW: HR=2.26(1.19-4.42); MAOW: HR=2.44(1.34-4.42); MAOB: HR=3.09(1.55-6.15)].

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

**DISCUSSION**

This analysis suggests that a truly metabolically normal obese individual is a rare phenotype, accounting for 1.3% of the U.S. population. Moreover, obese individuals are at higher risk of mortality than their non-obese counterparts regardless of whether they present with insulin resistance or a clustering of metabolic risk factors.

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

The name ‘metabolically normal’ implies MNOB are not at elevated health risk. For example, Brochu and colleagues (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 ≥2 CVD risk factors and all obese individuals regardless of their risk profile should be treated. The algorithm defines CVD risk using non-metabolic (age, smoking and personal/family CVD history) and metabolic factors (LDL, HDL, hypertension and glucose). Although important, many of the non-metabolic CVD factors cannot be altered. Thus, examination of modifiable metabolic factors may be more clinically relevant and useful.

That MAOB were older, more obese currently and 10 years prior may imply that MNOB 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 non-metabolic 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 healthcare (13). Regardless of the reasons as to why MNOB and MAOB are at similarly elevated mortality risk, these findings reinforce the importance of obesity reduction in all obese individuals.

**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 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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Figure Legends

Figure – Relative Risk of All-Cause Mortality by BMI category and Metabolic Status as defined by MetS factors (A) and Insulin resistance (B) criteria

*HR significantly different from MNNW referent (P <0.05). Figures are adjusted for age, sex, income, ethnicity, smoking status, and alcohol consumption. MN was defined as 1 or less MetS risk factors or HOMA < 2.5.