# Are Metabolically Healthy Overweight and Obesity Benign Conditions?

## A Systematic Review and Meta-analysis

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**Background:** Recent interest has focused on a unique subgroup of overweight and obese individuals who have normal metabolic features despite increased adiposity. Normal-weight individuals with adverse metabolic status have also been described. However, it remains unclear whether metabolic phenotype modifies the morbidity and mortality associated with higher body mass index (BMI).

**Purpose:** To determine the effect of metabolic status on all-cause mortality and cardiovascular events in normal-weight, overweight, and obese persons.

**Data Sources:** Studies were identified from electronic databases.

**Study Selection:** Included studies evaluated all-cause mortality or cardiovascular events (or both) and clinical characteristics of 6 patient groups defined by BMI category (normal weight/overweight/obesity) and metabolic status (healthy/unhealthy), as defined by the presence or absence of components of the metabolic syndrome by Adult Treatment Panel III or International Diabetes Federation criteria.

**Data Extraction:** Two independent reviewers extracted the data. Metabolically healthy people of normal weight made up the reference group.

**Data Synthesis:** Eight studies ($n$ = 61 386; 3988 events) evaluated participants for all-cause mortality and/or cardiovascular events. 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).

**Limitation:** Duration of exposure to the metabolic–BMI phenotypes was not described in the studies and could partially affect the estimates.

**Conclusion:** Compared with metabolically healthy normal-weight individuals, obese persons are at increased risk for adverse long-term outcomes even in the absence of metabolic abnormalities, suggesting that there is no healthy pattern of increased weight.

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Increased body mass index (BMI), particularly in the range classified as obesity (BMI ≥30 kg/m$^2$), has been associated with excess mortality risk (1–3). Recently, a meta-analysis of 2.88 million individuals found that grade 2 to 3 obesity (BMI ≥35 kg/m$^2$) was associated with higher all-cause mortality but that, paradoxically, overweight (BMI, 25 to 30 kg/m$^2$) was associated with lower all-cause mortality than normal weight (BMI, 18.5 to 25 kg/m$^2$) (4). These data highlight the complexity of the relationship between weight and mortality and suggest that additional factors, possibly metabolic, may affect the risk for death within BMI categories.

It is well recognized that individuals in the same BMI category can have substantial heterogeneity of metabolic features, such as lipid profile, glucose tolerance, blood pressure, and waist circumference. In this context, recent interest has focused on a unique subgroup of obese individuals with normal metabolic features despite their increased adiposity, a profile that has been described as "benign obesity" or "metabolically healthy obesity." Similarly, a subgroup of normal-weight individuals with adverse metabolic status has also been described (5–7). Previous reports on the effect of these metabolic–BMI phenotypes on morbidity and mortality have yielded contradictory results (8–10). In addition, the data from these individual studies might not be sufficient to demonstrate a possible differential risk for morbidity and death conferred by these phenotypes, which could hold important implications for targeted preventive strategies in practice. Thus, we conducted a systematic review and meta-analysis of observational studies to determine 1) the effect of metabolic status on risk for all-cause mortality and cardiovascular events in normal-weight, overweight, and obese persons and 2) the clinical characteristics of these metabolic–BMI phenotypes.

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## Methods

This systematic review and meta-analysis is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology guidelines (11) and is registered with the International Prospective Register of Systematic Reviews (CRD42013003607). The researchers are experienced in meta-analysis (12–18).

### Data Sources and Searches

We selected relevant studies published between 1950 and 5 June 2013. We searched Embase, PubMed, and abstracts from the 2011 and 2012 meetings of the Endocrine Society and the European Society of Endocrinology.

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The following combined text and Medical Subject Heading (MeSH) terms were used: *body mass index, overweight, obesity and metabolic syndrome*. The complete PubMed search was as follows: (("body mass index"[MeSH Terms] OR body mass index[Text Word]) OR ("overweight"[MeSH Terms] OR overweight[Text Word]) OR ("obesity"[MeSH Terms] OR obesity[Text Word])) AND (metabolic[All Fields] AND ("syndrome"[MeSH Terms] OR syndrome [Text Word])) AND ("mortality"[MeSH Terms] OR "survival rate" [Mesh Term] OR "cause of death" [Mesh Term]) OR (("Obesity"[Mesh]) AND benign [text]) OR (metabolically benign)). All potentially eligible studies were considered for review, regardless of primary outcome or language. A manual search was also performed by using references of key articles published in English.

### Study Selection

Studies were considered eligible if they were conducted in adults; presented original prospective or cross-sectional data; evaluated participants according to 3 categories of BMI, defined as normal weight (BMI ≥18 and <25 kg/m$^2$), overweight (BMI ≥25.0 and <30 kg/m$^2$), and obesity (BMI ≥30 kg/m$^2$); evaluated participants within these BMI categories according to metabolic status (healthy/unhealthy); and reported all-cause mortality, fatal or nonfatal cardiovascular (CV) events, baseline characteristics, or all of these. As shown in **Table 1**, the classification of participants in these studies as metabolically unhealthy was based on the presence of metabolic syndrome components by criteria from the Adult Treatment Panel III (waist circumference >88 cm; fasting triglyceride level >1.69 mmol/L [>150 mg/dL]; high-density-lipoprotein [HDL] cholesterol level <1.29 mmol/L [<50 mg/dL]; systolic blood pressure >130 mm Hg, diastolic blood pressure >85 mm Hg, or use of antihypertensive medication; fasting glucose level ≥6.1 mmol/L [≥110 mg/dL]) (19) or International Diabetes Federation (waist circumference ≥94 cm in men or ≥80 cm in women; fasting triglyceride level >1.69 mmol/L [≥150 mg/dL]; HDL cholesterol level <1.04 mmol/L [<40 mg/dL] in men or <1.29 mmol/L [<50 mg/dL] in women; systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg, antihypertensive medication, or history of hypertension; fasting glucose level ≥5.6 mmol/L [≥100 mg/dL] or glucose-lowering medication) (20). In addition, 2 studies (5, 21) assessed insulin resistance and inflammatory markers as part of the definition of metabolic status. Fatal and nonfatal CV events were defined as death due to CV disease or one of the following: myocardial infarction, the acute coronary syndrome, hospitalization for unstable angina or coronary catheterization that resulted in angioplasty or coronary artery bypass surgery, congestive heart failure, stroke, transient ischemic attack, and claudication.

We compared the number of events in individuals who were metabolically healthy and overweight, metabolically healthy and obese, metabolically unhealthy and normal weight, metabolically unhealthy and overweight, and metabolically unhealthy and obese (5 exposure groups) with the number of events in metabolically healthy people of normal weight (control group). We excluded studies that were retrospective, evaluated participants by using different thresholds for BMI categories, did not stratify participants into the preceding 6 groups, and did not provide any source of absolute number of events per group.

### Data Extraction and Quality Assessment

Two independent investigators reviewed study titles and abstracts. Studies that satisfied the inclusion criteria were retrieved for full-text evaluation. Studies selected for detailed analysis by these 2 investigators had an agreement value ($\kappa$) of 97%; the third investigator resolved disagreements.

Extracted data included clinical characteristics of participants, study design, duration of follow-up, and the number of participants who had an event according to BMI categories and metabolic status. Numerical data appearing in the articles were used. In the few studies that did not report these data, risk estimates were calculated from the survival curves. Unadjusted estimates were extracted, enabling inclusion of the maximum number of studies. Authors of studies with specific information missing were contacted by e-mail.

The Newcastle–Ottawa Scale (NOS) for assessing quality of nonrandomized studies in meta-analysis was applied (22). The NOS contains 8 items categorized into 3 domains (selection, comparability, and exposure). For each item, a series of response options is provided. A star system is used to enable semi-quantitative assessment of study quality, such that the highest-quality studies are awarded a maximum of 1 star per item; the exception is the comparability domain, which allows the assignment of 2 stars. As such, the NOS ranges from 0 to 9 stars (23).

### Data Synthesis and Analysis

An overall relative risk (RR) was calculated to assess the risk for all-cause mortality or CV events (fatal and nonfatal). The risk for events among metabolically healthy overweight, metabolically healthy obese, metabolically unhealthy normal-weight, metabolically unhealthy overweight, and metabolically unhealthy obese individuals was determined in comparison with risk among metabolically healthy normal-weight people. In addition, baseline clinical characteristics were compared (waist circumference, systolic and diastolic blood pressure, HDL lipoprotein cholesterol level, low-density lipoprotein [LDL] cholesterol level, triglyceride level, glucose level, and Homeostasis Model Assessment of Insulin Resistance score [24]).

We calculated pooled estimates of the RR risk by using a random-effects model (profile likelihood method). The likelihood approach with random effects was used to better account for the imprecision in the estimate of between-study variance (25). The Cochran *Q* test was used



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*Table 1.* **Characteristics of Included Studies**

| Study, Year (Reference) | Sample Size | Baseline CVD | Mean Age, *y* | Men, % |
|---|---|---|---|---|
| Kip et al, 2004 (47) | 780 women referred for coronary angiography for suspected myocardial ischemia | 37% with previous CVD | 58 | 0 |
| Meigs et al, 2006 (8) | 2902 participants without diabetes or CVD | None | 53 | 45 |
| Song et al, 2007 (48) | 25 626 women aged ≥45 y without diabetes or CVD (Women's Health Study) | None | 55 | 0 |
| Wildman et al, 2008 (5) | 5440 participants of NHANES 1999–2004 | None | 45 | 47.9 |
| Kuk and Ardern, 2009 (49) | 6011 participants of NHANES | 20% with previous CVD | 45 | 48 |
| Arnlöv et al, 2010 (9) | 1758 men without diabetes at age 50 y | None | 49.7 | 100 |
| Hosseinpanah et al, 2011 (50) | 6215 participants aged ≥30 y without CVD | None | 47.5 | 43.1 |
| Lind et al, 2011 (51) | 985 participants aged 70 y | 10% with previous CVD | 70 | 52 |
| Pajunem et al, 2011 (52) | 2849 participants | NA | 59.5 | 47 |
| Shea et al, 2011 (21) | 1907 participants | None | 44 | 23 |
| Voulgari et al, 2011 (10) | 550 without diabetes or CVD | None | 56.5 | 55 |
| Ogorodnikova et al, 2011 (53) | 17 544 participants | None | 56.5 | 35 |

ATP = Adult Treatment Panel; CVD = cardiovascular disease; HDL = high-density lipoprotein; NA = not available; NHANES = National Health and Nutrition Examination Survey.

to evaluate heterogeneity between studies (26). $I^2$ testing was performed to evaluate the magnitude of heterogeneity between studies, with values greater than 50% indicating moderate to high heterogeneity (27).

We explored heterogeneity between studies by using 2 strategies. First, we reran the meta-analysis, removing each study one at a time to determine whether a particular study accounted for the heterogeneity. Second, meta-regression analyses were carried out. Using random-effects univariate meta-regression models, we assessed clinical and methodological variables that influenced the association of phenotypes and outcomes. The adjusted $R^2$, which denotes the proportion of between-study variation explained by a covariate, was used to evaluate the influence of the covariate on the between-studies variance. Finally, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates.

We performed further analyses that included only studies with at least 10 years of follow-up to compare the metabolically healthy overweight and metabolically healthy obese groups to the reference group. This approach allows a longer time for the occurrence of events, which is the most appropriate strategy in evaluating a low-risk population.

The possibility of publication bias was evaluated by using a funnel plot of effect size against the SE for each trial. Funnel plot asymmetry was evaluated by the Peters test, with significant publication bias defined as a $P$ value less than 0.1 (28, 29). All statistical analyses were performed by using Stata software, version 11.0 (Stata Corp., College Station, Texas).

### Role of the Funding Source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## RESULTS

We identified 1443 studies through electronic searches and 12 through manual searches (**Appendix Figure 1**, available at www.annals.org), all published in English. Eighteen publications were excluded after full-text evaluation, of which 17 reported original studies (**Appendix Table 1**, available at www.annals.org) (30–46). Twelve studies fulfilled inclusion criteria ($n$ = 67 127) (5, 8–10, 21, 47–53).

### Study Characteristics

**Table 1** summarizes the included studies. Metabolic status was defined by Adult Treatment Panel III criteria in 8 studies (8–10, 47–49, 51, 53), International Diabetes Federation criteria in 2 studies (50, 52), and additional assessment of insulin resistance and inflammatory markers in 2 studies (5, 21). Of note, 7 of the 8 longitudinal studies defined metabolic status using Adult Treatment Panel III



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*Table 1*—Continued

| Current Smoking, % | Design | Follow-up, y | Primary Outcome | Definition of Metabolically Healthy |
|---|---|---|---|---|
| 20 | Prospective observational study | 3 | All-cause mortality | Absence of the metabolic syndrome as defined by ATP III criteria |
| 18.6 | Prospective observational study | 11 | CVD (fatal and nonfatal myocardial infarction, heart failure, stroke, or claudication) | Absence of the metabolic syndrome as defined by ATP III criteria |
| 11 | Interventional trial followed by prospective observational study | 10 | CVD (fatal and nonfatal myocardial infarction, stroke) | Absence of the metabolic syndrome as defined by ATP III criteria |
| 23 | Cross-sectional observational study | NA | NA | <2 abnormalities: elevated triglyceride, glucose, and C-reactive protein levels; decreased HDL cholesterol levels; insulin resistance; and hypertension |
| 32.1 | Prospective observational study | 8.7 | All-cause mortality | <2 metabolic components as defined by ATP III criteria |
| 51.5 | Prospective observational study | 30 | All-cause mortality | Absence of the metabolic syndrome as defined by ATP III criteria |
| 14.2 | Prospective observational study | 8.1 | Cardiovascular disease (fatal and nonfatal myocardial infarction, stroke) | Absence of the metabolic syndrome as defined by the International Diabetes Federation |
| 10 | Cross-sectional observational study | NA | NA | Absence of the metabolic syndrome as defined by ATP III criteria |
| 15 | Cross-sectional observational study | NA | NA | Absence of the metabolic syndrome as defined by the International Diabetes Federation |
| NA | Cross-sectional observational study | NA | NA | <2 abnormalities: elevated triglyceride, glucose, and C-reactive protein levels; decreased HDL cholesterol levels; insulin resistance; and hypertension |
| 12 | Prospective observational study | 6 | Heart failure | Absence of the metabolic syndrome as defined by ATP III criteria |
| 30 | Prospective observational study | 15 | CVD (fatal and nonfatal myocardial infarction, stroke) | Absence of the metabolic syndrome as defined by ATP III criteria |

criteria. Of the 8 longitudinal studies, 3 evaluated all-cause mortality as the outcome and 5 evaluated only CV events. In all 8 studies, the outcome evaluated in our meta-analysis was the primary aim. Overall, 3988 events (all-cause mortality plus fatal and nonfatal CV events) were reported. Of the 8 studies that evaluated incidence of CVD and death, 6 evaluated only participants without CVD at baseline and the other 2 had prevalence of previous CVD of 37% and 20%, respectively (47, 49). All were prospective observational studies, although the Women's Health Study had an initial interventional phase (48). In these 8 studies, the proportion of current smokers ranged from 11% to 51%; 5 evaluated physical activity (10, 47–50) and reported that their populations had an overall moderate degree of activity (although assessed by different scales).

Four studies were cross-sectional reports providing data only on baseline characteristics (5, 21, 51, 52). Two studies evaluated participants from the National Health and Nutrition Examination Survey (5, 49). Because they overlap in study population, we included only Wildmand and colleagues' study (5) in the analyses of prevalence and characteristics and included only Kuk and Ardern's study (49) in the analyses of all-cause mortality and CV events.

An evaluation of the included studies for possible bias is shown in **Appendix Table 2** (available at www.annals.org). In accordance with the NOS quality assessment scale, all prospective studies achieved at least 6 stars, indicating overall good quality.

Eleven studies ($n = 66\,556$) evaluated participants according to BMI categories and metabolic status. **Appendix Table 3** (available at www.annals.org) shows the distribution of participants in each category of BMI and metabolic status. When we pooled the data from the studies, 6.0% of participants had metabolically unhealthy normal weight and 8.9% had metabolically healthy obesity (**Appendix Figure 2**, available at www.annals.org). Eight studies ($n = 61\,386$; 3988 events) evaluated all-cause mortality or CV events, enabling assessment of the effect of BMI–metabolic phenotype on these outcomes.

## Effect of BMI Categories in Metabolically Healthy Individuals

### *Overweight*

In a pooled analysis of 7 studies, metabolically healthy overweight individuals had a similar risk for all-cause mortality or CV events compared with metabolically healthy normal-weight persons (RR, 1.10; CI, 0.90 to 1.24) (**Figure 1**, *A*), although significance was almost reached. The heterogeneity was not significant in the individual estimates when the magnitude of association was evaluated ($I^2 = 0\%$; $P = 0.065$), and there was no evidence of publication bias on the Peter regression test ($P = 0.59$). Recognizing the long-term course generally required for manifestation of CV risk, we repeated this analysis with restriction to studies that had at least 10 years of follow-up. This analysis demonstrated a similar occurrence of events



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in metabolically healthy overweight individuals compared with metabolically healthy normal-weight persons in studies with long-term follow-up (RR, 1.21; 95% CI, 0.91 to 1.61; $I^2 = 70\%$) (**Figure 1**, *B*).

#### *Obesity*

In a pooled analysis of 8 studies, metabolically healthy obese persons had a similar risk for all-cause mortality or CV events compared with the metabolically healthy normal-weight individuals (RR, 1.19; CI, 0.98 to 1.38) (**Figure 1**, *C*). Heterogeneity was not significant in the individual estimates when the magnitude of association was evaluated ($I^2 = 15.1\%$; $P = 0.148$), and there was no evidence of publication bias on the Peter regression test ($P = 0.79$). However, after we restricted analysis only to studies with at least 10 years of follow-up, the metabolically healthy obese group indeed had increased mortality and CV risk compared with the metabolically healthy normal-weight group (RR, 1.24; CI, 1.02 to 1.55; $I^2 = 33.6\%$) (**Figure 1**, *D*). These data indicate that, with long-term follow-up, metabolically healthy obesity is associated with increased mortality and CV risk.

### Effect of BMI Categories in Metabolically Unhealthy Individuals

#### *Normal Weight*

In pooled analysis of 8 studies, the metabolically unhealthy normal weight group had increased risk for all-cause mortality or CV events compared with metabolically healthy normal-weight persons (RR, 3.14; CI, 2.36 to 3.93) (**Figure 2**, *A*). All but 1 study reported a significant difference between the groups. However, there was significant heterogeneity in the individual estimates when the magnitude of association was evaluated ($I^2 = 97.1\%$; $P < 0.001$), with no evidence of publication bias on the Peter regression test ($P = 0.62$).

We reran the meta-analysis, excluding each study one at a time to determine whether a particular study was responsible for the heterogeneity. No individual study was responsible for the heterogeneity. We then performed a meta-regression analysis in an exploratory attempt to identify the sources of heterogeneity. In univariate meta-regression models, we evaluated the following covariates: duration of follow-up, proportion of current smokers, age, and sex. Duration of follow-up ($R^2_a = 50.7\%$; $P = 0.04$) and proportion of smokers ($R^2_a = 81.9\%$; $P = 0.002$) were associated with the between-study variance. Considering all of these exploratory analyses together, we performed a sensitivity analysis that excluded the 3 studies with a 30% or greater proportion of smokers (9, 49, 53). In a pooled analysis of the remaining 5 studies, the RR for all-cause mortality or CV events comparing metabolically unhealthy normal-weight persons to metabolically healthy normal-weight persons was 3.79 (CI, 3.19 to 4.34). This approach reduced the heterogeneity between individual efficacy estimates ($I^2 = 77.7\%$) but did not eliminate it. In addition, we performed a sensitivity analysis excluding the 3 studies with the highest base rates (9, 10, 47), but the heterogeneity remained.

#### *Overweight*

In a pooled analysis of 7 studies, the metabolically unhealthy overweight group had an increased risk for all-cause mortality or CV events compared with the reference group (RR, 2.70; CI, 2.08 to 3.30) (**Figure 2**, *B*). There was significant heterogeneity in the individual estimates ($I^2 = 96\%$; $P < 0.001$), with no evidence of publication bias on the Peter regression test ($P = 0.99$).

In an exploratory attempt to identify the sources of heterogeneity between studies, we performed the same sequential approaches as described previously. The study of Arnlöv and colleagues (9) fully explained the heterogeneity; in univariate meta-regression models, duration of follow-up ($R^2_a = 68.5$; $P = 0.05$) and proportion of current smokers ($R^2_a = 68.4$; $P = 0.03$) were the covariates associated with the between-study variance in univariate meta-regression. Thus, a sensitivity analysis was performed by excluding the study of Arnlöv and colleagues, which had the longest follow-up and highest proportion of smokers (9). In pooled analysis of the remaining 6 studies, the RR for all-cause mortality or CV events comparing the metabolically unhealthy overweight individuals to the reference group was 3.09 (CI, 2.80 to 3.25). This approach eliminated the heterogeneity between the individual efficacy estimates ($I^2 = 10.8\%$).

#### *Obesity*

In a pooled analysis of 8 studies, the metabolically unhealthy obese group had increased risk for all-cause mortality or CV events compared with the metabolically healthy normal-weight group (RR, 2.65; CI, 2.18 to 3.12) (**Figure 2**, *C*). All but 1 study reported a significant difference between groups. Again, there was significant heterogeneity in individual estimates ($I^2 = 95\%$; $P < 0.001$). There was no evidence of publication bias ($P = 0.100$).

As was seen for the analyses of metabolically unhealthy normal-weight individuals, exclusion of the 3 studies with proportion of smokers 30% or greater (9, 49, 53) reduced the heterogeneity ($I^2 = 88\%$) but did not eliminate it. However, when we performed a sensitivity analysis excluding the 3 studies with the highest base rates (9, 10, 47), the heterogeneity was reduced to 55.3%. In a pooled analysis of the remaining 5 studies, the relative risk for all-cause mortality or CV events comparing the metabolically unhealthy obese group to the reference group was 2.79 (CI, 2.56 to 3.01).

Having established that all metabolically unhealthy phenotypes had increased mortality compared with the metabolically healthy normal-weight group, we noted that the risk for events conferred by metabolically unhealthy normal weight was similar to that of both the metabolically unhealthy obese and overweight groups. Thus, we performed sensitivity analyses directly comparing metaboli-



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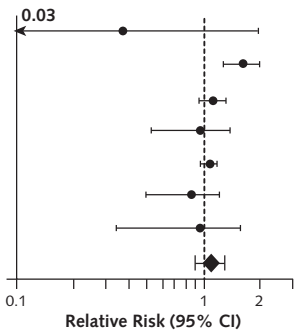
*Figure 1.* **Meta-analyses of metabolically healthy body mass index categories for the risk for all-cause mortality and cardiovascular events compared with metabolically healthy normal-weight persons (reference).**

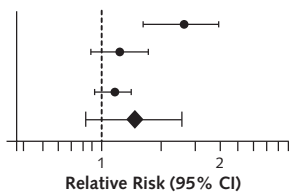
A.




| Study, Year (Reference) | Relative Risk (95% CI) | Weight, % | Metabolically Healthy Overweight Events/Participants, *n/N* | Metabolically Healthy Normal Weight Events/Participants, *n/N* |
|---|---|---|---|---|
| Kip et al, 2004 (47) | 0.37 (0.03–1.95) | 0.31 | 2/120 | 6/132 |
| Meigs et al, 2006 (8) | 1.63 (1.27–1.99) | 6.00 | 69/881 | 47/981 |
| Song et al, 2007 (48) | 1.12 (0.93–1.32) | 21.23 | 163/6730 | 278/12 943 |
| Kuk and Ardern, 2009 (49) | 0.96 (0.52–1.39) | 4.09 | 31/1158 | 54/1938 |
| Arnlöv et al, 2010 (9) | 1.08 (0.97–1.19) | 60.42 | 276/582 | 391/891 |
| Hosseinpanah et al, 2011 (50) | 0.86 (0.49–1.21) | 5.95 | 51/1447 | 64/1555 |
| Voulgari et al, 2011 (10) | 0.97 (0.34–1.58) | 2.00 | 18/127 | 16/109 |
| Overall | 1.10 (0.90–1.24) | 100.00 | 610/11 045 | 504/18 549 |

Heterogeneity: $I^2$ = 0%; $P$ = 0.07

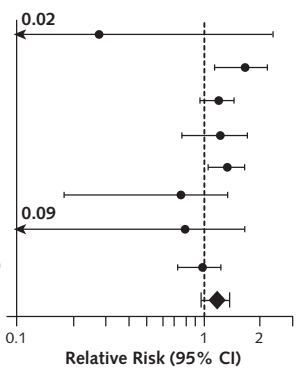
B.




| Study, Year (Reference) | Relative Risk (95% CI) | Weight, % | Metabolically Healthy Overweight Events/Participants, *n/N* | Metabolically Healthy Normal Weight Events/Participants, *n/N* |
|---|---|---|---|---|
| Meigs et al, 2006 (8) | 1.63 (1.27–1.99) | 20.60 | 69/881 | 47/981 |
| Song et al, 2007 (48) | 1.13 (0.94–1.32) | 35.62 | 163/6730 | 278/12 943 |
| Arnlöv et al, 2010 (9) | 1.08 (0.97–1.19) | 43.79 | 276/582 | 391/891 |
| Overall | 1.21 (0.91–1.61) | 100.00 | 508/8193 | 716/14 815 |

Heterogeneity: $I^2$ = 70%; $P$ = 0.02

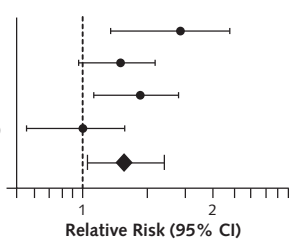
C.




| Study, Year (Reference) | Relative Risk (95% CI) | Weight, % | Metabolically Healthy Obese Events/Participants, *n/N* | Metabolically Healthy Normal Weight Events/Participants, *n/N* |
|---|---|---|---|---|
| Kip et al, 2004 (47) | 0.29 (0.02–2.35) | 0.55 | 1/77 | 6/132 |
| Meigs et al, 2006 (8) | 1.68 (1.17–2.19) | 8.35 | 19/236 | 47/981 |
| Song et al, 2007 (48) | 1.22 (0.98–1.47) | 26.77 | 77/2925 | 278/12 943 |
| Kuk and Ardern, 2009 (49) | 1.25 (0.77–1.72) | 9.67 | 24/689 | 54/1938 |
| Arnlöv et al, 2010 (9) | 1.36 (1.06–1.67) | 20.38 | 18/30 | 391/891 |
| Hosseinpanah et al, 2011 (50) | 0.77 (0.18–1.36) | 6.56 | 13/408 | 64/1555 |
| Voulgari et al, 2011 (10) | 0.63 (0.09–1.67) | 2.21 | 4/43 | 16/109 |
| Ogorodnikova et al, 2012 (53) | 1.00 (0.74–1.26) | 25.54 | 70/1167 | 242/4036 |
| Overall | 1.19 (0.98–1.38) | 100.00 | 226/5575 | 1098/22 585 |

Heterogeneity: $I^2$ = 15.1%; $P$ = 0.15

D.




| Study, Year (Reference) | Relative Risk (95% CI) | Weight, % | Metabolically Healthy Obese Events/Participants, *n/N* | Metabolically Healthy Normal Weight Events/Participants, *n/N* |
|---|---|---|---|---|
| Meigs et al, 2006 (8) | 1.68 (1.17–2.19) | 11.3 | 19/236 | 47/981 |
| Song et al, 2007 (48) | 1.22 (0.98–1.47) | 32.23 | 77/2925 | 278/12 943 |
| Arnlöv et al, 2010 (9) | 1.37 (1.06–1.66) | 25.49 | 18/30 | 391/891 |
| Ogorodnikova et al, 2012 (53) | 1.00 (0.74–1.26) | 30.98 | 70/1167 | 242/4036 |
| Overall | 1.24 (1.02–1.55) | 100.00 | 184/4358 | 958/18 851 |

Heterogeneity: $I^2$ = 33.6%; $P$ = 0.08

**A.** Metabolically healthy overweight group. **B.** Metabolically healthy overweight group, including only studies with at least 10 y of follow-up. **C.** Metabolically healthy obese group. **D.** Metabolically healthy obese group, including only studies with at least 10 y of follow-up. CV = cardiovascular.



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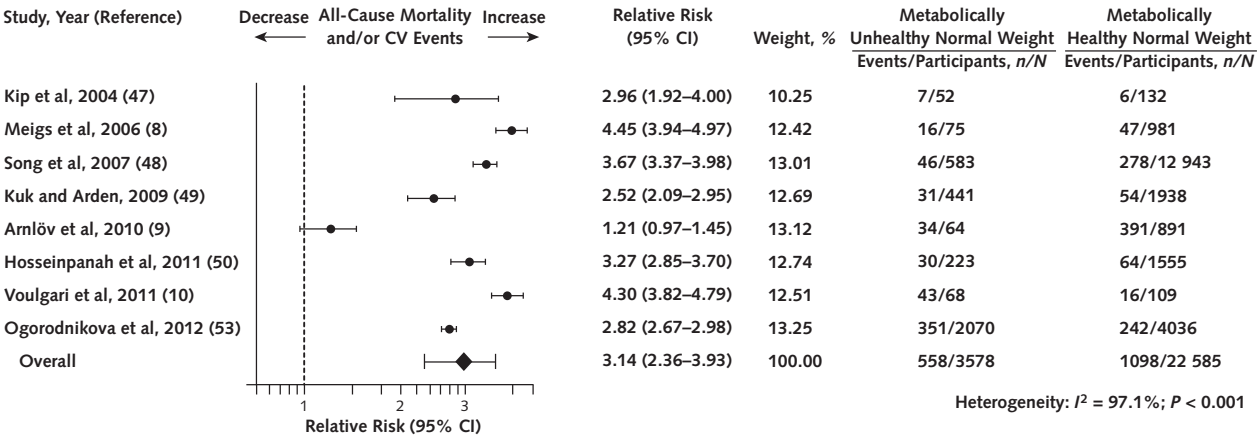
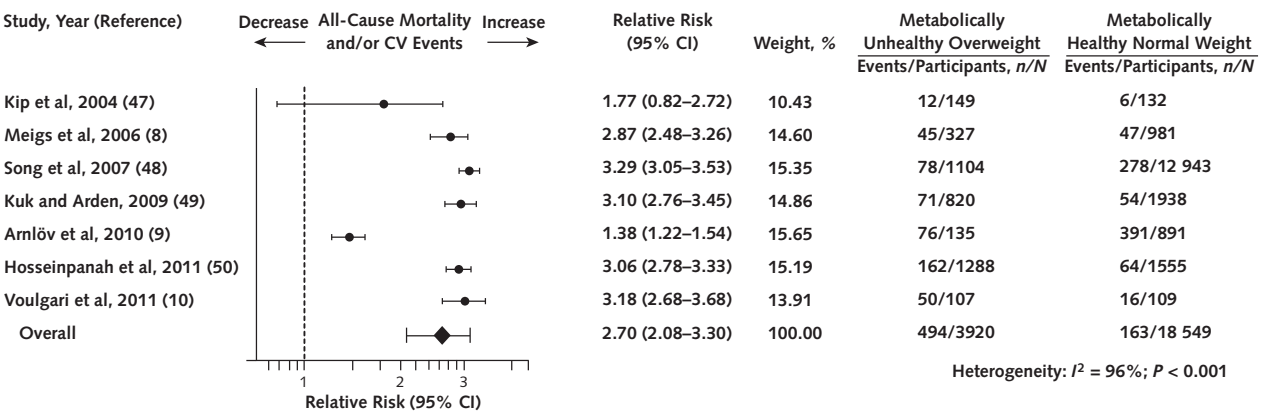
*Figure 2.* **Meta-analyses of metabolically unhealthy body mass index categories for the risk for all-cause mortality and cardiovascular events compared with metabolically healthy normal-weight persons (reference).**

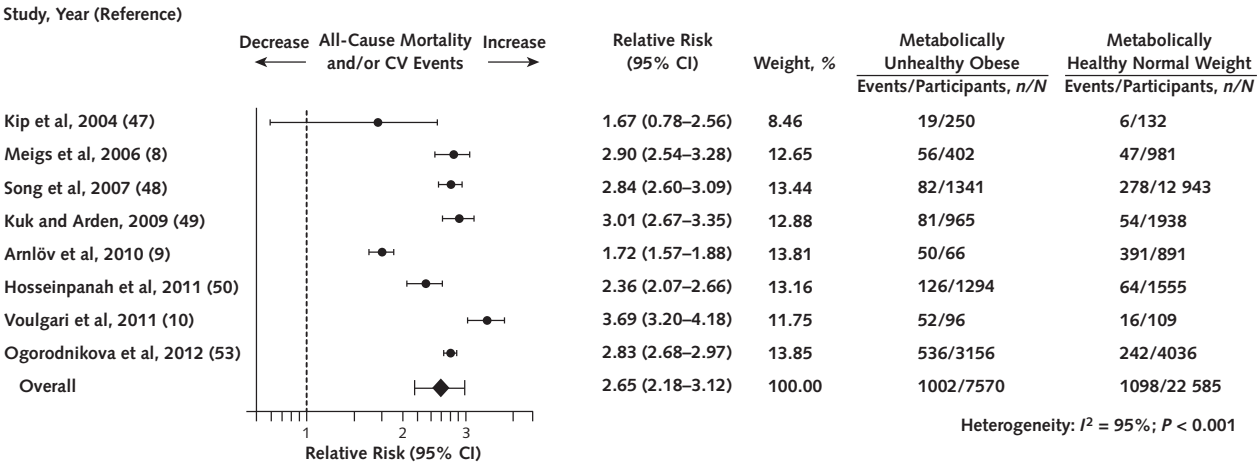
A.




B.




C.




**A.** Metabolically unhealthy normal-weight group. **B.** Metabolically unhealthy overweight group. **C.** Metabolically unhealthy obese group. CV = cardiovascular.



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*Table 2.* **Absolute Incidence of Events per Year of Follow-up, by Body Mass Index Category and Metabolic Status**

| Study, Year (Reference) | Normal Weight, % | | Overweight, % | | Obese, % | |
|---|---|---|---|---|---|---|
| | Metabolically Healthy | Metabolically Unhealthy | Metabolically Healthy | Metabolically Unhealthy | Metabolically Healthy | Metabolically Unhealthy |
| Kip et al, 2004 (47) | 1.51 | 4.48 | 0.55 | 2.68 | 0.43 | 2.53 |
| Meigs et al, 2006 (8) | 0.43 | 1.94 | 0.71 | 1.25 | 0.73 | 1.27 |
| Song et al, 2007 (48) | 0.21 | 0.79 | 0.24 | 0.70 | 0.26 | 0.61 |
| Kuk and Ardern, 2009 (49) | 0.32 | 0.80 | 0.30 | 0.99 | 0.40 | 0.96 |
| Arnlöv et al, 2010 (9) | 1.46 | 1.77 | 1.58 | 2.02 | 2.00 | 2.52 |
| Hosseinpanah et al, 2011 (50) | 0.50 | 1.66 | 0.43 | 1.55 | 0.39 | 1.20 |
| Voulgari et al, 2011 (10) | 2.45 | 10.54 | 2.36 | 7.78 | 1.55 | 9.02 |
| Ogorodnikova et al, 2011 (53) | 0.39 | 1.13 | Not available | Not available | 0.39 | 1.13 |

cally unhealthy normal-weight persons with these groups. The metabolically unhealthy normal-weight group had risk for all-cause mortality and CV events similar to that of the metabolically unhealthy obese group, which, in theory, is the highest-risk group (RR, 1.12; CI, 0.92 to 1.37) (**Appendix Figure 3**, *A* [available at www.annals.org]). Furthermore, the metabolically unhealthy normal-weight individuals had similar mortality and CV risk compared with metabolically unhealthy overweight persons (RR, 1.13; CI, 0.93 to 1.37) (**Appendix Figure 3**, *B*). In addition, 2 sensitivity analyses were performed: 1) Because Kip and colleagues' study (47) had the highest proportion of participants with previous CVD, we excluded this study from the meta-analysis and confirmed that the results did not change (data not shown); and 2) because Hosseinpanah and colleagues' study (50) was the only longitudinal study that defined metabolic status using International Diabetes Federation criteria, we performed a sensitivity analysis excluding this study and confirmed that the results did not change (data not shown).

**Table 2** presents the absolute incidence of events per year of follow-up by BMI and metabolic status and shows that these rates varied widely between studies (including 10-fold differences within some categories). Because differences in the incidence of events between metabolically healthy obese and metabolically healthy normal-weight persons were evident only after 10 years, the risk for events is probably not linear over time. Thus, to estimate the incremental absolute risk conferred by metabolically healthy obesity, we pooled data from the 2 studies with the most similar follow-up of 10 to 11 years (8, 48) and observed an absolute risk increase of 0.7% during this time.

### Clinical Characteristics According to BMI Category and Metabolic Status

Having established that both BMI and metabolic status confer risk for death and CV events, we next sought to compare baseline clinical characteristics between the BMI–metabolic categories in the 8 studies that provided such data ($n = 62\,355$). **Figure 3** shows the weighted mean difference of each clinical characteristic compared with the metabolically healthy normal-weight group. In both the metabolically healthy and unhealthy strata, there was a stepwise increase in systolic blood pressure, diastolic blood pressure, waist circumference, and Homeostasis Model Assessment of Insulin Resistance from normal weight to overweight to obesity. In other words, when we compared persons with the same metabolic status (healthy or unhealthy), those with higher BMI had increased levels of each of these risk factors. A similar inverse association was observed for HDL cholesterol. In contrast, this BMI gradient was not evident for triglycerides, glucose, and LDL cholesterol.

## Discussion

This study yields 3 key findings. First, compared with metabolically healthy normal-weight persons, metabolically healthy obese individuals are at increased risk for all-cause mortality and CV events over the long term (≥10 years). Second, all phenotypes with unhealthy metabolic status present increased risk, regardless of normal weight, overweight, or obesity. Third, blood pressure, waist circumference, and insulin resistance increased, and HDL cholesterol decreased, across the BMI categories in both metabolically healthy and unhealthy subgroups.

Previous meta-analyses evaluating BMI and mortality have not considered the presence of metabolic factors, although excess mortality was already evident for obese individuals in some reports (3, 54). Of interest, a recent meta-analysis observed an increased risk for grade 2 to 3 obesity as opposed to grade 1 (BMI, 30 to 35 kg/m$^2$) (4). In addition, in that study, overweight was associated with lower mortality (4). In contrast, our analyses showed that obese individuals have an increased risk for death and CV events over the long-term regardless of metabolic status, and that metabolically unhealthy overweight is also associated with these adverse outcomes. One possible explanation for the conflicting results reported in the earlier meta-analysis (4) is that the control group in that study included individuals with normal weight, who could be metabolically healthy or unhealthy. Considering our results demonstrate that metabolically unhealthy normal-weight individuals have an increased risk for events equal to that of



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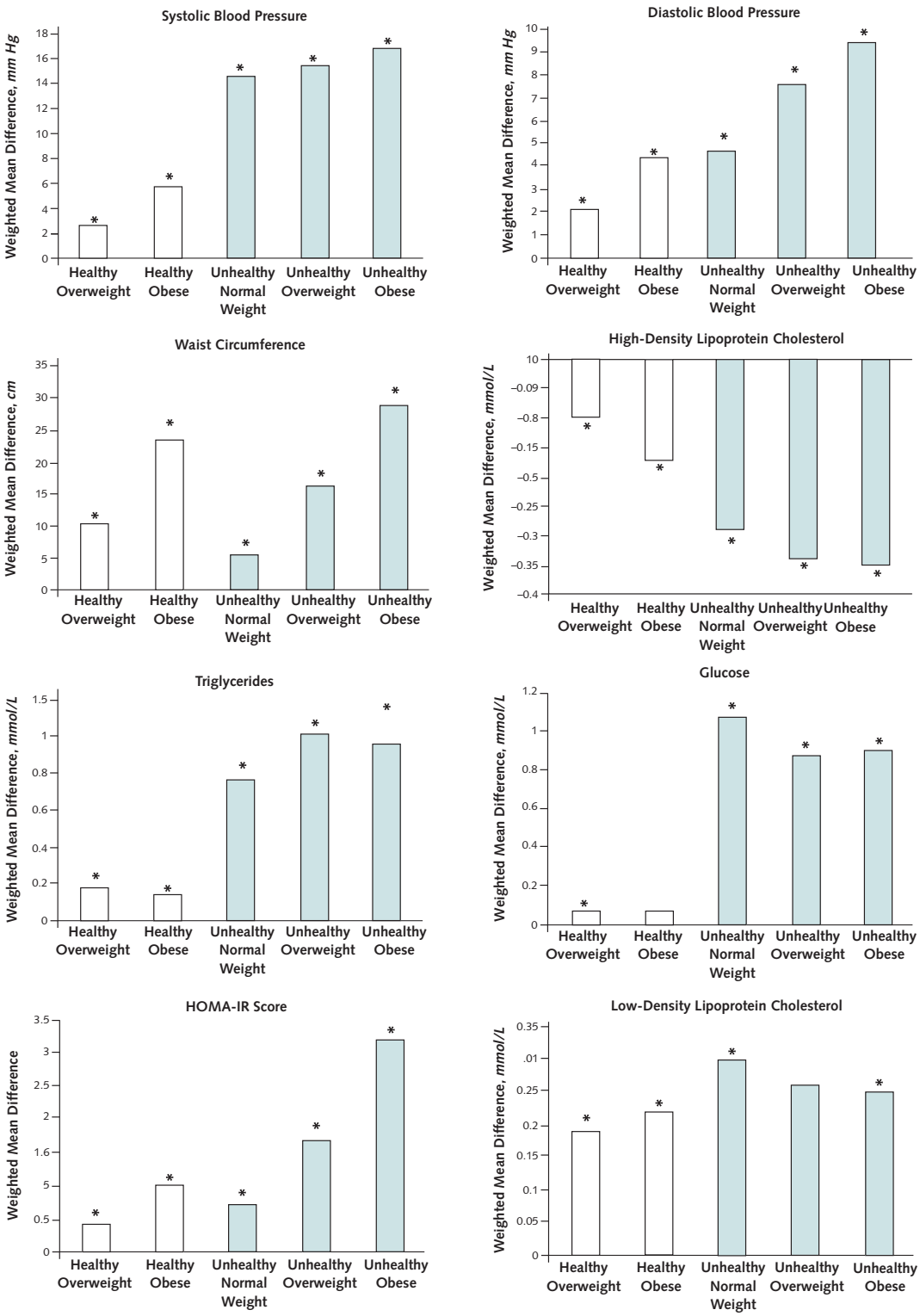
*Figure 3.* **Meta-analyses of various clinical characteristics, by metabolic–body mass index categories.**




Data shown as weighted mean difference compared with metabolically healthy normal-weight persons (reference). To convert cholesterol, triglyceride, and glucose values to traditional units (mg/dL), divide by 0.0259, 0.0113, and 0.0555, respectively. HOMA-IR = Homeostasis Model Assessment of Insulin Resistance.
* $P < 0.05$.



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metabolically unhealthy obese persons, studies that grouped all normal-weight individuals as the reference are indeed including a high-risk population in the control group, which could bias results and conclusions. Our findings highlight the need for comprehensive evaluation of not only BMI but also metabolic factors for prediction of future morbidity and mortality. Thus, it is essential that the reference group in studies evaluating BMI phenotypes should be metabolically healthy and of normal weight.

It is also important to recognize that duration of follow-up is a critical element in evaluating low-risk populations for future events. In the study of Arnlöv and colleagues, (9) which had the longest follow-up (30 years), an increased incidence of CV events in metabolically healthy obese and overweight participants emerged only after about 10 years. Similarly, a previous report (45) observed that individuals with metabolically healthy obesity had an increased risk for incident hypertension that was not apparent after 4 years of follow-up; it emerged only after 8 years. Although these clinical outcomes occurred only after long-term follow-up, it should be noted that, regardless of metabolic status, excess weight is associated in the short term with subclinical vascular disease, including impaired vasoreactivity (51), abnormalities in left ventricular measures (41, 51), chronic inflammation (42, 44), and increased carotid artery intima–media thickness and coronary calcification (33, 40).

Thus, taken together, these data suggest a model in which excess weight is associated initially with the development of subclinical metabolic and vascular dysfunction that ultimately leads to an increased incidence of CV events and mortality over the long term. In this regard, previous reports that evaluated metabolically healthy obese individuals over short-term follow-up (10, 43) or that compared these individuals with control groups not fully characterized for CV risk (43) might have contributed to the concept of a "benign obesity" phenotype that is not associated with adverse outcomes. Our results do not support this concept and show that there is no "healthy" pattern of obesity. Even within the same category of metabolic status (healthy or unhealthy), we show that certain CV risk factors (blood pressure, waist circumference, low HDL cholesterol level, insulin resistance) progressively increase from normal weight to overweight to obese. This finding again argues against the notion that increased BMI can be harmless. Furthermore, considering a worldwide prevalence of approximately 200 million people with metabolically healthy obesity (55), the absolute risk increase of 0.7% over 10 to 11 years associated with this condition (as compared with metabolically healthy normal-weight persons) translates to 1.4 million incident deaths or CV events over this time.

Particular attention should be given to individuals with metabolic unhealthy status despite normal weight. Indeed, this group had a similar rate of events as that in their metabolically unhealthy overweight and obese peers. A possible explanation is that this group might represent the most severe subtype along the phenotypic spectrum of individuals genetically predisposed to CV disease, such that they have unfavorable metabolic features, even without excess weight. This concept is supported by the surprising observation that this group had the highest weighted mean difference in LDL cholesterol and glucose levels compared with the metabolically healthy normal-weight group (even higher than their metabolically unhealthy overweight and obese peers) (**Figure 3**).

Strengths of this study include a large sample size that has been well characterized with respect to both BMI and metabolic factors, enabling the determination of robust estimates for the risks associated with 6 BMI–metabolic categories. A limitation is that most studies did not consider the use of medications (antihypertensive or lipid-lowering agents) that could interfere with the estimated risk for events. Nevertheless, because all studies were performed after 2004, we believe that patients were probably treated similarly on the basis of current clinical practice recommendations. In addition, duration of exposure to the current BMI and metabolic factors and longitudinal changes in BMI and metabolic status were not described in the studies and could partially affect the estimates. However, considering the challenges in reducing weight and the effect of aging on the incidence of metabolic disease, the transition of individuals to higher weight categories (that is, normal weight/overweight to obese) is more likely than the transition to lower weight categories (that is, obese to overweight/normal weight). Thus, the potential confounding effect of longitudinal changes in weight and metabolic status in our analyses was probably conservative, insofar as differences in the incidence of events might have been greater if persistently healthy normal-weight persons made up the control group. Another limitation is that analyses on obesity subgroups (grades 1 to 3) could not be performed because of the paucity of such data.

Two important limitations in our statistical analyses also need to be considered. First, we have pooled unadjusted estimates in this meta-analysis; thus, we did not account for other covariates possibly associated with mortality, such as physical activity and, most important, smoking. In this regard, we note that the proportion of current smokers was higher among persons of normal weight than among overweight or obese individuals in 7 of 8 longitudinal studies (8–10, 47, 48, 50, 53), rendering the potential confounding effect of smoking probably less relevant to our results. Second, our exploratory analyses could not fully explain the significant heterogeneity in the analyses of metabolically unhealthy normal-weight and metabolically unhealthy obese persons. As such, these estimates might lack precision and should be interpreted with caution. Indeed, the high heterogeneity in the analyses of these subgroups may further reflect the wide variation in the absolute rates of events between studies shown in **Table 2**. We believe, however, that these limitations do not obscure the



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main results of this meta-analysis. Finally, we recognize that publication bias and quality limitations of individual studies may still be relevant despite best efforts to conduct a comprehensive search and the lack of statistical evidence of bias.

Of note, our findings should be generalized carefully. Because higher BMI has been reported to confer lesser relative mortality risk in elderly persons than in young and middle-aged populations, our results might not be generalizable to older people (56, 57). Another consideration is that all studies in this meta-analysis evaluated participants in a community setting; thus, the results might not reflect the effect of BMI in an acute setting, such as critical care, where overweight and obesity have been reported to be protective in some studies (58). Conversely, however, the current results pertain to the majority of the general population.

In conclusion, our meta-analysis supports the concept of heterogeneity of metabolic status among individuals within the same BMI range. Metabolically healthy obese individuals are at increased risk for death and CV events over the long term compared with metabolically healthy normal-weight persons, suggesting that increased BMI is not a benign condition even in the absence of metabolic abnormalities. In addition, all metabolically unhealthy individuals (normal weight, overweight, obese) had increased risk for events compared with metabolically healthy normal-weight individuals. Thus, in evaluating CV and mortality risk, it is important to consider both BMI and metabolic status to reliably estimate long-term outcome.

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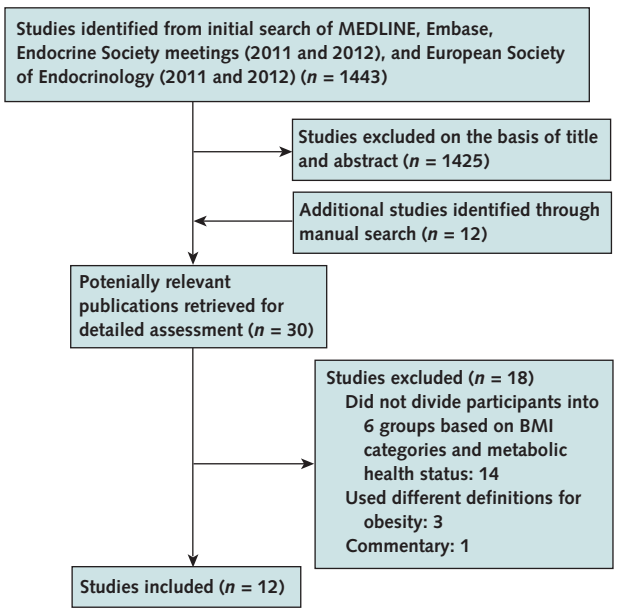
Drafting of the article: C.K. Kramer.
Critical revision of the article for important intellectual content: C.K. Kramer, B. Zinman, R. Retnakaran.
Final approval of the article: C.K. Kramer, B. Zinman, R. Retnakaran.
Statistical expertise: C.K. Kramer.
Obtaining of funding: B. Zinman.
Administrative, technical, or logistic support: B. Zinman.
Collection and assembly of data: C.K. Kramer, R. Retnakaran.

*Appendix Figure 1.* **Summary of evidence search and selection.**




BMI = body mass index.



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*Appendix Table 1.* **Characteristics of Excluded Studies After Full-Text Evaluation**

| Study, Year (Reference) | Sample Size | Subgroups Evaluated | Design | Primary Aim | Follow-up, y | Outcome | Conclusion | Reason for Exclusion |
|---|---|---|---|---|---|---|---|---|
| Young and Gelskey, 1995 (30) | 2792 adults aged 18–74 y | Nonobese, noncentrally obese, and centrally obese | Cross-sectional | Investigate whether individuals who are overall obese but have low waist-to-hip ratios have unfavorable metabolic profile | NA | NA | Noncentral obesity is not metabolically benign | Evaluated only obese individuals |
| Brochu et al, 2001 (31) | 43 postmenopausal women | Healthy and unhealthy obese | Cross-sectional | Investigate metabolic characteristics of healthy and unhealthy obese | NA | NA | Healthy obese persons had less visceral fat and earlier age-related onset of obesity | Evaluated only obese individuals |
| Karelis et al, 2005 (32) | 88 postmenopausal women | Healthy and unhealthy obese | Cross-sectional | Investigate inflammatory state in healthy obese women | NA | NA | Healthy obese women had favorable inflammation profile compared with unhealthy obese women | Evaluated only obese individuals |
| Stefan et al, 2008 (33) | 314 individuals | Normal-weight, overweight, and healthy and unhealthy obese | Cross-sectional | Characterize the metabolically healthy obese phenotype | NA | NA | There exists a metabolically healthy obese phenotype; this group had less ectopic liver fat than the unhealthy obese group | Did not stratify normal-weight and overweight participants according to metabolic status |
| Succurro et al, 2008 (34) | 197 participants | Healthy and unhealthy normal-weight and obese | Cross-sectional | Investigate metabolic characteristics of healthy and unhealthy | NA | NA | Unhealthy normal-weight and obese individuals exhibited poorer β-cell function and metabolic profile compared with their healthy peers | Did not present data for individuals categorized as overweight |
| Tarantino et al, 2009 (35) | 42 young obese participants | Healthy and unhealthy based on insulin resistance | Cross-sectional | Investigate inflammatory markers in metabolically healthy and unhealthy | NA | NA | C-reactive protein level, fibrinogen level, and spleen diameter were increased in young obese insulin-resistant patients | Evaluated only obese individuals |
| Messier et al, 2010 (36) | 113 obese postmenopausal women | Healthy and unhealthy obese by different definition | Cross-sectional | Investigate metabolic profile in healthy obese by using different definitions | NA | NA | Body composition and metabolic profile vary according to definition of metabolically healthy/unhealthy | Evaluated only obese individuals |
| Romero-Corral et al, 2010 (37) | 6171 participants from NHANES III | Healthy and unhealthy normal-weight (by proportion of body fat) | Prospective | Investigate metabolic characteristics and mortality in healthy and unhealthy | 8.8 | Total and CV mortality | Unhealthy normal weight is associated with adverse metabolic profile and, in women, with increased CV mortality compared with healthy individuals. | Evaluated obesity by body fat and included only normal-weight individuals |
| Calori et al, 2011 (38) | 2011 middle-aged individuals | Healthy and unhealthy normal-weight plus overweight and obese | Prospective | Investigate whether metabolically healthy obese had increased mortality | 15 | All-cause mortality, CVD and cancer mortality | The healthy obese group had similar mortality rates compared with the healthy normal-weight plus overweight group | Combined normal-weight and overweight individuals as a single group |
| Kantartzis et al, 2011 (39) | 262 nondiabetic individuals participated in a 9-mo lifestyle intervention program | Metabolically healthy obese and unhealthy | Interventional study (lifestyle) | Investigate metabolic variables after lifestyle intervention in unhealthy and healthy obese individuals | 0.75 | NA | Insulin sensitivity improved during the lifestyle intervention in unhealthy obese individuals | Evaluated only obese individuals |
| Khan et al, 2011 (40) | 475 participants from the Study of Women's Health Across the Nation; women aged 45–58 y; no baseline CVD | Normal-weight and overweight plus obese (healthy and unhealthy) | Cross-sectional | Evaluate subclinical CVD | NA | NA | Metabolically healthy overweight/obese women had significantly greater subclinical CVD burden than normal-weight women | Combined overweight and obese individuals as a single group |

*Continued on following page*

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*Appendix Table 1*—**Continued**

| Study, Year (Reference) | Sample Size | Subgroups Evaluated | Design | Primary Aim | Follow-up, *y* | Outcome | Conclusion | Reason for Exclusion |
|---|---|---|---|---|---|---|---|---|
| Park et al, 2011 (41) | 2540 participants without CVD | Healthy and unhealthy normal-weight, overweight and obese | Cross-sectional | Investigate the effect of healthy obesity on cardiovascular structure and function | NA | NA | Healthy obesity was associated with subtle changes in left ventricular structure and function | Definition of obesity: BMI ≥25 kg/m$^2$ |
| Wildman et al, 2011 (42) | 1889 postmenopausal women from Women's Health Initiative Study | Healthy and unhealthy normal-weight and overweight plus obese | Cross-sectional | Investigate inflammatory markers in metabolically healthy and unhealthy | NA | NA | Healthy overweight/obese women had increased levels of inflammatory markers compared with normal-weight healthy women | Combined overweight and obese individuals as a single group |
| Hamer and Stamatakis, 2012 (43) | 22 203 participants without baseline CVD | Healthy and unhealthy normal-weight plus overweight and obese | Prospective | Investigate whether metabolically healthy obese had increased mortality | 7 | All-cause mortality and CVD mortality | Healthy obese groups had similar mortality rates compared with healthy normal-weight plus overweight group | Combined normal-weight and overweight individuals as a single group |
| Marques-Vidal et al, 2012 (44) | 881 obese individuals | Healthy obese by different definition | Cross-sectional | Investigate inflammatory state in healthy obese by using different definitions | NA | NA | Healthy obese individuals had decreased levels of C-reactive protein compared with unhealthy by all definitions. Interleukin-6 and tumor-necrosis factor-$\alpha$ also reduced depending on the definition | Evaluated only obese individuals |
| Lee et al, 2013 (45) | 2352 participants without CVD | Healthy and unhealthy normal-weight, overweight and obese | Prospective | Investigate association between obesity phenotypes and incidence of hypertension | 8 | Incidence of hypertension | Healthy obese persons had increased risk for hypertension | Definition of obesity: BMI ≥25 kg/m$^2$ |
| Ortega et al, 2013 (46) | 21 651 participants without baseline CVD | Healthy normal-weight, healthy and unhealthy and obese | Prospective | Investigate the fitness of these groups and whether metabolically healthy obese had increased mortality | 14.3 | All-cause mortality, CVD and cancer mortality | Metabolically healthy obese phenotype is associated with greater fitness; mortality did not significantly differ between metabolically healthy obese and healthy normal-weight participants | Did not present data for individuals categorized as overweight or provide crude data |

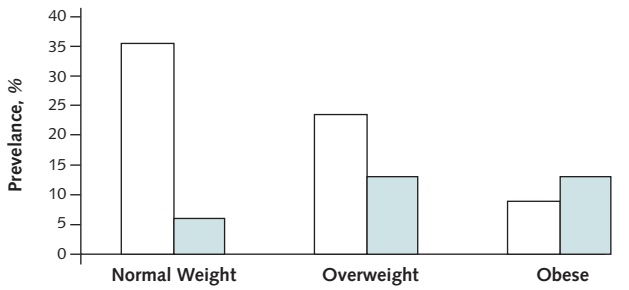
BMI = body mass index; CV = cardiovascular; CVD = cardiovascular disease; NA = not applicable; NHANES = National Health and Nutrition Examination Survey.

*Appendix Table 2.* **Newcastle–Ottawa Quality Assessment Scale for Cohort Studies†**

| Study, Year (Reference) | Selection | Comparability | Outcome |
|---|---|---|---|
| Kip et al, 2004 (47) | *** | * | ** |
| Meigs et al, 2006 (8) | **** | * | *** |
| Song et al, 2007 (48) | *** | * | *** |
| Wildman et al, 2008 (5) | **** | * | NA |
| Kuk and Ardern, 2009 (49) | **** | * | *** |
| Arnlöv et al, 2010 (9) | *** | * | *** |
| Hosseinpanah et al, 2011 (50) | **** | * | *** |
| Lind et al, 2011 (51) | **** | * | NA |
| Pajunem et al, 2011 (52) | **** | * | NA |
| Shea et al, 2011 (21) | **** | * | NA |
| Voulgari et al, 2011 (10) | **** | * | *** |
| Ogorodnikova et al, 2011 (53) | **** | * | *** |

NA = not applicable.
† Asterisks reflect the score given to each domain as explained in the Methods section.

*Appendix Figure 2.* **Prevalence of metabolically healthy and unhealthy individuals in normal-weight, overweight, and obese groups.**




*Appendix Table 3.* **Distribution of Participants, by Body Mass Index Category and Metabolic Status**

| Study, Year (Reference) | Normal Weight, *n (%)* | | Overweight, *n (%)* | | Obese, *n (%)* | |
|---|---|---|---|---|---|---|
| | Metabolically Healthy | Metabolically Unhealthy | Metabolically Healthy | Metabolically Unhealthy | Metabolically Healthy | Metabolically Unhealthy |
| Kip et al, 2004 (47) | 132 (16.9) | 52 (6.6) | 120 (15.4) | 149 (19.1) | 77 (9.8) | 250 (32) |
| Meigs et al, 2006 (8) | 981 (33.8) | 75 (2.6) | 881 (30) | 327 (11.2) | 236 (8.1) | 402 (13.9) |
| Song et al, 2007 (48) | 12 943 (50.5) | 583 (2.3) | 6730 (26.3) | 1104 (4.3) | 2925 (11.4) | 1341 (5.2) |
| Wildman et al, 2008 (5) | 1429 (26.3) | 440 (8) | 978 (17.9) | 925 (17) | 528 (9.7) | 1140 (20.9) |
| Kuk and Ardern, 2009 (49) | 1938 (32.2) | 441 (7.3) | 1158 (19.3) | 820 (13.6) | 689 (11.5) | 965 (16) |
| Arnlöv et al, 2010 (9) | 891 (50.7) | 64 (3.6) | 582 (33.1) | 125 (7.1) | 30 (1.7) | 66 (3.7) |
| Hosseinpanah et al, 2011 (50) | 1555 (25) | 223 (3.6) | 1447 (23.3) | 1288 (20.7) | 408 (6.6) | 1294 (20.8) |
| Lind et al, 2011 (51) | 319 (32.4) | 19 (1.9) | 333 (33.8) | 94 (9.5) | 102 (10.3) | 118 (12) |
| Pajunem et al, 2011 (52) | 712 (25) | 205 (7.2) | 418 (14.7) | 811 (28.5) | 94 (3.3) | 609 (21.4) |
| Shea et al, 2011 (21) | 456 (23.9) | 146 (7.6) | 367 (19.2) | 220 (11.5) | 339 (17.7) | 379 (19.9) |
| Voulgari et al, 2011 (10) | 109 (19.8) | 68 (12.4) | 127 (23) | 107 (19.4) | 43 (7.8) | 96 (17.4) |
| Ogorodnikova et al, 2011 (53) | 4036 (23) | 2070 (11.8) | 7115 (40.5) | | 1167 (6.6) | 3156 (17.9) |



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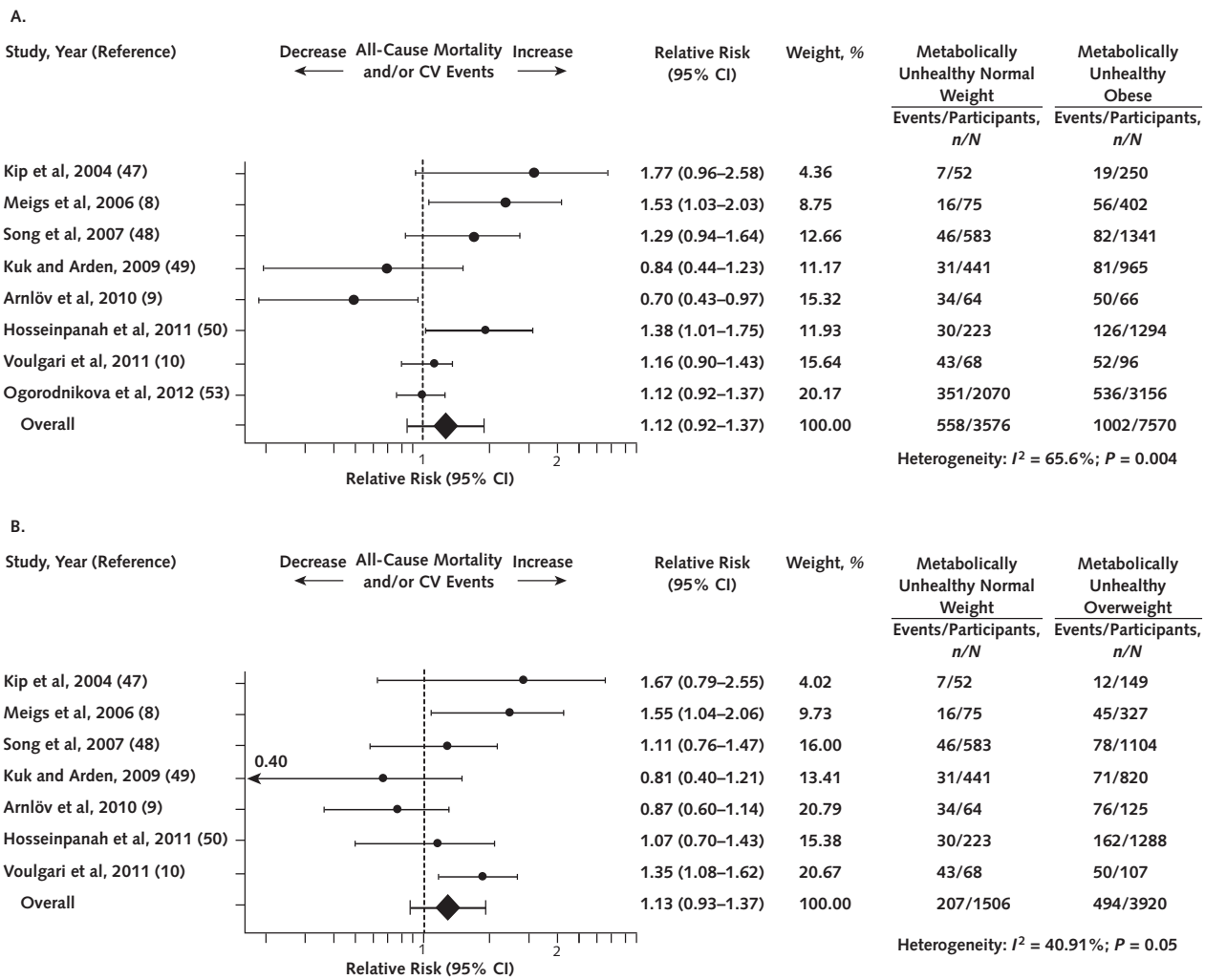
*Appendix Figure 3.* **Meta-analyses of unhealthy normal-weight phenotype for the risk for all-cause mortality and cardiovascular events compared with metabolically unhealthy obese (A) and metabolically unhealthy overweight (B) persons.**




CV = cardiovascular.



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