


# Metabolically healthy overweight/obesity are associated with increased risk of cardiovascular disease in adults, even in the absence of metabolic risk factors: A systematic review and meta-analysis of prospective cohort studies

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## Summary

This review examined the risk of cardiovascular disease in adults with metabolically healthy overweight/obesity. A systematic review and meta-analysis using data from Medline, EMBASE, SCOPUS and Cochrane Library searched from inception up to 31st October 2019. We included prospective cohort studies of adults who are metabolically healthy or unhealthy. Outcomes were fatal and nonfatal cardiovascular events, all-cause mortality. Pooled relative risk was calculated for each outcome in populations with metabolically healthy overweight and metabolically healthy obesity using metabolically healthy normal weight as reference. A random-effects model was used for meta-analysis, and risk of bias assessment tool for nonrandomized studies assessed risk of bias within each study. Twenty-three prospective cohort studies with 4,492,723 participants were included. Cardiovascular disease risk was increased in metabolically healthy groups with overweight (RR = 1.34, CI: 1.23–1.46,  $n = 20$ ,  $I^2 = 90.3\%$ ) and obesity (RR = 1.58, CI: 1.34–1.85,  $n = 21$ ,  $I^2 = 92.2$ ) compared with a reference group with metabolically healthy normal weight. Cardiovascular disease risk was similar irrespective of the number of risk factors used to define metabolically healthy and the risk remained in the group with no metabolic risk factors. Cardiovascular disease risk is increased in populations with overweight and obesity classified as metabolically healthy even when there were no metabolic risk factors.

## KEYWORDS

cardiovascular disease, metabolic health, obesity, overweight

## 1 | INTRODUCTION

The global prevalence of obesity has reached epidemic proportions with an estimated 671 million people having obesity in 2016.<sup>1</sup> There is a well-established link between obesity, metabolic abnormalities (dyslipidaemia, dysglycaemia and hypertension) and cardiovascular disease (CVD),<sup>2</sup> but it has been proposed that a subgroup of people with overweight/obesity and fewer or no metabolic abnormalities

may not carry an increased risk of CVD.<sup>3</sup> These subgroups are referred to as having metabolically healthy overweight (MHOW) and metabolically healthy obesity (MHO).<sup>4,5</sup> This concept is complex, and the prevalence of MHO/OW varies between 10% and 40% depending on the type of population and the definition of metabolic health used in the study.<sup>3,6,7</sup> The definition of the MHO/OW phenotype remains unclear and contentious.<sup>8</sup> The number of metabolic parameters (triglycerides, high-density lipoprotein cholesterol, fasting blood glucose,

systolic and diastolic blood pressure) that need to be within normal parameters to be considered metabolically healthy has not been clearly defined. This uncertainty has led to inconsistent results from studies examining the association between MHO/OW by any definition and development of CVD.

The available systematic reviews and meta-analyses have concluded that MHO/OW is associated with an increased risk of developing CVD.<sup>9–14</sup> Kramer et al. combined the risk of all-cause mortality and cardiovascular events in their analysis,<sup>10</sup> but some studies showed a stronger association for CVD mortality than all-cause mortality<sup>15,16</sup> or no association between MHO/OW and all-cause mortality.<sup>12</sup> Eckel et al. suggested that the cause of the high heterogeneity and conflicting results observed in previous reviews was related to the absence of a standard definition for metabolic syndrome (MS) and the use of different outcome definitions.<sup>11</sup> Since the review performed in 2016,<sup>12</sup> there have been several large prospective cohort studies examining the relationship between MHO/OW and CVD with strict definitions of metabolic health (i.e., having no metabolic risk factors). The earlier systematic review by Eckel et al. pooled relative risk from three studies with strict definitions of metabolic health,<sup>11</sup> and Zheng et al. reported pooled relative risk from two such studies.<sup>12</sup> Both studies reported no association between MHO phenotype with no metabolic risk factors and risk of CVD; however, these findings are unreliable because of the small number of studies. The latest systematic review by Yeh et al. published early in 2019 failed to report on the risk of CVD in MHO participants who have no risk factors, included studies with an obesity cut-off less than 30 kg/m<sup>2</sup> and examined only four obesity phenotypes.<sup>14</sup> Given the conflicting results from previous studies, the availability of more recent studies, including a total of seven studies of MHO/OW populations without metabolic risk factors, and the need to determine if overweight/obesity is associated with CVD in the absence of metabolic risk factors, we conducted a systematic review of the available literature to examine the association between MHO/OW and the risk of CVD events in adult men and women aged 18 years and older.

## 2 | METHODS AND MATERIAL

This systematic review and meta-analysis were conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines.<sup>17</sup> The study protocol was registered in the International Prospective Register of Systematic Reviews<sup>18</sup> registration number: CRD42019103850.

### 2.1 | Data source and searches

A systematic literature search was performed using Medline, EMBASE, SCOPUS databases and Cochrane Library from inception up to the 31st October 2019. Each database was searched using the same comprehensive search terms (Table S1). Hand-search of references from relevant publications was also performed.

Two independent reviewers analysed citations from the electronic databases for relevant studies based on their title and abstract after removal of duplicate articles. Any disagreements were resolved by consensus or through consultation with a third investigator.

### 2.2 | Study selection

Studies were considered eligible for inclusion if they met the following criteria:

- prospective cohort design;
- population included adult men and women 18 years and older without pre-existing CVD, diabetes mellitus, cancer or chronic kidney disease;
- exposure consisted of a combination of body mass index (BMI) categories or waist circumference and metabolic health and BMI categories included: normal weight (BMI = 18.5–24.9 kg/m<sup>2</sup>), overweight (BMI = 25–29.9 kg/m<sup>2</sup>) and obese (BMI ≥ 30 kg/m<sup>2</sup>);
- metabolic health was defined in three separate ways as (i) absence of or (ii) presence of ≤1 or ≤2 metabolic abnormalities according to NCEP ATP III or IDF criteria of MS definition or (iii) other criteria (absence of hypertension, diabetes mellitus and dyslipidaemia);
- reference group was individuals with metabolically healthy normal weight (MHNW);
- exposure groups stratified according to metabolic health status and weight classification as follows: metabolically healthy normal weight (MHNW), metabolically healthy overweight (MHOW), metabolically healthy obese (MHO), metabolically unhealthy normal weight (MUNW), metabolically unhealthy overweight (MUOW) and metabolically unhealthy obesity (MUO);
- included outcomes consisting of fatal and nonfatal cardiovascular events and all-cause mortality. Fatal and nonfatal CV events were defined as death due to CVD or one of the following: myocardial infarction, acute coronary syndrome, angina, coronary revascularization, coronary artery bypass surgery, congestive heart failure, stroke and transient ischaemic attack;
- if multiple studies were available from the same cohort, the most recent study was included.

Studies were excluded using the following criteria:

- subjects younger than 18 years;
- subjects not human or with BMI in the underweight range;
- studies with abstract or full text missing;
- studies not stratified according to BMI categories and metabolic health;
- cross-sectional studies, case studies, case reports, case series and letter to editors;
- studies in languages other than English.

MS components (risk factors) used to define metabolic health according to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and International Diabetes Federation (IDF):

systolic BP,  $\geq 130$  mmHg, and diastolic BP,  $\geq 85$  mmHg;  
triglycerides,  $\geq 1.7$  mmol/L;  
high-density lipoprotein cholesterol (HDL cholesterol),  $\leq 1.03$  mmol/L (men) and  $\leq 1.29$  mmol/L (women);  
fasting glucose,  $\geq 6.1$  mmol/L (ATP III) and  $\geq 5.6$  mmol/L (IDF);  
waist circumference,  $\geq 102$  cm (men) and  $\geq 88$  cm (women) for ATP III and  $\geq 94$  cm (men) and  $\geq 80$  cm (women) for IDF.

MS was defined as the presence of three or more of the above metabolic risk factors.

### 2.3 | Quality assessment

Two independent reviewers assessed the quality of included cohort studies using the validated risk of bias assessment tool for non-randomized studies (RoBANS).<sup>19</sup> The tool contains a table with six domains: participant selection, confounding variables, intervention measurement, blinding of outcome assessment, incomplete outcome data and selective outcome reporting. Each study was allocated low, high or unclear RoB in each domain. Studies with a low risk of bias for all six domains were considered high quality, studies with a low risk of bias for five domains were considered moderate quality and studies with a low risk of bias for four or less domains were considered low quality. The RoB scores are presented in (Table S2).

### 2.4 | Data extraction

Two independent reviewers carried out data extraction using a standardized form. The variables extracted are described in Table 1.

### 2.5 | Data analysis

The pooled relative risk (RR) of CVD, all-cause mortality and cardiovascular mortality were calculated from the outcomes for the MHOW and MHO phenotypes with MHNW used as the reference population.

Heterogeneity was investigated using Cochrane's Q test and  $I^2$  statistic. If heterogeneity was present ( $p$  value of Q test  $< 0.1$  and  $I^2 > 25\%$ ) a random-effects model was used. Sources of heterogeneity were explored by fitting each covariate (outcome definition, study quality, criteria for defining metabolic health, geographic location, duration of follow-up, number of risk factors in metabolically healthy and sample size) into a meta-regression model if these data were available. If the  $p$  value after adding the variable was less than 0.05,

then that variable was considered a source of heterogeneity and subgroup analysis was performed accordingly.

Publication bias was assessed using funnel plots and Egger's test. If the funnel plot was asymmetrical, a contour enhanced funnel plot was constructed to distinguish whether heterogeneity or publication bias was the cause of asymmetry. All analyses were conducted using STATA version 16.

## 3 | RESULTS

### 3.1 | Study characteristics

There were 4,353 citations identified from the Medline, PubMed, EMBASE, SCOPUS and Cochrane Library databases. One hundred seven-eight studies were identified after screening abstracts and removing duplicates. Five studies were identified through manual searching, resulting in 183 studies receiving full-text review. Of the 183 studies, 23 prospective cohort studies with a total of 4,492,723 participants were eligible for systematic review and meta-analysis (Figure 1).

Of the 23 studies analysed (Table 1), 18 studies included data for both male and female subjects<sup>6,7,16,20-34</sup> with three studies providing data separated by sex.<sup>25,27,32</sup> Two studies reported data for female participants,<sup>35,36</sup> and three reported data for male subjects only.<sup>15,37,38</sup> Participants were from diverse geographical locations: 11 studies were from Europe,<sup>7,16,20-22,25,30-33,38</sup> six from North America,<sup>15,24,28,34-36</sup> three from the Middle East,<sup>23,29,37</sup> two from Asia<sup>26,27</sup> and one from Oceania (Australia).<sup>6</sup> No studies detailed the ethnic origins of their subjects. Sample size ranged from 1,650<sup>16</sup> to 3.5 million subjects.<sup>20</sup>

Studies used different criteria to define metabolic health. Nine studies<sup>7,15,26-28,33,36-38</sup> used the NCEP ATP III criteria,<sup>39</sup> nine studies<sup>6,16,21-23,29-32</sup> used IDF criteria<sup>40</sup> and the remaining five studies<sup>20,24,25,34,35</sup> used absence of hypertension, diabetes and dyslipidaemia to define metabolic health.

All studies used BMI = 25– $<30$  kg/m<sup>2</sup> and BMI  $\geq 30$  kg/m<sup>2</sup> as the definition of overweight and obesity, respectively. Metabolic health was defined differently across studies: Nine used the absence of MS, three used the presence of two or less risk factors, four studies used one or less risk factors and seven studies used the absence of any risk factors.

Seventeen studies reported CVD as the only outcome,<sup>6,7,20-30,32,35-37</sup> four studies reported cardiovascular mortality in addition to combined CVD and all-cause mortality as outcomes.<sup>15,16,31,38</sup> Two studies reported all-cause mortality as the only outcome.<sup>33,34</sup> Most studies<sup>6,7,15,16,20,22-24,27-29,31,35-38,41</sup> reported CVD as a composite outcome that included the following presentations of CVD: coronary artery disease (angina, ischaemic heart disease and myocardial infarction), cerebrovascular disease or heart failure.

RoB was evaluated using the RoBANS tool.<sup>19</sup> All studies included in the meta-analysis achieved an overall quality score of 5–6/6.

**TABLE 1** Study characteristics

| Author               | Year | Country         | Study design         | Mean or median years of follow-up | Sample size | %Male        | Mean age (years)    | Criteria for definition of metabolic health   | Number of metabolic risk factors in metabolically healthy | Obesity measurement (cut-off)   | Outcome          |
|----------------------|------|-----------------|----------------------|-----------------------------------|-------------|--------------|---------------------|---|---|---------------------------------|------------------|
| Appleton et al.      | 2013 | Australia       | Prospective cohort   | 8.2 <sup>a</sup>                  | 3,743       | Not reported | Not reported        | Presence of one or less risk factors according to IDF criteria  | 0 or 1  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD              |
| Arnlov et al.        | 2009 | Sweden          | Prospective          | 30.0 <sup>a</sup>                 | 1,758       | Not reported | Not reported        | Presence of two or less risk factors according to ATP III criteria  | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | ACM, CVM, MCE    |
| Aung et al.          | 2014 | USA             | Prospective study    | 7.4 <sup>a</sup>                  | 3,700       | Not reported | Not reported        | Presence of two or less metabolic abnormalities   | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD              |
| Bo et al.            | 2012 | Italy           | Prospective cohort   | 9.0                               | 1,658       | 47.0         | Not reported        | Presence of two or less risk factors according to harmonization definition                                    | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD, ACM, CVM    |
| Caleyachetty et al.  | 2017 | United Kingdom  | Prospective cohort   | 5.4                               | 3,500,000   | 45.5         | Not reported        | Presence of no metabolic abnormalities (diabetes, hypertension or hypercholesterolaemia)                      | 0   | BMI $\geq$ 30 kg/m <sup>2</sup> | Stroke, CHD, HF  |
| Dhana et al.         | 2016 | The Netherlands | Prospective cohort   | 10.3 <sup>a</sup>                 | 5,314       | 40.0         | 68.0                | Presence of two or less risk factors according to IDF criteria  | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD              |
| Eckel et al.         | 2018 | USA             | Prospective cohort   | 24.0 <sup>a</sup>                 | 90,257      | 0            | Not reported        | Presence of no metabolic abnormalities (diabetes, hypertension, hypercholesterolaemia)                        | 0   | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD, MI, Stroke. |
| Hansen et al.        | 2017 | Denmark         | Prospective          | 10.6                              | 6,238       | 48.9         | 46.3 men 45.7 women | Presence of no metabolic risk factors   | 0   | BMI $\geq$ 30 kg/m <sup>2</sup> | IHD              |
| Hinnouho             | 2015 | United Kingdom  | Prospective cohort   | 17.4                              | 7,122       | 69.7         | Not reported        | Presence of two or less risk factors according to ATP III criteria  | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD              |
| Hosseinihanah et al. | 2011 | Iran            | Prospective          | 8.4 <sup>a</sup>                  | 6,215       | 43.1         | 47.4                | Presence of no dysmetabolic status defined as having metabolic syndrome according to IDF criteria or diabetes | 0 or 1  | BMI $\geq$ 30 kg/m <sup>2</sup> | CVD              |
| Hyun-Jung Lee et al. | 2018 | South Korea     | Retrospective cohort | 7.4                               | 354,083     | 52.7         | 45.8                | Presence of no risk factor according to ATP III criteria  | 0   | BMI $\geq$ 30 kg/m <sup>2</sup> | Stroke           |
| Katzmarzyk et al.    | 2005 | Canada          | Observational cohort | 10.2                              | 19,172      | 100          | 43.1                | Presence of two or less risk factors according to ATP III criteria  | $\leq$ 2  | BMI $\geq$ 30 kg/m <sup>2</sup> | ACM, CVM         |

TABLE 1 (Continued)

| Author          | Year | Country   | Study design              | Mean or median years of follow-up | Sample size | %Male | Mean age (years) | Criteria for definition of metabolic health   | Number of metabolic risk factors in metabolically healthy | Obesity measurement (cut-off)   | Outcome          |
|-----------------|------|---|---------------------------|-----------------------------------|-------------|-------|------------------|---|---|---|------------------|
| Lassale et al.  | 2017 | Denmark, France, Germany, Greece, Italy, The Netherlands, Norway, Spain, Sweden, United Kingdom | Prospective case-cohort   | 12.2 <sup>a</sup>                 | 10,474      |       | 53.6             | Presence of two or less risk factors according to IDF criteria  | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | CHD              |
| Loprinzi et al. | 2017 | USA   | Prospective               | 8.6 <sup>a</sup>                  | 7,579       | 49.0  | 46.0             | Presence of no risk factor according to the American National Heart, Lung, and Blood Institute Guidelines | 0   | BMI ≥ 30 kg/m <sup>2</sup>  | ACM              |
| Lu et al.       | 2014 | China   | Prospective observational | 10.0                              | 211,641     | 34.1  | Not reported     | Presence of two or less risk factors according to ATP III criteria  | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | CVD              |
| Meigs et al.    | 2006 | USA   | Prospective observational | 11.4                              | 2,902       | 45.0  | 53.0             | Presence of two or less risk factor according to ATP III criteria   | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | CVD              |
| Mirzaei et al.  | 2017 | Iran  | Prospective cohort        | 12.0                              | 7,167       | 44.8  | 46.3             | Presence of two or less risk factors according to IDF criteria  | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | CVD              |
| Morkedal et al. | 2014 | Norway  | Prospective cohort        | 12.2                              | 61,299      | 46.1  | Not reported     | Presence of one or no risk factors according to IDF criteria  | 0 or 1  | BMI ≥ 30 kg/m <sup>2</sup> or Waist circumference >94 cm in men >80 cm in women | AMI, HF          |
| Ortega et al.   | 2013 | Sweden  | Longitudinal              | 24.0                              | 43,265      | 75.7  | 44.2             | Presence of one or no risk factor according to IDF criteria   | 0 or 1  | BMI ≥ 30 kg/m <sup>2</sup>  | ACM, CVD, CVM    |
| Song et al.     | 2007 | USA   | Prospective               | 10.2                              | 25,626      | 0     | Not reported     | Presence of two or less risk factors according to ATP III criteria  | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | CVD, CHD, Stroke |
| Thomsen et al.  | 2014 | Denmark   | Prospective               | 3.6 <sup>a</sup>                  | 71,527      | 43.7  | Not reported     | Presence of two or less risk factors according to IDF criteria  | ≤2  | BMI ≥ 30 kg/m <sup>2</sup>  | MI, IHD          |

(Continues)

TABLE 1 (Continued)

| Author      | Year | Country         | Study design       | Mean or median years of follow-up | Sample size | %Male | Mean age (years) | Criteria for definition of metabolic health                                   | Number of metabolic risk factors in metabolically healthy | Obesity measurement (cut-off)                                  | Outcome |
|-------------|------|-----------------|--------------------|-----------------------------------|-------------|-------|------------------|---|---|--|---------|
| Twig et al. | 2015 | Israel          | Cohort             | 6.1                               | 31,684      | 100   | 31.2             | Presence of none of the metabolic abnormalities according to ATP III criteria | 0   | BMI $\geq$ 30 kg/m <sup>2</sup>                                | CHD     |
| van der A   | 2014 | The Netherlands | Prospective cohort | 13.4                              | 20,299      | 45.8  | Not reported     | Presence of no risk factors according to ATP III criteria                     | 0   | Waist circumference $\geq$ 102 cm in men $\geq$ 88 cm in women | ACM     |

Abbreviations: ACM, all-cause mortality; ATP III, Adult Treatment Panel III; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; CVM, cardiovascular mortality; IDF, International Diabetes Federation; IHD: ischaemic heart disease; MI, myocardial infarction.

<sup>a</sup>Median age.

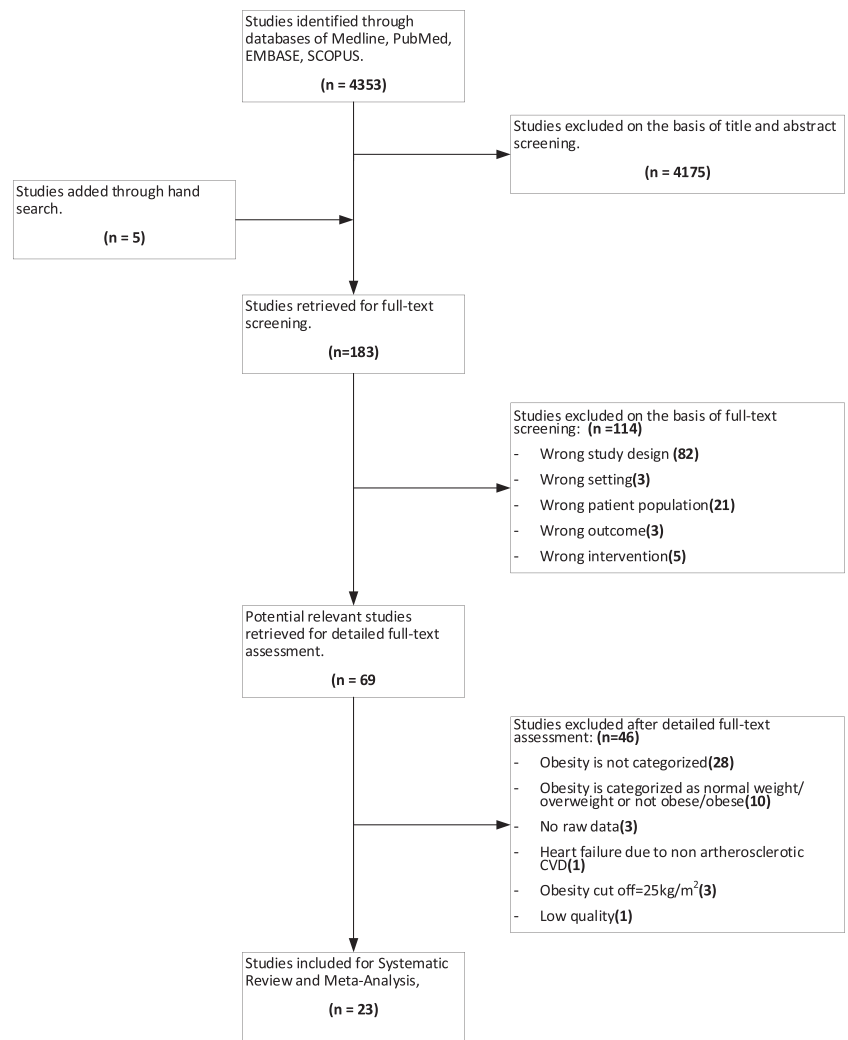
### 3.2 | MHOW and risk of cardiovascular events

As one study<sup>31</sup> did not report raw data for MHOW, data were pooled from 20 studies, which investigated the risk of CVD in those with MHOW compared with MHNW (Table S3). There was an increased risk of CVD in the group with MHOW compared with the group with MHNW (RR = 1.34, CI: 1.23–1.46,  $n$  = 20,  $I^2$  = 90.3%); however, heterogeneity was high (Figure 2). The risk of CVD did not differ significantly from the overall risk regardless of whether the CVD outcome was defined as composite (RR = 1.36, CI: 1.20–1.53,  $n$  = 15,  $I^2$  = 91.8%) or single entities of CVD (noncomposite) (RR = 1.30, CI: 1.18–1.43,  $n$  = 5,  $I^2$  = 62.8%). Relative risk did not differ according to study quality (high quality: RR = 1.43, CI: 1.29–1.58,  $n$  = 11,  $I^2$  = 80.1%; moderate quality: RR = 1.22, CI: 1.07–1.38,  $n$  = 9,  $I^2$  = 82.5%); sample size ( $\geq$ 6,000: RR = 1.33, CI: 1.19–1.47,  $n$  = 14,  $I^2$  = 93.6%;  $<$ 6,000: RR = 1.36, CI: 1.14–1.64,  $n$  = 6,  $I^2$  = 50.7%); geographic location (Europe: RR = 1.34, CI: 1.18–1.52,  $n$  = 9,  $I^2$  = 93.7%; North America: RR = 1.54, CI: 1.18–2.03,  $n$  = 5,  $I^2$  = 78.3%); or study follow-up duration ( $<$ 10 years: RR = 1.34, CI: 1.08–1.68,  $n$  = 7,  $I^2$  = 86.8%;  $\geq$ 10 years: RR = 1.34, CI: 1.22–1.47,  $n$  = 13,  $I^2$  = 82.6%). Interestingly, the relative risk was similar irrespective of the quantity of risk factors used to define metabolically healthy (0: RR = 1.51, CI: 1.21–1.88,  $n$  = 5,  $I^2$  = 86.2%;  $\leq$ 1: RR = 1.25, CI: 0.87–1.80,  $n$  = 3,  $I^2$  = 74.8%;  $\leq$ 2: RR = 1.29, CI: 1.21–1.38,  $n$  = 12,  $I^2$  = 54.5%). The risk of CVD remained high even when there were no metabolic risk factors. The risk of CVD was different if the study used the ATP III or IDF criteria when compared with those studies that used ‘absence of hypertension, diabetes and dyslipidaemia’ (‘other’ criteria) to define metabolic health (NCEP ATP III: RR = 1.31, CI: 1.20–1.44,  $n$  = 8,  $I^2$  = 44.6%; IDF: RR = 1.22, CI: 1.07–1.39,  $n$  = 8,  $I^2$  = 74.5%; ‘Other’ criteria: RR = 1.68, CI: 1.53–1.85,  $n$  = 4,  $I^2$  = 33.5%). There was a statistically significant subgroup difference for criteria used to define metabolic health ( $Q$  = 20.15,  $p$  < 0.01) (Figure 2). Furthermore, the pooled effect size for risk of CVD in MHOW compared with MHNW did not change when the study by Caleyachetty et al. (2017) with the greatest weighting was removed from analysis (data not shown). However, these results should be interpreted with caution because of the small number of studies used in the subgroup analysis.

The pooled relative risk from studies with disaggregated data for females and males was different (females: RR = 1.46, CI: 1.26–1.69,  $n$  = 3,  $I^2$  = 44.3%; males: RR = 1.22, CI: 1.14–1.30,  $n$  = 3,  $I^2$  = 0.0%). There was a statistically significant subgroup difference for gender ( $Q$  = 4.75,  $p$  = 0.03) (Figure S1). However, caution is needed in the interpretation because of the small number of studies.

There was a significantly increased risk of all-cause mortality (RR = 1.22, CI: 1.02–1.46,  $n$  = 5,  $I^2$  = 48.8%) and CVD mortality (RR = 1.34, CI: 1.12–1.61,  $n$  = 4,  $I^2$  = 0.0%) in the group with MHOW compared with the group with MHNW (Figures S2 and S3); however, there were too few studies to reliably assess this risk.

**FIGURE 1** Flow chart for literature search, study selection and reasons for exclusion



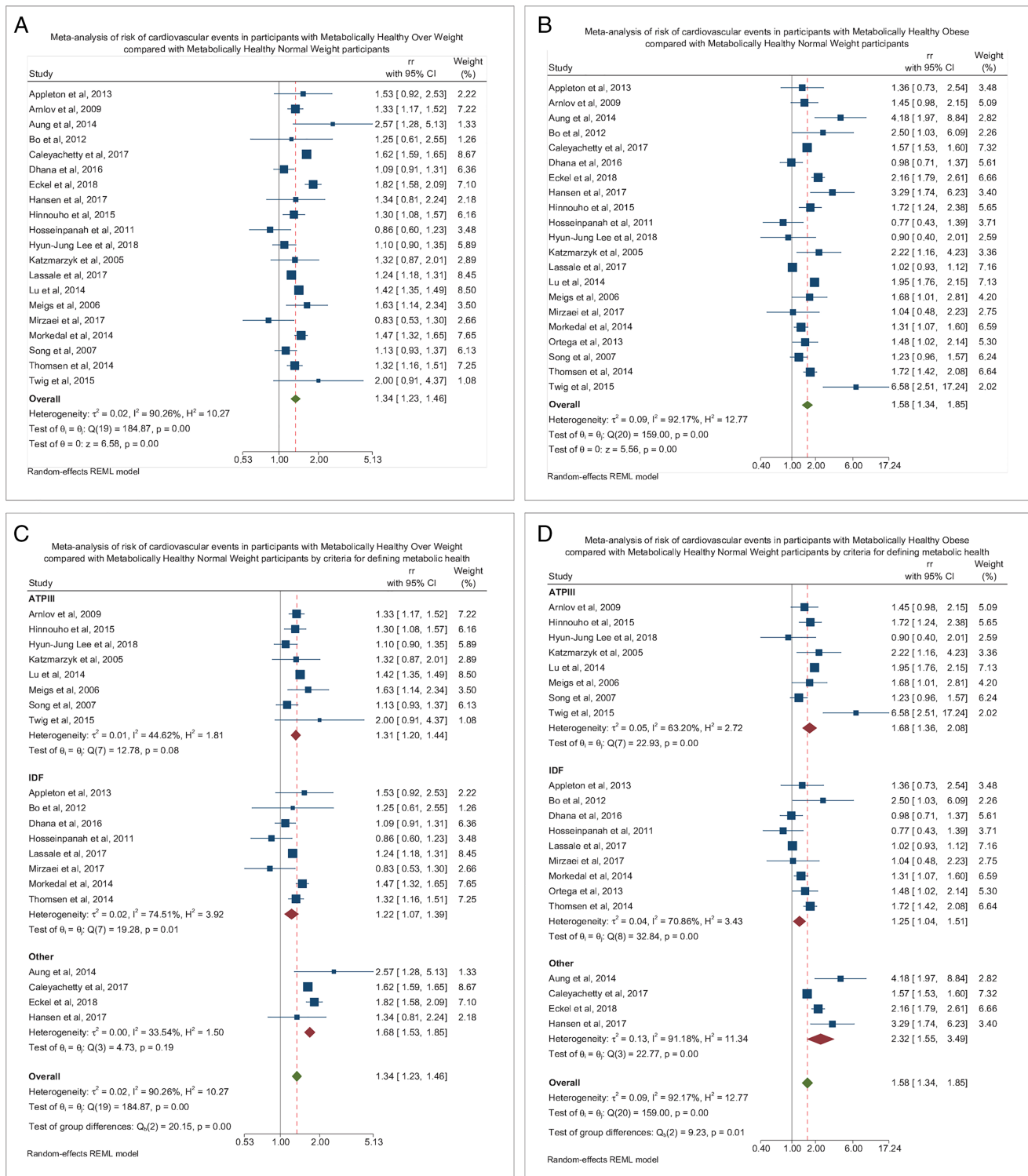
### 3.3 | MHO and risk of CVD

Twenty-one studies investigated the association between MHO and risk of CVD (Table S3). There was an increased risk of CVD in the group with MHO compared with the group with MHNW (RR = 1.58, CI: 1.34–1.85;  $I^2 = 92.2\%$ ); however, heterogeneity was high (Figure 2). This risk of CVD did not differ significantly from the overall effect size regardless of whether the CVD outcome was defined as composite (RR = 1.64, CI: 1.37–1.96,  $n = 16$ ,  $I^2 = 88.4\%$ ) or single entities of CVD (noncomposite) (RR = 1.43, CI: 0.99–2.07,  $n = 5$ ,  $I^2 = 91.8\%$ ). The pooled RR did not differ significantly according to study quality (high: RR = 1.58, CI: 1.38–1.81,  $n = 12$ ,  $I^2 = 69.8\%$ ; moderate: RR = 1.67, CI: 1.07–2.62,  $n = 9$ ,  $I^2 = 96.4\%$ ; sample size ( $\geq 6,000$ : RR = 1.57, CI: 1.31–1.88,  $n = 15$ ,  $I^2 = 93.9\%$ ;  $< 6,000$ : RR = 1.65, CI: 1.12–2.42,  $n = 6$ ,  $I^2 = 67.8\%$ ); geographic location (Europe: RR = 1.47, CI: 1.22–1.76,  $n = 10$ ,  $I^2 = 90.8\%$ ; North America: RR = 1.95, CI: 1.36–2.80,  $n = 5$ ,  $I^2 = 78.0\%$ ); or study follow-up duration ( $< 10$  years: RR = 1.89, CI: 1.13–3.17,  $n = 7$ ,  $I^2 = 94.5\%$ ;  $\geq 10$  years: RR = 1.51, CI: 1.27–1.79,  $n = 14$ ,  $I^2 = 83.8\%$ ). As for the MHO group, the risk in the MHO group was similarly increased

irrespective of the quantity of risk factors used to define metabolically healthy (0: RR = 2.18, CI: 1.28–3.71,  $n = 5$ ,  $I^2 = 94.7\%$ ;  $\leq 1$ : RR = 1.29, CI: 1.10–1.52,  $n = 4$ ,  $I^2 = 0.0\%$ ;  $\leq 2$ : RR = 1.54, CI: 1.26–1.88,  $n = 12$ ,  $I^2 = 86.6\%$ ). The risk of CVD remained high even when there were no metabolic risk factors.

The risk of CVD differed according to whether ATP III or IDF criteria were used, compared with those studies that used absence of hypertension, diabetes and dyslipidaemia ('other' criteria) to define metabolic health (NCEP ATP III: RR = 1.68, CI: 1.36–2.08,  $n = 8$ ,  $I^2 = 63.2\%$ ; IDF: RR = 1.25, CI: 1.04–1.51,  $n = 9$ ,  $I^2 = 70.9\%$ ; other criteria: RR = 2.32, CI: 1.55–3.49,  $n = 4$ ,  $I^2 = 91.8\%$ ). There was a statistically significant subgroup difference for criteria used to define metabolic health ( $Q = 9.23$ ,  $p = 0.01$ ) (Figure 2). Furthermore, the pooled effect size for risk of CVD in MHO compared with MHNW did not change when the study by Caleyachetty et al. (2017) with the greatest weighting was removed from analysis (data not shown). Again, these results should be interpreted with caution because of the small number of studies.

The pooled RR from studies with disaggregated data for females and males were similar (females: RR = 1.71, CI: 1.28–2.28,  $n = 3$ ,  $I^2 = 61.1\%$ ; males: RR = 2.15, CI: 1.88–2.46,  $n = 3$ ,  $I^2 = 0.0\%$ ). Although



**FIGURE 2** A, Meta-analysis of risk of cardiovascular events in participants with metabolically healthy overweight compared with metabolically healthy normal weight participants. B, Meta-analysis of risk of cardiovascular events in participants with metabolically healthy obesity compared with metabolically healthy normal weight participants. C, Meta-analysis of risk of cardiovascular events in participants with metabolically healthy overweight compared with metabolically healthy normal weight participants by criteria for defining metabolic health. D, Meta-analysis of risk of cardiovascular events in participants with metabolically healthy obesity compared with metabolically healthy normal weight participants by criteria for defining metabolic health

the risk of CVD appears to be greater in males than females, the number of studies was too few to reliably comment on the difference.

There was a significantly increased risk of all-cause mortality (RR = 1.59, CI: 1.02–2.47,  $n = 6$ ,  $I^2 = 86.2\%$ ) but not of

cardiovascular mortality (RR = 2.22, CI: 0.96–5.11,  $n = 4$ ,  $I^2 = 81.9$ ) in the group with MHO compared with the group with MHNW (Figures S4 and S5).

It is important to note that although overweight/obesity increases the risk of CVD in individuals who are metabolically-healthy, this study also determined that metabolic abnormality confers an even greater risk of CVD in individuals with normal weight (pooled RR = 3.07; CI: 2.27–4.15,  $n = 20$ ,  $I^2 = 99.17\%$ ) (data not shown).

### 3.4 | Investigating heterogeneity and publication bias

The results of the meta-analysis for MHOW had high heterogeneity except for studies with a sample size <6,000 ( $I^2 = 50.68\%$ ) and those studies that used ATP III criteria to define metabolic health ( $I^2 = 44.62\%$ ). High heterogeneity was also observed in the MHO analysis except in studies where metabolic health was defined by  $\leq 1$  risk factor ( $I^2 = 0.00\%$ ) and the high-quality studies where the heterogeneity was moderate ( $I^2 = 69.81\%$ ). Despite the high heterogeneity, the overall effect size did not significantly differ across subgroups in both the MHOW and MHO analyses; meta-regression and analysis of subgroup difference identified that the criteria used to define metabolic health in both MHOW and MHO populations, and gender in MHOW populations as a cause of heterogeneity (Tables 2 and 3).

The MHOW analysis showed no evidence of publication bias using a funnel plot and contour-enhanced funnel plot (Figures S6 and S7) or Egger's test (Table 2). The MHO analysis showed no evidence of publication bias using a funnel plot and contour-enhanced funnel plot (Figures S8 and S9) or Egger's test, except within studies grouped according to the criteria used to define metabolic health in which a small study effect was observed for studies using 'absence of hypertension, diabetes and dyslipidaemia' to define metabolic health (Egger's test Coef = 4.67;  $p$  value = 0.001) and studies with sample size <6,000 (Egger's test Coef = 3.19;  $p$  value = 0.001) (Table 3).

## 4 | DISCUSSION

This systematic review is the most up to date meta-analysis performed in the field with obesity categorized into six phenotypes and includes nine new studies with an additional 4,012,796 participants.<sup>20–22,25,26,29,34,35,37</sup> Some previous reviews included studies which classified obesity into two categories by either combining normal weight and overweight or using obesity cut-off of 25 kg/m<sup>2</sup>. Unlike previous reviews this review did not include individuals with overweight in the comparator population.<sup>9,14</sup> The use of a comparator group with MHNW enabled a more accurate estimate of the risk of CVD, cardiovascular mortality and all-cause mortality attributable to having MHOW/MHO.

The data confirmed an increased risk of CVD in people classified as having MHOW or MHO when compared with a cohort with normal weight and metabolically healthy, consistent with literature by Kramer et al.,<sup>10</sup> Fan et al.,<sup>9</sup> Eckel et al.,<sup>11</sup> Zheng et al.,<sup>12</sup> Ortega et al.<sup>13</sup> and Yeh et al.<sup>14</sup> However, this data also identified an increased risk of

CVD in the population with MHOW/MHO in the absence of any metabolic risk factors, perhaps the most robust definition of optimal metabolic health. This could be interpreted as evidence that the concept of MHOW/obesity does not exist. This is a new finding, and previous studies by Eckel<sup>11</sup> and Zheng<sup>12</sup> did not identify a statistically significant increased risk of CVD in populations with MHOW and MHO without metabolic risk factors. This finding may have practical implications where individuals with overweight or obesity without established CVD should be encouraged to achieve normal weight to decrease the risk of developing CVD even in the absence of cardio-metabolic risk factors.

However, caution is needed when interpreting these new data because of the high heterogeneity and limited numbers of studies. There was no clear dose-response curve established, that is, no graded increase in CVD risk when 0,  $\leq 1$  or  $\leq 2$  MS risk factor criteria were used for defining metabolically healthy within the groups with MHOW or MHO. However, the limited power from the small number of studies in each group could have resulted in a failure to detect a difference in effect size. Many studies reported the outcome data for participants without risk factors together with those having one or two risk factors in the definition of metabolic health, making it a challenge to relate the magnitude of cardiovascular risk directly to the number of risk factors with certainty.

This study revealed evidence of an increased risk of cardiovascular mortality and all-cause mortality in people with MHOW/MHO.

We performed meta-regressions and subgroup analyses to investigate heterogeneity and demonstrated that the risk of CVD in groups with MHO and MHOW compared with MHNW was not affected by the outcome definition, sample size, duration of follow-up, geographic location or quantity of metabolic risk factors used in the definition. The pooled effect size for risk of CVD in groups with MHOW/MHO compared with MHNW did not change when the study by Caleyachetty et al. (2017) with the greatest weighting was removed from analysis. All included studies were of high ( $n = 11$ ) or moderate quality ( $n = 10$ ) and there was no indication that quality affected the overall effect sizes; however, there was less heterogeneity in high-quality studies examining the risk of CVD in populations with MHO ( $I^2 = 69.81\%$ ). The results suggest that males and females with MHOW or MHO are at increased risk of CVD. The risk appeared to be greater for MHOW in females than males but was greater for MHO in males than females; this raises the possibility of differential effects between men and women, but this would need to be confirmed with much larger samples.

A limitation of these findings is the high heterogeneity observed for each pooled relative risk. Meta-regression analysis in both groups with MHO and MHOW identified that the criteria used by each study for defining metabolic health were a cause of some heterogeneity. There was a noticeable difference in the pooled relative risk according to whether ATP III or IDF criteria were used to define metabolic health compared with those studies that used absence of hypertension, diabetes and dyslipidaemia to define metabolic health. This emphasizes the need for a standard criteria that can be used to define metabolic health in future research. Another limitation was that most studies did not include cardiorespiratory fitness (CRF) and

**TABLE 2** Subgroups analysis of the risk of cardiovascular disease in participants with metabolically healthy overweight compared with participants with metabolically healthy normal weight

| Subgroup  | Effect size RR (95% CI) | Number of studies | Egger's test for small study effects:<br>Statistic & p value | Test of group difference:<br>Statistic & p value |
|---|-------------------------|-------------------|--|--|
| Overall   | 1.34 (1.23–1.46)        | 20                | $z = -0.22$<br>$p = 0.83$                                    | –  |
| Outcome   |                         |                   |  |  |
| Composite                                       | 1.36 (1.20–1.53)        | 15                | $z = -0.05, p = 0.96$  | $Q_b = 0.32$                                     |
| Noncomposite                                    | 1.30 (1.18–1.43)        | 5                 | $z = -0.19, p = 0.85$  | $p = 0.57$                                       |
| Quality   |                         |                   |  |  |
| High  | 1.43 (1.29–1.58)        | 11                | $z = -0.58, p = 0.56$  | $Q_b = 3.72$                                     |
| Moderate  | 1.22 (1.07–1.38)        | 9                 | $z = 0.60, p = 0.55$   | $p = 0.05$                                       |
| Sample size                                     |                         |                   |  |  |
| <6,000  | 1.36 (1.14–1.64)        | 6                 | $z = 1.55, p = 0.12$   | $Q_b = 0.07$                                     |
| ≥6,000  | 1.33 (1.19–1.47)        | 14                | $z = -1.49, p = 0.14$  | $p = 0.80$                                       |
| Criteria for defining metabolic health          |                         |                   |  |  |
| ATP III   | 1.31 (1.20–1.44)        | 8                 | $z = 0.45, p = 0.66$   | $Q_b = 20.15$                                    |
| IDF   | 1.22 (1.07–1.39)        | 8                 | $z = -1.23, p = 0.22$  | $P < 0.001$                                      |
| Other   | 1.68 (1.53–1.85)        | 4                 | $z = 0.90, p = 0.37$   |  |
| Number of risk factors in metabolically healthy |                         |                   |  |  |
| 0   | 1.51(1.21–1.88)         | 5                 | $z = -0.00, p = 0.99$  | $Q_b = 1.87$                                     |
| 1 or less                                       | 1.25 (0.87–1.80)        | 3                 | $z = -0.19, p = 0.85$  | $p = 0.39$                                       |
| 2 or less                                       | 1.29 (1.21–1.38)        | 12                | $z = 0.00, p = 0.99$   |  |
| Geographic location                             |                         |                   |  |  |
| Asia  | 1.27 (1.00–1.63)        | 2                 |  | $Q_b = 3.92$                                     |
| Australia                                       | 1.53 (0.92–2.53)        | 1                 |  | $p = 0.42$                                       |
| Europe  | 1.35 (1.23–1.48)        | 9                 | Europe: $z = -0.99, p = 0.32$                                |  |
| Middle East                                     | 0.99 (0.67–1.46)        | 3                 |  |  |
| North America                                   | 1.54 (1.20–1.96)        | 5                 | North America: $z = 0.82, p = 0.41$                          |  |
| Duration of follow up                           |                         |                   |  |  |
| <10 years                                       | 1.34 (1.08–1.68)        | 7                 | $z = 0.62, p = 0.5360$                                       | $Q_b = 0.00$                                     |
| 10+ years                                       | 1.34 (1.22–1.47)        | 13                | $z = -0.53, p = 0.5947$                                      | $p = 0.98$                                       |
| Gender  |                         |                   |  |  |
| Female  | 1.46 (1.26–1.69)        | 3                 | $p = 0.94$   | $Q_b = 4.75$                                     |
| Male  | 1.22 (1.14–1.30)        | 3                 | $p = 0.46$   | $p = 0.03$                                       |

Note: Egger's test of small study effects and meta-regression analysis were not done for geographic location because of small numbers in some groups. Gender: studies with mixed females and males participants. z Test statistics for Egger's test.  $Q_b$  Test statistics for test of group difference.  $p = p$  Value. ATP III: Adult Treatment Panel III criteria for metabolic syndrome. IDF: International Diabetes Federation criteria for metabolic syndrome. Other: metabolic health defined by absence of hypertension, diabetes and dyslipidaemia.

physical activity (PA). The review by Ortega et al. found that the difference in all-cause mortality and CVD mortality/morbidity between MHO and MHNW was largely explained by difference in CRF between the two phenotypes.<sup>13</sup> A state-of-the-art-review on prevention and treatment of obesity indicated the significance of including CRF and PA as covariates in the models when comparing risk of CVD in MHO and MHNW.<sup>42</sup> Moholdt T et al. showed that in coronary artery disease, PA was more important than weight for predicting survival<sup>43</sup> and changes in PA were much more important than changes in weight for predicting survival.<sup>44</sup>

## 5 | RECOMMENDATIONS

This research suggests that there is increased risk of CVD in people with MHOW or MHO. There is a need for a standard definition of metabolic health. It is recommended that future research examining the relationship between MHOW, MHO and the risk of CVD:

- categorize metabolic risk factors into discrete groups of no risk factors, one, two or three or more risk factors and define metabolically healthy as having no risk factors.

**TABLE 3** Subgroups analysis of the risk of cardiovascular disease in participants with metabolically healthy obesity compared with participants with metabolically healthy normal weight

| Subgroup  | Effect size (95% CI) | Number of studies | Egger's test for small study effects: Statistic & p value | Test of group difference: Statistic & p value |
|---|----------------------|-------------------|---|---|
| Overall   | 1.58 (1.34–1.85)     | 21                | $z = 1.46$<br>$p = 0.14$                                  | -   |
| Outcome   |                      |                   |   |   |
| Composite                                       | 1.64 (1.37–1.96)     | 16                | $z = 1.12, p = 0.26$                                      | $Q_b = 0.39$                                  |
| Noncomposite                                    | 1.43 (0.99–2.07)     | 5                 | $z = 0.58, p = 0.56$                                      | $p = 0.53$                                    |
| Quality   |                      |                   |   |   |
| High  | 1.58 (1.38–1.81)     | 12                | $z = 0.32, p = 0.75$                                      | $Q_b = 0.05$                                  |
| Moderate  | 1.67 (1.07–2.62)     | 9                 | $z = 1.10, p = 0.27$                                      | $p = 0.82$                                    |
| Sample size                                     |                      |                   |   |   |
| <6,000  | 1.65 (1.12–2.42)     | 6                 | $z = 0.78, p = 0.44$                                      | $Q_b = 0.05$                                  |
| ≥6,000  | 1.57 (1.31–1.88)     | 15                | $z = 3.19, p = 0.001$                                     | $p = 0.82$                                    |
| Criteria for defining metabolic health          |                      |                   |   |   |
| ATP III   | 1.68 (1.36–2.08)     | 8                 | $z = 0.92, p = 0.36$                                      | $Q_b = 9.23$                                  |
| IDF   | 1.25 (1.04–1.51)     | 9                 | $z = 0.26, p = 0.80$                                      | $p = 0.01$                                    |
| Other   | 2.32 (1.55–3.49)     | 4                 | $z = 4.67, p < 0.001$                                     |   |
| Number of risk factors in metabolically healthy |                      |                   |   |   |
| 0   | 2.18 (1.28–3.71)     | 5                 | $z = 0.75, p = 0.45$                                      | $Q_b = 4.46$                                  |
| 1 or less                                       | 1.29 (1.10–1.52)     | 4                 | $z = -0.76, p = 0.45$                                     | $p = 0.11$                                    |
| 2 or less                                       | 1.54 (1.26–1.88)     | 12                | $z = 1.48, p = 0.14$                                      |   |
| Geographic location                             |                      |                   |   |   |
| Asia  | 1.47 (0.71–3.05)     | 2                 |   |   |
| Australia                                       | 1.36 (0.73–2.54)     | 1                 |   | $Q_b = 2.16$                                  |
| Europe  | 1.46 (1.23–1.74)     | 10                | Europe: $z = 1.76, p = 0.08$                              | $p = 0.71$                                    |
| Middle East                                     | 1.67 (0.46–5.98)     | 3                 |   |   |
| North America                                   | 1.95 (1.36–2.78)     | 5                 | North America: $z = 1.23, p = 0.22$                       |   |
| Duration of follow up                           |                      |                   |   |   |
| <10 years                                       | 1.89 (1.13–3.17)     | 7                 | $z = 0.9, p = 0.37$                                       | $Q_b = 0.66$                                  |
| 10+ years                                       | 1.51 (1.27–1.79)     | 14                | $z = 0.68, p = 0.49$                                      | $p = 0.42$                                    |
| Gender  |                      |                   |   |   |
| Female  | 1.71 (1.28–2.29)     | 3                 | $p = 0.51$  | $Q_b = 1.99$                                  |
| Male  | 2.15 (1.88–2.46)     | 3                 | $p = 0.18$  | $p = 0.16$                                    |

Note: Egger's test of small study effects and meta-regression analysis were not done for geographic location because of small numbers in some groups. Gender: studies with mixed females and males participants.  $z$  Statistic for Egger's tests.  $Q_b$  Statistics for test of group difference.  $p = p$  Value. ATP III: Adult Treatment Panel III criteria for metabolic syndrome. IDF: International Diabetes Federation criteria for metabolic syndrome. Other: Metabolic health defined by absence of hypertension, diabetes and dyslipidaemia.

- design prospective cohorts with sufficient sample size and follow-up duration to determine CVD risk within population subgroups.
- consider inclusion of other factors associated with metabolic health (e.g., CRF, PA, hepatic fat and inflammatory status determined by C-reactive protein levels)
- report changes in metabolic parameters over time.
- include and report data on participants from other regions (e.g., Oceania, Africa, South America, Asia and Middle East) to increase diversity of the study population.

## 6 | CONCLUSIONS

This systematic review and meta-analysis found an increased risk of CVD in populations with overweight and obesity considered metabolically healthy compared with those classified as normal weight and metabolically healthy. The risk was similar regardless of whether the definition of metabolically healthy included those who had none, one or less, two or less metabolic risk factors. The risk of CVD remained high even when there were no metabolic

risk factors. Hence the term 'metabolically healthy' may be a misnomer.

### CONFLICT OF INTEREST

No conflict of interest was declared by the authors in relation to the research, authorship and publication of this study. All authors declared that there is no support from or financial relationship with any organization that might have an interest in the submitted work in the previous 36 months and that there is no other relationships or activities that could appear to have influenced the submitted work.

### AUTHOR CONTRIBUTIONS

Mark McEvoy (PhD), A/Professor of Epidemiology: lead investigator, planning and supervising progress of study; one of the independent investigators who conducted quality assessment of the studies; wrote and reviewed the paper from draft stage to completion. Katie Wynne (PhD), A/Professor of Endocrinology: planning and supervising progress of the study; third investigator who was consulted for resolution of any disagreement during data search; reviewed the paper from draft stage to completion. Emma Croker (MBBS), Advanced Trainee in Endocrinology: planning the study, literature search, reviewed literature; one of the independent investigators who analysed citations for relevant studies and conducted data extraction; reviewed the paper from draft stage to completion. John Attia (PhD), Professor of Medicine and Epidemiology: reviewed the paper from draft stage to completion. George S Odongo (MPH), Statistician: performed data analysis. Jacob Opió (Master Clinical Epidemiology), PhD Candidate: planning the study including drawing study protocol; made search terms, performed literature search and review; one of the independent investigators who analysed citations, extracted data and conducted quality assessment, wrote and reviewed the paper from draft stage to completion.

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#### SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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