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# Metabolically Healthy Obesity and Risk of Mortality

## Does the definition of metabolic health matter?

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**OBJECTIVE**—To assess the association of a “metabolically healthy obese” phenotype with mortality using five definitions of metabolic health.

**RESEARCH DESIGN AND METHODS**—Adults ( $n = 5,269$ ; 71.7% men) aged 39–62 years in 1991 through 1993 provided data on BMI and metabolic health, defined using data from the Adult Treatment Panel-III (ATP-III); criteria from two studies; and the Matsuda and homeostasis model assessment (HOMA) indices. Cross-classification of BMI categories and metabolic status (healthy/unhealthy) created six groups. Cox proportional hazards regression models were used to analyze associations with all-cause and cardiovascular disease (CVD) mortality during a median follow-up of 17.7 years.

**RESULTS**—A total of 638 individuals (12.1% of the cohort) were obese, of whom 9–41% were metabolically healthy, depending on the definition. Regardless of the definition, compared with metabolically healthy, normal-weight individuals, both the metabolically healthy obese (hazard ratios [HRs] ranged from 1.81 [95% CI 1.16–2.84] for ATP-III to 2.30 [1.13–4.70] for the Matsuda index) and the metabolically abnormal obese (HRs ranged from 1.57 [1.08–2.28] for the Matsuda index to 2.05 [1.44–2.92] for criteria defined in a separate study) had an increased risk of mortality. The only exception was the lack of excess risk using the HOMA criterion for the metabolically healthy obese (1.08; 0.67–1.74). Among the obese, the risk of mortality did not vary as a function of metabolic health apart from when using the HOMA criterion (1.93; 1.15–3.22). Similar results were obtained for cardiovascular mortality.

**CONCLUSIONS**—For most definitions of metabolic health, both metabolically healthy and unhealthy obese patients carry an elevated risk of mortality.

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**O**besity is a major public health problem that has reached epidemic proportions worldwide (1). It is associated with numerous metabolic and cardiovascular disturbances such as insulin resistance, type 2 diabetes, hypertension, and dyslipidemia (2–5). However, these cardiometabolic abnormalities are not found in all obese people (6,7), as evidenced by the occurrence of a subset of apparently healthy obese subjects referred

to as metabolically healthy obese (MHO) (8,9). Several studies have confirmed the existence of MHO individuals (10–16), accounting for as much as 40% of the obese population. MHO individuals display a favorable metabolic profile, characterized by high levels of insulin sensitivity, a low prevalence of hypertension, and a favorable lipid and inflammation profile.

The long-term health consequences of obesity among those who are metabolically

healthy remain unclear. Obesity is known to carry an elevated risk of mortality (17), but few studies have examined associations of the MHO phenotype with mortality, and the evidence from these studies is mixed. In general population samples from Scotland and England, MHO individuals were not at increased risk of all-cause and cardiovascular disease (CVD) mortality compared with healthy nonobese individuals (18), a finding replicated in an Italian study of obesity and insulin sensitivity (19). However, overweight and obese individuals without the metabolic syndrome had an increased risk of mortality compared with normal-weight individuals without the metabolic syndrome in a Swedish cohort of middle-aged men (20). Furthermore, in the U.S. National Health and Nutrition Examination Survey III (21), metabolically healthy and abnormal obese individuals had similar elevations in mortality risk compared with metabolically healthy, normal-weight subjects. Several factors may have contributed to these inconsistencies. The comparison group varies when estimating risk of mortality in the MHO phenotype; risk is compared either with metabolically healthy nonobese (18,19) or metabolically healthy, normal-weight people (20,21). Another difference between the studies is that metabolic health is defined in different ways, with little consensus on how best to define it. Therefore, the objective of the current study is to assess whether there is consistency in the association of the MHO phenotype with all-cause and CVD mortality using different definitions of metabolic health and reference groups.

## RESEARCH DESIGN AND METHODS

### Participants

Data were drawn from the Whitehall II cohort, established in 1985 as a longitudinal study among 10,308 (6,895 male and 3,413 female) U.K. government employees (i.e., civil servants) (22). All civil servants aged 35–55 years in 20 London-based departments were invited

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to participate by letter; 73% agreed. The baseline examination (phase 1) took place from 1985 to 1988 and involved a clinical examination and a self-administered questionnaire. Subsequent phases of data collection alternated between postal questionnaire alone (phases 2 [1988–1990], 4 [1995–1996], 6 [2001], and 8 [2006]) and postal questionnaire accompanied by a clinical examination (phases 3 [1991–1993], 5 [1997–1999], 7 [2002–2004] and 9 [2007–2009]). Data on metabolic factors for the current study were drawn from phase 3, considered the “baseline” for the purpose of these analyses. All participants provided written consent and the University College of London ethics committee approved the study.

### Baseline measurements

**BMI.** With the patients in only underwear, weight was measured to the nearest 0.1 kg on digital Soehnle electronic scales (Leifheit AS, Nassau, Germany). With the participant standing erect in bare feet with the head in the Frankfurt plane, height was measured to the nearest 1 mm using a stadiometer. Reproducibility of measurements over 1 month (correlation coefficient = between-subject variability/[total between + within subject variability]), undertaken for 331 participants, was 0.99 for both weight and height. BMI was calculated by dividing weight (in kilograms) by height (in meters squared) and categorized using the World Health Organization classification (23): underweight, <18.5 kg/m<sup>2</sup>; standard weight, 18.5–24.9 kg/m<sup>2</sup>; overweight, 25–29.9 kg/m<sup>2</sup>; and obese, ≥30 kg/m<sup>2</sup>, with the <18.5 category (*n* = 80) removed from the analysis.

**Metabolic health factors.** We used standard operating protocols to measure the various components to define metabolic status. Blood pressure was measured twice in the sitting position after 5 min of rest with a Hawksley random-zero sphygmomanometer (Lynjay Services Ltd, Worthing, U.K.). The average of the two readings was considered the measured blood pressure. Venous blood was taken in the fasting state or at least 5 h after a light, fat-free breakfast before undergoing a 2-h, 75-g oral glucose tolerance test (OGTT). Serum for lipid analyses was refrigerated at –4°C and assayed within 72 h. HDL-cholesterol (HDL-c) was measured by precipitating non-HDL-c with dextran sulfate–magnesium chloride using a centrifuge and measuring cholesterol in the supernatant. Serum triglyceride was

determined by enzymatic colorimetric method (glycerol-3-phosphate oxidase/phenol and aminophenazone [GPO-PAP]). The concentration of LDL-cholesterol (LDL-c) was calculated using the Friedewald formula when serum triglycerides were lower than 4.5 mmol/L. Blood glucose was measured using the glucose oxidase method (24) (YSI Model 2300 STAT PLUS Analyzer; YSI Corporation, Yellow Springs, OH) (mean coefficient of variation, 2.9–3.3%). Insulin was measured by radioimmunoassay using polyclonal guinea pig antiserum at age 49 years and by double antibody enzyme-linked immunosorbant assay at age 61 years. Homeostasis model assessment (HOMA) of insulin resistance (HOMA-IR) calculation was based on model-derived estimates (rather than linear approximations) using the HOMA2 calculator version 2.2

$$10,000/\sqrt{[(\text{fasting glucose} \times \text{fasting insulin}) \times (\text{mean glucose} \times \text{mean insulin during OGTT})]}$$

(<http://www.dtu.ox.ac.uk/index.php?maindoc=/homa/index.php>, Diabetes Trials Unit, University of Oxford, Oxford, U.K.) (25,26). C-reactive protein (CRP) was measured in serum stored at –80°C using a high-sensitivity immunonephelometric assay in a BN ProSpec nephelometer (Dade Behring, Deerfield, IL). Names of medications as provided by the participants were coded using the British National Formulary to identify antihypertensive and lipid-lowering drugs and medication for diabetes.

**Cross-classification of BMI and metabolic status.** We used five definitions to cross-classify individuals: the Adult Treatment Panel-III (ATP-III) definition of metabolic syndrome (27), Wildman criterion (12), Karelis criterion (28), the OGTT derived from the Matsuda index (13,29) and the HOMA index (11) (Supplementary Table 1).

The ATP-III definition (27) of metabolic normality required individuals to have one or none of the following components (waist circumference criterion was not used because of collinearity with BMI): triglycerides ≥1.7 mmol/L or use of lipid-lowering drugs, systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or use of antihypertensive drugs, glucose ≥5.6 mmol/L or use of medications for diabetes, and HDL-c <1.04 mmol/L for men and <1.29 mmol/L for women.

Participants were considered metabolically healthy by Wildman criterion (12) if they had one or none of the following components: blood pressure ≥130/85 mmHg or use of antihypertensive drugs, triglycerides ≥1.7 mmol/L or use of lipid-lowering drugs, fasting glucose ≥5.6 mmol/L or use of medications for diabetes, HOMA-IR above the 90th percentile among all participants, CRP above the 90th percentile among all participants, and HDL-c <1.3 mmol/L.

Karelis criterion (28) required metabolically healthy subjects to have 4 of 5 of the following components: triglycerides ≤1.7 mmol/L or use of lipid-lowering drugs, HDL-c ≥1.3 mmol/L, LDL-c ≤2.6 mmol/L, HOMA ≤2.7, and CRP ≤3.0 mg/L.

The Matsuda index (13,29) was calculated as follows:

Mean glucose and mean insulin were obtained using the average glucose and insulin levels, respectively, from the OGTT. The Matsuda index was divided into quartiles, and subjects were classified as metabolically healthy if they belonged to the upper quartile of this index (≥186.16 for men and ≥157.68 for women).

The HOMA index (11) was divided into quartiles, and participants were classified as metabolically healthy if they belonged to the three lower quartiles (≤1.70 for men and ≤1.52 for women) of this index.

We used these definitions alongside data on BMI to create six phenotypes: metabolically healthy, normal weight (MH-NW); metabolically healthy overweight; MHO; metabolically abnormal, normal weight; metabolically abnormal overweight; and metabolically abnormal obese (MAO).

**Covariates.** Sociodemographic covariates included age, sex, occupational position, ethnicity (white vs. nonwhite), and marital status (single, married/cohabiting, divorced, widowed). Occupational position is a three-level variable representing high (administrative), intermediate (professional or executive), and low (clerical or support) grades. This measure is a comprehensive marker of socioeconomic circumstances and is related to salary, social status, and level of responsibility at work (22). Behavioral measures included smoking status (never, current, or ex-smoker);

alcohol intake (assessed via questions about the number of alcoholic drinks consumed in the past 7 days and categorized as no alcohol [none or <1 unit/week], moderate drinker [1–14 units/week for women and 1–21 units/week for men], heavy drinker [>14 units for women and >21 units for men]); physical activity (categorized as active [ $\geq 2.5$  h/week of moderate or  $\geq 1$  h/week of vigorous physical activity], inactive [ $< 1$  h/week of moderate and  $< 1$  h/week of vigorous physical activity], or moderately active [not active or inactive]); and consumption of fruits and vegetables (assessed using the question, “How often do you eat fresh fruits or vegetables?”; responses were given on a two-point scale:  $\geq 1$  fruit or vegetable/day, or  $< 1$  fruit or vegetable/day). Missing data on covariates during phase 3 (1991–1993;  $< 1\%$ ) were replaced with data from the phase immediately before or after that phase.

### Mortality follow-up

Study members are linked to the National Health Services death and electronic patient records with the use of a National Health Services identification number. A total of 10,297 participants (99.9%) were traced successfully and have been followed through these registers. Mortality data, which included the cause of death, were available through the National Health Services Central Registry until 31 January 2010. We also examined CVD mortality (ICD-9: 390.0–458.9; ICD-10: I00–I99).

### Statistical analysis

Analyses were undertaken using STATA 11 software. The characteristics of the sample are presented as mean  $\pm$  SD or percentage, as appropriate, by BMI category and for the obese as a function of metabolic health using the ATP-III definition. We used ANOVA to test for differences in baseline characteristics between groups for continuous variables and the  $\chi^2$  test for dichotomous measures.

Cox proportional-hazard regression models with follow-up period as the time scale were used to examine the relationship between BMI category/metabolic phenotypes (using the five definitions mentioned earlier) and mortality. The proportional hazards assumptions were confirmed by Schoenfeld tests. The analytic sample comprised 331 South Asian and 200 black participants. The interaction term between ethnicity and BMI/metabolic status phenotypes suggested no differences across ethnic groups ( $P$  for interaction

$\geq 0.10$  and  $\leq 0.56$ ). Similarly, the interaction term for sex revealed no differences between men and women ( $P$  for interaction  $\geq 0.11$  and  $\leq 0.59$ ). This allowed us to combine ethnic groups and men and women in the analysis. In the first set of analyses, we used the MH-NW category as the reference. Hazard ratios (HRs) and 95% CIs were adjusted sequentially for age and sex (data not shown) and then adjusted further for occupational position, ethnicity, marital status, smoking status, alcohol intake, physical activity, and fruit and vegetable consumption. We then ran a second set of analyses, stratified by BMI category, to allow us to compare the risk of mortality as a function of metabolic health status in each strata of BMI. The metabolically healthy group within each BMI category was the reference in these analyses. Both sets of analyses were repeated with CVD mortality as the outcome.

In sensitivity analyses we repeated the analyses after replacing occupational position with education and excluding all deaths that occurred in the first 5 years of follow-up to take into account possible effects of reverse causation as an explanation of our findings. We also replicated analyses using absolute rates of mortality and finally using non-CVD mortality as an outcome.

**RESULTS**—A total of 8,223 participants attended the clinical examination at baseline, when BMI and metabolic factors were assessed; 5,269 of these individuals had data on all the components necessary for analysis of body size phenotypes. The participants included in the analytic sample ( $n = 5,269$ ) compared with those who were excluded were more likely to be men (71.7% vs. 64.9%;  $P < 0.001$ ), obese (12.1% vs. 5.4%;  $P < 0.001$ ), and married or cohabiting (77.5% vs. 75.2%;  $P = 0.001$ ). They were less likely to be current smokers (12.3% vs. 16.1%;  $P < 0.001$ ) and to have a higher occupational position (37.4% vs. 39.9%;  $P = 0.003$ ). Although these differences were statistically significant because of the large sample size, the absolute differences were small in general.

Baseline characteristics of participants included in the analysis are presented in Table 1. A total of 44.8% of the participants were normal weight, 43.1% were overweight, and 12.1% were obese. Triglycerides, fasting glucose, 2-h glucose level, fasting insulin, blood pressure,

CRP, and HOMA-IR were higher in MAO than in MHO participants ( $P < 0.001$  for all these components), whereas HDL-c was higher in MHO than in MAO participants using the ATP-III definition.

Supplementary Table 2 shows the prevalence of the six phenotypes created using the five definitions. Among obese participants, 236 (37.%) were classified as metabolically healthy by the ATP-III definition (27), 146 (22.9%) by the Wildman criteria (12), 119 (18.7%) by the Karelis criteria (28), 57 (9.0%) by the Matsuda index (13,29) and 260 (40.8%) using the HOMA index (11). In the entire analytic sample, using the various definitions, the prevalences of the MHO phenotype are 4.5% (ATP-III), 2.8% (Wildman), 2.3% (Karelis), 1.1% (Matsuda), and 4.9% (HOMA).

During the median follow-up of 17.7 years, 413 deaths occurred (7.8% of the total population): 76 deaths (11.9%) were among obese, 175 (7.7%) among overweight, and 162 (6.9%) among normal-weight participants. Among the 126 CVD deaths, 44 (34.9%) were among normal-weight individuals, 58 (46.0%) among overweight, and 24 (19.1%) among obese individuals.

Table 2 shows the associations of BMI categories and metabolic health factors with all-cause and CVD mortality. Compared with normal-weight individuals, the obese (HR 1.68 [95% CI 1.27–2.22]) but not the overweight (1.01 [0.82–1.26]) had an increased risk of mortality. All ATP-III (27) components and all components of the Wildman criterion (12), the HOMA index (11), and CRP as defined by Karelis (28) were associated with an increased risk of mortality, whereas the Matsuda index (13,29), LDL-c, and HOMA as defined by Karelis (28) were not. Results for CVD mortality were similar.

Table 3 depicts the associations between the six BMI/metabolic categories and all-cause and CVD mortality with the MH-NW group as the reference. The MHO group did not have an increased risk of all-cause and CVD mortality, whatever the definition of metabolic health, but the MHO group had a greater risk of death (all-cause mortality) for all definitions except for the HOMA index (HR 1.08 [95% CI 0.67–1.74]). The mortality hazard in the MAO group was higher compared with the MH-NW group, whatever the definition of metabolic abnormality. Similar results were obtained for CVD

Table 1—Sample characteristics at baseline (1991–1993) as a function of BMI

| Characteristics at baseline                | BMI (kg/m <sup>2</sup> )                 |                                            |                                                  | P value |
|--------------------------------------------|------------------------------------------|--------------------------------------------|--------------------------------------------------|---------|
|                                            | Normal<br>(18.5–24.9 kg/m <sup>2</sup> ) | Overweight<br>(25–29.9 kg/m <sup>2</sup> ) | Obese (≥30 kg/m <sup>2</sup> )<br>MHO*      MAO* |         |
| N (%)                                      | 2,362 (44.8)                             | 2,269 (43.1)                               | 236 (4.5)      402 (7.6)                         |         |
| Male, %                                    | 73.2                                     | 75.1                                       | 38.1      62.7                                   | <0.001  |
| Age (years)                                | 49.2 (6.1)                               | 50.1 (6.0)                                 | 49.5 (5.8)      50.2 (5.9)                       | <0.0001 |
| White, %                                   | 89.9                                     | 88.1                                       | 83.9      88.8                                   | 0.02    |
| Married/cohabiting, %                      | 77.1                                     | 79.5                                       | 69.1      74.1                                   | <0.001  |
| Occupational grade, %                      | 44.9                                     | 45.9                                       | 44.1      44.8                                   | <0.001  |
| Current smoker, %                          | 12.1                                     | 12.2                                       | 13.6      13.4                                   | <0.001  |
| Moderate drinker, %                        | 66.2                                     | 63.4                                       | 54.7      58.9                                   | <0.001  |
| Physically active, %                       | 45.3                                     | 43.3                                       | 33.05      38.8                                  | <0.001  |
| ≥1 Serving of fruits vegetables per day, % | 62.0                                     | 57.9                                       | 68.6      53.7                                   | <0.001  |
| Triglycerides (mmol/L)                     | 1.3 (0.9)                                | 1.7 (1.1)                                  | 1.2 (0.5)      2.5 (1.7)                         | <0.0001 |
| LDL-c (mmol/L)                             | 4.3 (1.0)                                | 4.6 (1.1)                                  | 4.4 (1.1)      4.6 (1.0)                         | <0.0001 |
| HDL-c (mmol/L)                             | 1.5 (0.4)                                | 1.3 (0.4)                                  | 1.5 (0.3)      1.2 (0.3)                         | <0.0001 |
| Fasting glucose (mmol/L)                   | 5.2 (0.6)                                | 5.3 (0.7)                                  | 5.1 (0.4)      5.7 (1.2)                         | <0.0001 |
| 2-h Glucose level (mmol/L)                 | 5.5 (1.8)                                | 5.7 (2.0)                                  | 5.8 (1.7)      6.8 (3.0)                         | <0.0001 |
| Fasting insulin (μUI/mL)                   | 6.3 (3.3)                                | 8.6 (5.4)                                  | 10.1 (5.8)      15.3 (9.6)                       | <0.0001 |
| HOMA-IR                                    | 0.7 (0.4)                                | 1.0 (0.6)                                  | 1.1 (0.6)      1.7 (1.1)                         | <0.0001 |
| CRP (mg/L)                                 | 1.8 (6.3)                                | 2.0 (3.0)                                  | 3.2 (3.7)      4.1 (4.4)                         | <0.0001 |
| Systolic blood pressure (mmHg)             | 119.1 (13.7)                             | 123.1 (12.9)                               | 121.9 (13.5)      130.7 (12.7)                   | <0.0001 |
| Diastolic blood pressure (mmHg)            | 78.4 (9.0)                               | 82.3 (8.8)                                 | 81.1 (9.3)      87.2 (8.9)                       | <0.0001 |

Values are mean (SD) unless otherwise indicated. \*MHO and MAO defined using the ATP-III.

mortality. Analyses using absolute rates, using deaths per 1,000 person-years (Supplementary Table 3), excluding deaths in the first 5 years ( $n = 63$ ) of follow-up (Supplementary Table 4), using non-CVD mortality as an outcome (Supplementary Table 5), and adding menopausal status as a covariate (data not shown) yielded similar results to those reported in Table 3.

Figure 1 and Supplementary Fig. 1 present HRs for all-cause and CVD mortality as a function of metabolic health in an analysis stratified by BMI category. Compared with their metabolically healthy counterparts, the metabolically abnormal normal-weight and overweight individuals had higher all-cause mortality risk using the ATP III definition (27). This was not the case among the obese, in whom greater mortality risk—both all-cause and CVD mortality—was observed among the metabolically abnormal compared with metabolically healthy individuals using only the HOMA index criterion (11) (HR 1.93 [95% CI 1.15–3.24] for all-cause mortality). The results for CVD mortality (Supplementary Fig. 1) were largely similar to those found for all-cause mortality, albeit with wider CIs due to the small number of deaths from CVD.

**CONCLUSIONS**—This study assessed the association of five different definitions of the MHO phenotype with all-cause and CVD mortality. Our results show that 9–41% of the obese population qualify as being metabolically healthy, depending on the method used to ascertain metabolic health. In relation to four of the five definitions, both MHO and MAO participants had an elevated risk of mortality compared with MH-NW individuals. The metabolically healthy overweight individuals were not at increased risk of mortality regardless of the methods used; however, this was not the case for the metabolically abnormal overweight individuals. Our results show that obese individuals, irrespective of their metabolic status, carry an excess risk of mortality.

Direct comparison of our results with other studies is made difficult by the use of a different reference group to assess risk (18); often the reference group combines the normal and overweight individuals or uses a different definition of metabolic health status (21). No previous study has compared a range of definitions of metabolic status within the sample analytic framework. Arnlov et al. (20), using the National Cholesterol Education Program criteria, and Kuk and Ardern (21), using insulin resistance by HOMA and

the MetSyn criteria, also found an increased risk for all-cause mortality when comparing MHO to MH-NW individuals. However, Calori et al. (19), who estimated insulin resistance using HOMA (insulin sensitive <2.5; insulin resistant ≥2.5), and Hamer and Stamatakis (18), who used a definition based on blood pressure, HDL-c, diabetes diagnosis, waist circumference, and low-grade inflammation, did not find greater risk of all-cause and CVD mortality in MHO compared with metabolically healthy nonobese individuals. In our study the MHO group did not carry excess risk of mortality compared with the MH-NW group only when using the HOMA index (11) to assess metabolic status. This implies that four of the five definitions used in this article show the risk of mortality in MHO individuals to be higher than MH-NW and similar to MAO individuals. The HOMA index is a measure of pancreatic  $\beta$ -cell function, whereas the Matsuda index is a composite measure of hepatic and muscle insulin sensitivity. Our results suggest that the HOMA index might be particularly useful in distinguishing obese individuals at a greater risk of mortality.

We used a range of methods, based on insulin resistance and clustering of metabolic abnormalities, to better understand

**Table 2—The association of individual risk factors used to define metabolic health with all-cause and CVD mortality**

|                                               | All-cause mortality | CVD mortality     |
|-----------------------------------------------|---------------------|-------------------|
| <b>BMI</b>                                    |                     |                   |
| Normal weight                                 | 1.0 (reference)     | 1.0 (reference)   |
| Overweight                                    | 1.01 (0.82–1.26)    | 1.24 (0.84–1.84)  |
| Obese                                         | 1.68 (1.27–2.22)    | 2.15 (1.29–3.59)  |
| <b>ATP-III components</b>                     |                     |                   |
| Triglycerides ≥1.7 mmol/L or medication       | 1.37 (1.12–1.67)    | 1.51 (1.06–2.16)  |
| Blood pressure ≥130/85 mmHg or medication     | 1.41 (1.16–1.72)    | 2.07 (1.42–3.03)  |
| Fasting glucose ≥5.6 mmol/L or medication     | 1.22 (1.00–1.51)    | 1.30 (0.90–1.89)  |
| HDL-c <1.03 mmol/L, men (<1.29 mmol/L, women) | 1.59 (1.29–1.97)    | 2.30 (1.60–3.30)  |
| <b>Wildman criteria</b>                       |                     |                   |
| HDL-c <1.3 mmol/L                             | 1.28 (1.04–1.57)    | 1.49 (1.02–2.17)  |
| HOMA >90th percentile                         | 1.61 (1.23–2.10)    | 1.89 (1.19–2.98)  |
| CRP >90th percentile                          | 1.86 (1.45–2.38)    | 2.12 (1.37–3.26)  |
| <b>Karelis criteria</b>                       |                     |                   |
| LDL-c >2.6 mmol/L                             | 0.95 (0.47–1.93)    | 2.09 (0.29–15.11) |
| CRP >3.0 mg/L                                 | 1.44 (1.15–1.81)    | 1.62 (1.08–2.42)  |
| HOMA >2.7                                     | 1.38 (0.79–2.40)    | 1.67 (0.68–4.10)  |
| Matsuda index                                 | 1.12 (0.88–1.43)    | 1.30 (0.81–2.09)  |
| HOMA index, AU                                | 1.43 (1.16–1.76)    | 1.26 (0.87–1.84)  |

Values shown as HR (95% CI). Analyses are adjusted for age, sex, occupational position, physical activity, smoking, alcohol, fruit and vegetable consumption, marital status, and ethnicity.

the MHO phenotype. The five methods did not identify the same subgroups of individuals; only 23 subjects (3.6%) among the obese are classified as MHO using all five definitions. Taking the results obtained for the obese and the overweight

phenotypes, our results suggest that criteria for metabolic health status using established cut-offs like those in the ATP-III criterion (27) are more reasonable because the threshold for risk has been validated on multiple occasions.

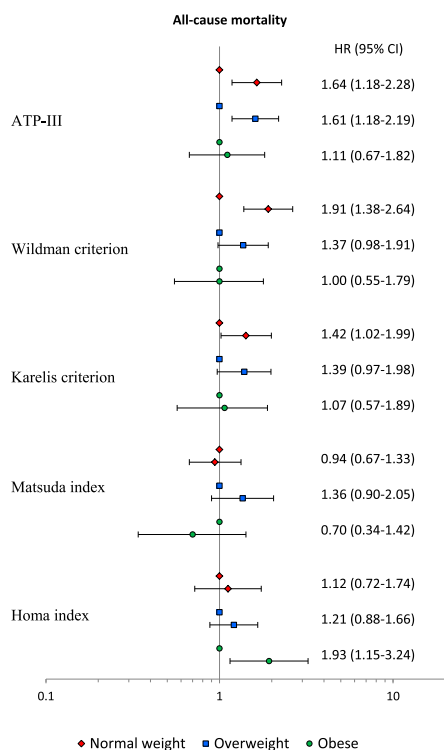
However, criteria that are based on risk distribution (percentile), as the Matsuda (13,29) or HOMA indices (11), lead to less consistent results across studies. This is principally because the distribution of risk is likely to vary among different populations (obese, clinical, as a function of age, or even in the general population), and a threshold such as the top quartile may not translate well across populations. To examine obesity phenotypes we constructed six groups: metabolically healthy or metabolically abnormal normal weight, metabolically healthy or metabolically abnormal overweight, and metabolically healthy or metabolically abnormal obese, as has been done previously (20,21). This is in contrast to other studies that used only four groups: nonobese metabolically healthy or unhealthy and obese metabolically healthy or unhealthy (18,19), making the assumption that normal weight and overweight individuals have the same risk. We preferred to test this assumption and, as the results show, there is little difference between the normal weight and overweight groups. So, for mortality risk, the analyses could have been based on four categories of BMI/metabolic health phenotypes.

In analyses comparing individuals within the same BMI category and using the metabolically healthy as the reference group, we found that in normal and overweight groups metabolic abnormality carried some excess risk when the criteria for metabolic health were ATP-III (27),

**Table 3—The association of BMI/metabolic health status with all-cause and CVD mortality**

|                            | Definitions of metabolic health |                  |                  |                  |                  |
|----------------------------|---------------------------------|------------------|------------------|------------------|------------------|
|                            | ATP-III (27)                    | Wildman (12)     | Karelis (28)     | Matsuda (13,29)  | HOMA (11)        |
| <b>All-cause mortality</b> |                                 |                  |                  |                  |                  |
| MH-NW*                     | 1.0                             | 1.0              | 1.0              | 1.0              | 1.0              |
| MH-OW                      | 0.94 (0.69–1.27)                | 1.12 (0.79–1.59) | 0.98 (0.66–1.44) | 0.77 (0.49–1.22) | 0.96 (0.77–1.24) |
| MHO                        | 1.81 (1.16–2.84)                | 2.11 (1.21–3.67) | 1.86 (1.02–3.41) | 2.30 (1.13–4.70) | 1.08 (0.67–1.74) |
| MA-NW                      | 1.63 (1.18–2.25)                | 1.86 (1.35–2.54) | 1.41 (1.02–1.95) | 0.96 (0.69–1.35) | 1.12 (0.72–1.74) |
| MA-OW                      | 1.47 (1.11–1.95)                | 1.51 (1.12–2.03) | 1.34 (0.99–1.82) | 1.04 (0.75–1.44) | 1.17 (0.87–1.59) |
| MAO                        | 2.01 (1.43–2.83)                | 2.23 (1.58–3.15) | 2.05 (1.44–2.92) | 1.57 (1.08–2.28) | 2.14 (1.56–2.94) |
| <b>CVD mortality</b>       |                                 |                  |                  |                  |                  |
| MH-NW*                     | 1.0                             | 1.0              | 1.0              | 1.0              | 1.0              |
| MH-OW                      | 1.03 (0.55–1.91)                | 1.43 (0.70–2.90) | 1.26 (0.61–2.59) | 0.46 (0.17–1.28) | 1.16 (0.74–1.80) |
| MHO                        | 2.49 (1.05–5.91)                | 2.05 (0.58–7.21) | 1.26 (0.29–5.56) | 1.89 (0.43–8.33) | 1.04 (0.41–2.66) |
| MA-NW                      | 2.11 (1.16–3.84)                | 2.34 (1.26–4.35) | 1.33 (0.71–2.48) | 0.74 (0.39–1.40) | 0.54 (0.19–1.52) |
| MA-OW                      | 2.30 (1.37–3.88)                | 2.24 (1.25–4.00) | 1.55 (0.87–2.78) | 1.14 (0.64–2.05) | 1.15 (0.66–1.99) |
| MAO                        | 2.94 (1.56–5.56)                | 3.57 (1.85–6.89) | 2.75 (1.44–5.28) | 1.75 (0.89–3.41) | 2.63 (1.51–4.60) |

Values are shown as HR (95% CI). Analyses are adjusted for age, sex, occupational grade, physical activity, smoking, alcohol, fruit and vegetable consumption, marital status, and ethnicity. MA-NW, metabolically abnormal, normal weight; MA-OW, metabolically abnormal, overweight; MH-OW, metabolically healthy, overweight. \*MH-NW is the reference category.



**Figure 1**—Association of abnormal metabolic health status with all-cause mortality in analyses stratified by BMI categories. Analyses adjusted for age, sex, occupational position, physical activity, smoking, alcohol, fruit and vegetable consumption, marital status, and ethnicity.

Wildman (12), or Karelis (28), but no excess risk was observed for the Matsuda (13,29) or the HOMA indices (11). In the obese group, the risk of mortality did not differ as a function of metabolic health except for that based on the HOMA index (11). These results can be understood in light of results showing a favorable metabolic profile for a range of measures when the HOMA index was used to identify MHO individuals (15). The study in question compared different methods (hyperinsulinemic-euglycemic clamp, Matsuda index, HOMA index, Karelis and Wildman criteria) to identify MHO individuals; those identified using the HOMA index had lower levels of BMI, central fat mass, fasting glucose, and insulin. This suggests that the HOMA index might be a more efficient measure of health status in the obese population.

Given the obesity epidemic, a better understanding of the extent to which the MHO phenotype carries risks for health is important. Identifying mechanisms of this favorable metabolic profile would improve the treatment of obese patients

to reduce cardiometabolic risk (16). The mechanisms underlying the favorable metabolic profile of MHO individuals remain unclear. It has been suggested that adipose cell size could be a link between obesity and insulin resistance. Comparing the size of adipose cells between MHO and MAO individuals, McLaughlin et al. (30) found that the MAO group had a higher proportion of small adipose cells, which were seen to have adverse effects, compared with MHO individuals. Meigs et al. (11) reported that MHO individuals also had a lower amount of visceral fat content. There is some evidence to suggest that MHO people might be less responsive to lifestyle interventions for improvement of insulin sensitivity (31,32), but these findings are based on small-scale studies. Our findings and those of several other studies (20,21) suggest that the adverse effects of obesity on survival cannot be eliminated by targeting only metabolic health.

The main strengths of this study include the large sample size and the nearly 18-year follow-up for mortality. We also were able to replicate the findings for CVD mortality. Furthermore, to our knowledge, this is the first study that evaluated the risk of all-cause and CVD mortality associated with BMI/metabolic phenotypes using five different definitions to identify the MHO phenotype that have been published. We adjusted for several covariates, including occupational position, ethnic group, alcohol consumption, marital status, physical activity, smoking, and dietary behavior, which allowed us to minimize the potential for confounding by these factors. Replacing occupational position with education in the analysis did not change the results. The most important limitation of the study is that participants of the Whitehall II study are mainly office-based civil servants and are not fully representative of the British population because the study does not include unemployed or individuals in “blue-collar” professions. However, they cover a wide socioeconomic range, with >10-fold difference between the highest and lowest salaries. Another limitation is the lack of ethnic diversity in the study sample, although tests suggested no heterogeneity in associations as a function of ethnicity, which could be due to the limited sample size of racial/ethnic minorities. We were unable to assess the change in metabolic status during the follow-up period; it is possible that some participants who were healthy

at baseline developed metabolic risk factors.

Our study focuses on mortality as an outcome, but findings for morbidity are mixed. One study showed MHO to have a cardiovascular risk profile between that of healthy nonobese and MAO (33). A longitudinal study (11) showed that the MHO phenotype was associated with a reduced risk of developing CVD, whereas others studies have shown that obese individuals without metabolic syndrome had an increased risk for cardiovascular events (20). Further large-scale studies are required to assess the impact of the MHO phenotype on morbidity related to obesity for example, CVD, cancers, respiratory diseases, and depression.

In summary, our data suggest that the MHO phenotype exists even though there are large variations in prevalence rates as a function of criteria used to define this phenotype. However, MHO individuals do not seem to be at a lower risk for all-cause and CVD mortality compared with MH-NW individuals—in effect their risk of mortality was similar to that of the MAO group. This risk was independent of the definition used except for the HOMA index, for which MHO did not carry excess risk. Our analyses suggest that thresholds to define metabolic health elaborated on the basis of the distribution of the risk factor may not be useful because they cannot be generalized across populations.

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G.-M.H. performed statistical analyses and drafted the manuscript. S.C. and A.S.-M. contributed to the interpretation of results and revised the manuscript. A.D. helped with the statistical analyses. G.D.B. and M.K. edited and reviewed the manuscript. G.-M.H. is the guarantor of this work and, as such, had full access to all the data in the study and takes

responsibility for the integrity of the data and the accuracy of the data analysis.

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