

# BMJ Open Does high-carbohydrate intake lead to increased risk of obesity? A systematic review and meta-analysis

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## ABSTRACT

**Objectives** The present study aimed to test the association between high and low carbohydrate diets and obesity, and second, to test the link between total carbohydrate intake (as a percentage of total energy intake) and obesity.

**Setting, participants and outcome measures** We sought MEDLINE, PubMed and Google Scholar for observation studies published between January 1990 and December 2016 assessing an association between obesity and high-carbohydrate intake. Two independent reviewers selected candidate studies, extracted data and assessed study quality.

**Results** The study identified 22 articles that fulfilled the inclusion and exclusion criteria and quantified an association between carbohydrate intake and obesity. The first pooled strata (high-carbohydrate versus low-carbohydrate intake) suggested a weak increased risk of obesity. The second pooled strata (increasing percentage of total carbohydrate intake in daily diet) showed a weak decreased risk of obesity. Both these pooled strata estimates were, however, not statistically significant.

**Conclusions** On the basis of the current study, it cannot be concluded that a high-carbohydrate diet or increased percentage of total energy intake in the form of carbohydrates increases the odds of obesity. A central limitation of the study was the non-standard classification of dietary intake across the studies, as well as confounders like total energy intake, activity levels, age and gender. Further studies are needed that specifically classify refined versus unrefined carbohydrate intake, as well as studies that investigate the relationship between high fat, high unrefined carbohydrate–sugar diets.

**PROSPERO registration number** CRD42015023257.

## INTRODUCTION

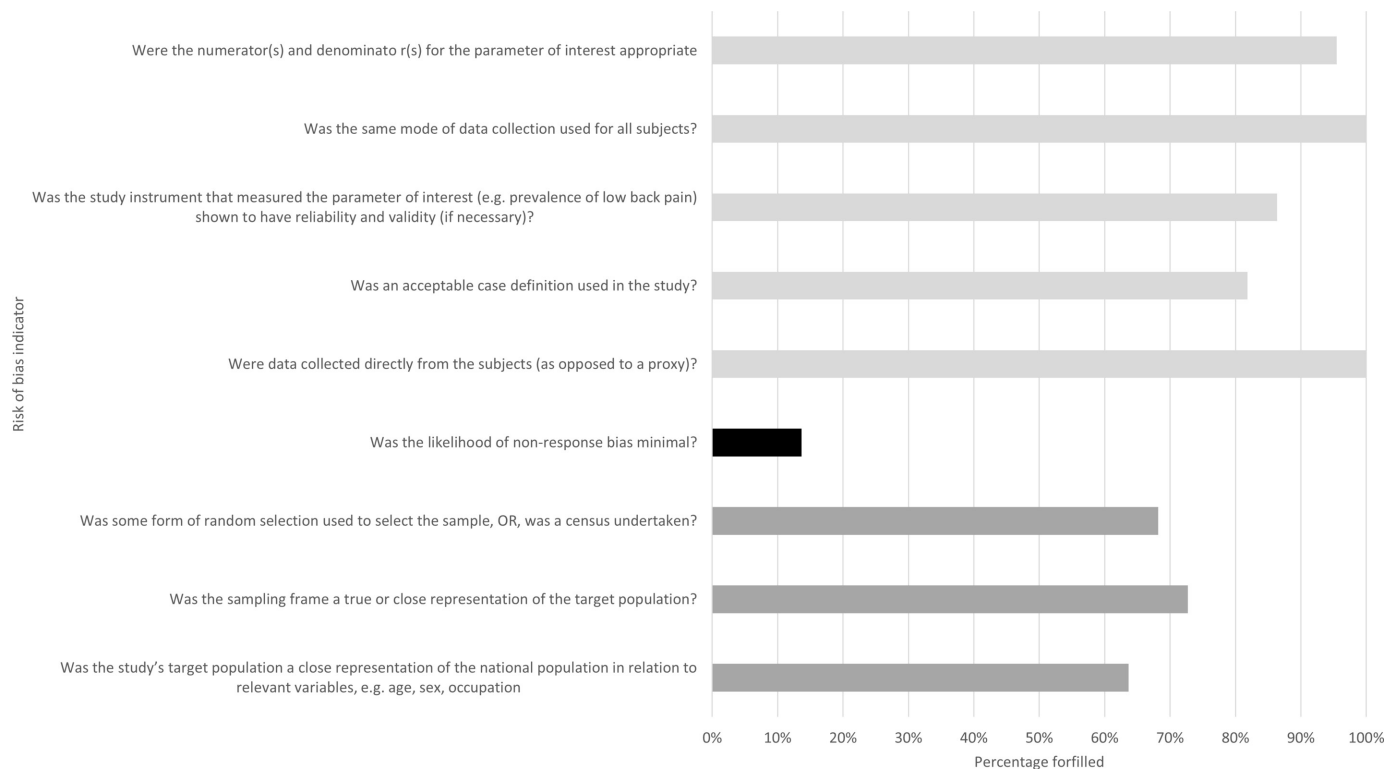
Global estimates in 2005 indicated 937 million people were overweight and 328 million were obese.<sup>1</sup> In 2010, an estimated 3.4 million deaths, 3.9% of years of life lost, and 3.8% of disability-adjusted life-years worldwide, were attributed to overweight and obesity.<sup>2</sup> The rate of change of obesity in this global study indicated significant increases in both men and women. In men the proportion of adults with a body mass index (BMI) of 25 or greater increased from 28.8% in 1980 to 36.9% in

## Strengths and limitations of this study

- Systematic review of observational studies across low income, middle income countries and high income countries and first to explore this angle as far as we are aware.
- The scarcity of studies and/or data that either measured obesity risk versus total carbohydrate intake or alternatively measured obesity risk on the basis of a high versus low carbohydrate intake is a limitation.
- The non-standardised instruments for total dietary and total carbohydrate intake across studies is a further limitation.
- The heterogeneity in the classification of dietary carbohydrates and variation in staple carbohydrates is especially emphasised across different countries/cultures as well as developed versus developing settings and has been further compounded by socioeconomic changes over the last three decades.
- Studies with high heterogeneity and varying design and measurement quality may limit the quality of evidence from this study.

2013 and for women increased from 29.8% to 38%. These increases occurred in both developed and low income, middle income countries. In addition, significant increases in obesity were also recorded among children and adolescents in developed countries that indicated 23.8% of boys were either overweight or obese and 22.6% of girls. Overweight and obesity is also increasing in children and adolescents in low income, middle income countries and has risen from 8.1% in 1980 to 12.9% in 2013 for boys and from 8.4% to 13.4% for girls.<sup>2</sup> The relationship between dietary intake, and specifically the role of carbohydrates and obesity at a population level, is also unclear.

The aetiology of obesity increasingly reflects excessive calorie intake matched with higher levels of sedentary activity that occur in the face of a worldwide urban migration. In this scenario, traditional diets are often replaced with low cost energy dense



**Figure 1** Risk of bias assessment of the nine indicators comparing the Hoy *et al*<sup>14</sup> instrument (light grey, low risk; medium grey, moderate risk; black, high risk).

foodstuffs produced by the industrialised food.<sup>3–5</sup> Body weight is ultimately determined by the interaction of genetic, environmental and psychosocial factors acting through the physiological mediators of energy intake and energy expenditure.<sup>6–8</sup> Nevertheless, carbohydrates have been linked to disease for many decades<sup>9</sup> and more recently with an epidemic of type 2 diabetes.<sup>10</sup> Although there is no consistent evidence that carbohydrates have driven the current levels of global obesity, carbohydrates form a major component of most national diets.<sup>11</sup>

The objective of this systematic review/meta-analysis is to investigate the relationship between carbohydrate intake and obesity. More specifically, the first question is whether a high versus low carbohydrate diet is a risk factor for obesity and second, whether total carbohydrate intake is a risk factor related to obesity?

## MATERIALS AND METHODS

### Registration of protocol with PROSPERO

In accordance with the guidelines, the systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 8 June 2015. The protocol was also formally peer reviewed and published in *BMJ Open*. Carbohydrate intake, obesity, metabolic syndrome and cancer risk? A two-part systematic review and meta-analysis protocol to estimate attributability.<sup>12</sup>

This systematic review was aligned to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

guidelines<sup>13</sup> to ensure all necessary steps have been followed (see online supplementary table 1).

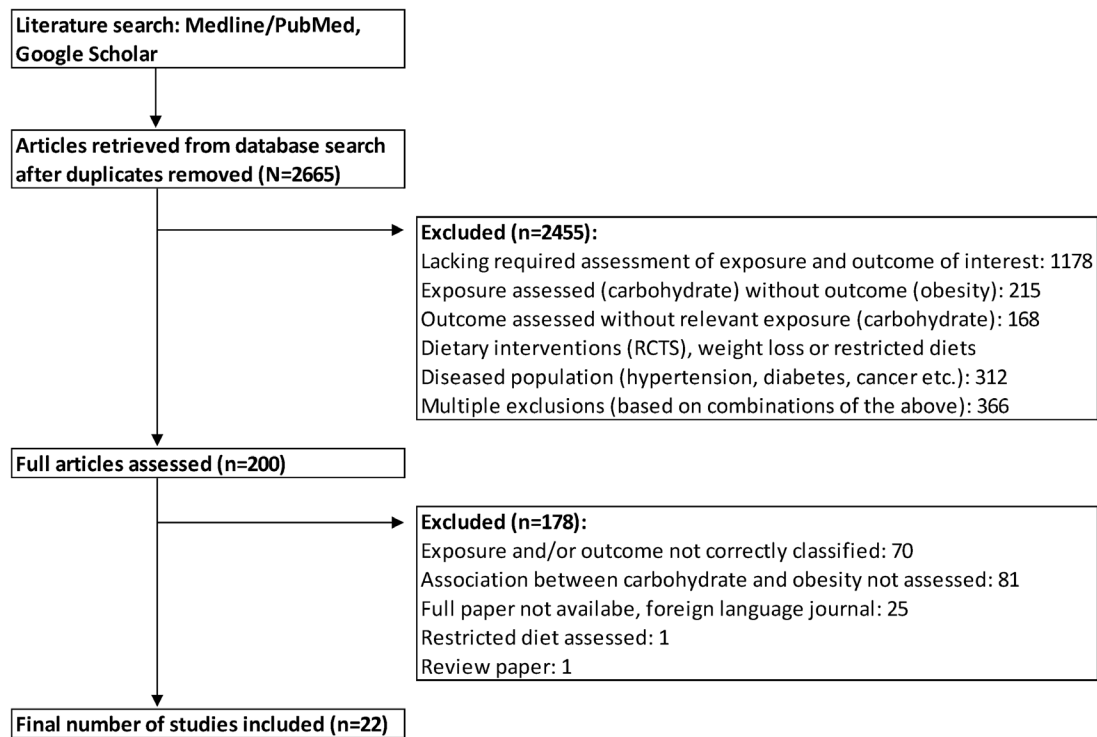
### Data sources and searches

We used MEDLINE/PubMed and Google Scholar to identify suitable studies that evaluated the determinants of obesity including the effect of high versus low carbohydrate diets, as well as the percentage of carbohydrates in total dietary intake. Studies published between 1 January 1980 and 31 December 2016 were included. In addition, web-based studies that were unpublished (eg, reports or unpublished theses) were evaluated using research engines like Google Scholar. The following keywords or medical subject headings on MEDLINE/PubMed and Google Scholar were used:

('carbohydrate' OR 'low carbohydrate' OR 'low carb' OR 'high carbohydrate' OR 'high carb') AND ('composition' OR 'diet' OR 'dietary' OR 'intake' OR 'determinant') AND ('obesity' OR 'obese') AND ('attributable' OR 'odds' OR 'risk' OR 'hazard' OR 'prevalence').

### Study screening and selection

We included studies examining healthy adults (18 years or older). We also included studies on people who were overweight or obese, but otherwise excluded (after evaluation) studies of populations restricted to specific diseases, conditions or metabolic disorders. Of specific interest were general population studies that investigated the prevalence of obesity in relation to detailed dietary intake.<sup>11</sup> Studies quantifying dietary intake in terms of



**Figure 2** PRISMA flow diagram for study selection following search and selection/exclusion process. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

total carbohydrate intake as a percentage of total energy, and high versus low carbohydrate intake in relation to the odds of obesity, were included.

Two authors (KS, BS) independently screened study titles and abstracts for potential eligibility. Screening questions were developed and pilot-tested with a subset of records before implementation. Full texts of potentially eligible studies were retrieved and the two authors independently applied inclusion/exclusion criteria to identify appropriate studies in this review. Disagreement was assessed using the kappa statistic and was resolved through discussion and a third arbitrator. We developed a summary table with characteristics of included studies. Reasons for exclusion of studies were documented.

### Appraisal of the quality of included studies

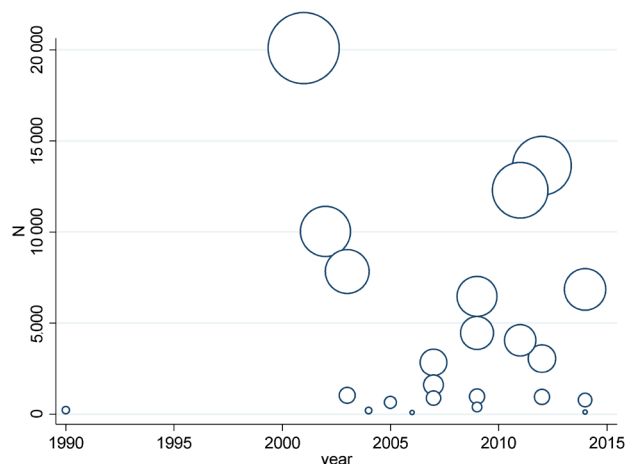
Three reviewers (KS, CS, TM) were content experts and one reviewer was an experienced biostatistician and epidemiologist (BS). The contents experts only assessed potential publications with respect to the appropriateness of the research questions being tested. The biostatistician only evaluated the appropriateness of the individual study methods employed to ensure that an OR was developed to assess the relationship between carbohydrate intake and the risk of obesity.

Two reviewers (BS, KS) also evaluated studies for quality and bias using an adapted version of the Risk of Bias Tool for Prevalence Studies developed by Hoy *et al.*<sup>14</sup> The tool has nine indicators to assess risk of bias which include the representativeness of sample, sampling

frame, random selection, non-response bias, direct informant and reliability/validity of the instrument(s). We dichotomised the quality appraisal for each item on the Hoy scale as ‘low risk’, that is, 0 or ‘high risk’, that is, 1. We further classified a response rate <80% with no assessment of responders versus non-responders as high risk in our assessment of the non-response indicator. If the selected text of the manuscript was unclear with regards to a specific indicator, when then assigned a high risk of bias. A study was considered to have a high overall risk of bias if  $\leq 3$  criteria were met, moderate risk of bias if 4–6 criteria were met and low risk of bias if studies met 7–9 criteria. The detailed assessment of risk of bias for the selected 22 studies are presented in online supplementary table 2. Only 1 study was scored as having a high risk of bias, 7 scored a medium risk of bias and the majority (n=14) were scored as low risk of bias. The potential of non-response bias appeared high based on the 80% minimum response rate cut-off. The sampling frame and strategy were the next least fulfilled criteria based on the bias criteria indicators on the Hoy instrument (figure 1).

### Inclusion and exclusion criteria

We included cross-sectional, case-control or cohort studies assessing risk factors for obesity including dietary carbohydrate intake (carbohydrate percentage intake of total energy and high vs low carbohydrate intake). Case series or case reports without controls were excluded. We excluded studies assessing restricted dietary interventions as our primary objective was to assess reported



**Figure 3** Study sample size by year (combined strata).

carbohydrate intake and measured obesity in normal diet. Studies not performed in human participants were excluded, as were studies lacking primary data and/or explicit method description. Studies with major ethical issues were also excluded. The classification of obesity was based on BMI or visceral obesity (waist circumference). We considered both published and unpublished studies. No language restriction was applied.

#### Data extraction and management

Feedback was solicited from the research team regarding the draft list of data variables for extraction. Data extraction forms were developed and pilot-tested in Distiller SR. One person (BS) extracted all the information. A second person (KS) verified 20% of studies for general characteristics information and 100% of studies regarding outcome data. Disagreements were resolved by consensus or by a third team member. Information on the descriptive and quantitative characteristics of studies included the following: publication details (eg, year of publication, language, publication status), characteristics of study (eg, study design, methods, country, setting, sample size, number of centres (if applicable), duration of follow-up, source of funding), characteristics of population (eg, age, gender, ethnicity, cointerventions, information regarding respondent bias or representativeness of the included population) and details about the exposure (eg, type of diet, percentage of total calories obtained from carbohydrate consumption, method of assessing carbohydrate consumption; type of educational or other interventions and description, type of professional delivering intervention). Following extraction of data we noted the need to stratify the studies in two exposure strata, namely:

- ▶ High versus low carbohydrate intake.
- ▶ Total carbohydrate percentage intake of total energy.

#### Data synthesis/analysis

Data were analysed using a random-effect meta-analysis model and incorporating a restricted maximum-likelihood variance estimator. Effect measures were presented

as ORs with 95% CIs. All analyses were performed using R software V.3.2.0 or later (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria; <http://www.R-project.org/>). The following packages were of R software were used for the meta-analyses: ‘meta’ V.4.2–0 (General Package for Meta-Analysis) and ‘metafor’ V.1.9–7 (A comprehensive collection of functions for conducting meta-analyses in). Recent Grading of Recommendations Assessment, Development, and Evaluation (GRADE) guidelines were used for preparing summary tables for the primary outcomes.<sup>15 16</sup>

#### Heterogeneity

We assessed statistical heterogeneity in our meta-analysis using the  $I^2$  statistic. If the  $I^2$  was greater than 50% we regarded this as substantial heterogeneity.

#### Publication bias

We investigated publication bias using funnel plots and Eggers test.<sup>17</sup> In cases where asymmetry was present based on visual assessment, we performed exploratory analyses to investigate and adjust this using trim and/or fill analysis.<sup>18</sup>

#### Sensitivity analysis

To further identify potential sources of heterogeneity, we performed the following subgroup analysis by type of carbohydrate intake that is, high versus low classification compared with carbohydrate percentage intake of total energy.

## RESULTS

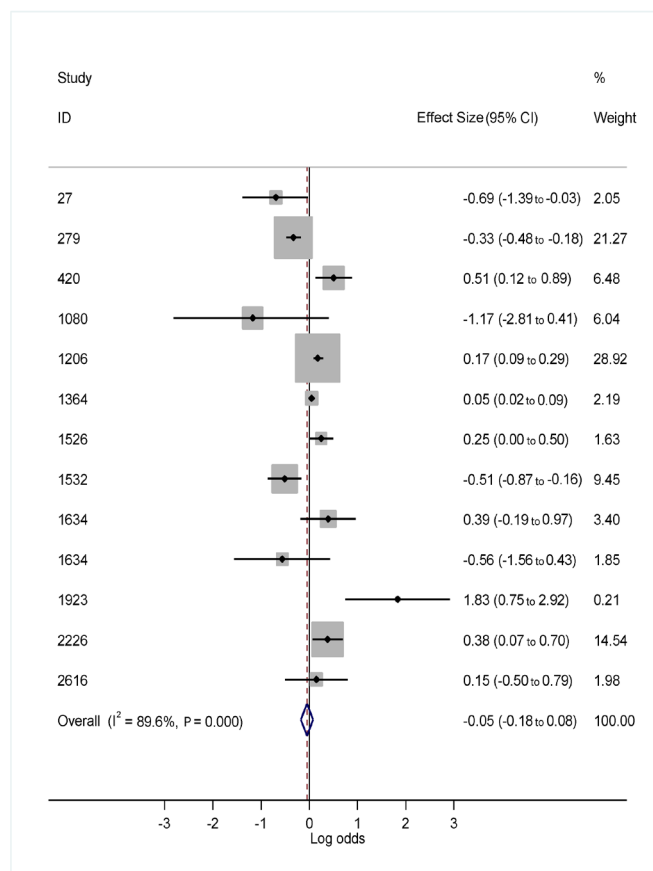
Of 2665 retrieved citations, 200 articles were selected following abstract screening, following which 22 articles met the inclusion criteria. **Figure 2** shows our search and selection/exclusion process. There was high agreement between articles selected based on abstract screening between the two reviewers (96.12% agreement between two independent raters, \*kappa statistic=0.633,  $P<0.001$ ). **Figure 3** shows that all but one of the eligible and selected articles were published since 2000. There were a few large studies in early 2000s, a decrease in sample size of studies in mid-2000s period and then increase in sample size from 2009.

The ORs of becoming obese based on carbohydrate intake were tested using two strata of data (**table 1**). Stratum 1 was based on high versus low classification of carbohydrate intake while stratum two assessed carbohydrate percentage intake of total energy. In stratum 1, 13 adult-based studies showed a non-significant pooled OR of 1.043 (95% CI: 0.933 to 1.154) indicating a slight positive relationship between high-carbohydrate intake and obesity (**figure 4**). Within this stratum, eight studies showed an increased risk of obesity and five studies a reduced risk of obesity. Of the eight studies showing an increased risk, four Korean-based studies, making up

**Table 1** ORs (and log odds) for developing obesity as a result of high versus low carbohydrate diet (strata 1) or increasing carbohydrate intake percentage (strata 2)

Strata	Identification Number	Study	Exposure measured	OR	95% CI	Log OR	95% CI	Sample size
1	27	Ahluwalia <i>et al</i> <sup>48</sup>						
1	279	Bowman and Spence <sup>49</sup>	Above 55% calories (high) vs 0%–30% calories (very low)	0.72	0.62 to 0.84	-0.14	-0.21 to -0.08	10014
1	420	Choi <i>et al</i> <sup>50</sup>	Quartile (Q) 4 vs 1	1.66	1.13 to 2.43	0.22	0.05 to 0.39	3050
1	1080	Jackson <i>et al</i> <sup>51</sup>	Tertiale 3 vs 1 for Carbohydrate intake	0.31	0.06 to 1.50	-0.51	-1.22 to 0.18	2842
1	1206	Kim <i>et al</i> <sup>52</sup>	Tertiale 3 vs 1 for white rice and kimchi	1.19	1.09 to 1.33	0.08	0.04 to 0.12	13618
1	1364	Lin <i>et al</i> <sup>53</sup>	Rice dietary pattern	1.05	1.02 to 1.09	0.02	0.01 to 0.04	1030
1	1526	Meng <i>et al</i> <sup>54</sup>	Staple food and vegetables higher obesity (Q4 vs Q1 higher proportion carb intake)	1.28	1.00 to 1.64	0.11	0 to 0.22	768
1	1532	Merchant <i>et al</i> <sup>55</sup>	Quartiles of carbohydrate intake compared with the lowest intake category (Q4 vs Q1)	0.60	0.42 to 0.85	-0.22	-0.38 to -0.07	4451
1	1634	Murtaugh <i>et al</i> <sup>56</sup>	High versus low: carbohydrate (% energy)—non-Hispanic (white)	1.48	0.83 to 2.63	0.17	-0.08 to 0.42	1599
1	1634	Murtaugh <i>et al</i> <sup>56</sup>	High versus low: carbohydrate (% energy)—Hispanic	0.57	0.21 to 1.54	-0.24	-0.68 to 0.19	871
1	1923	Rathnayake <i>et al</i> <sup>57</sup>	Percent of energy from carbohydrate: high (≥70%)	6.26	2.11 to 18.57	0.80	0.32 to 1.27	100
1	2226	Song <i>et al</i> <sup>58</sup>	Energy from Carbohydrates (Q5 vs Q1)	1.46	1.07 to 2.01	0.16	0.03 to 0.30	6845
1	2616	Youn <i>et al</i> <sup>59</sup>	Q4 vs Q1 carbohydrate intake	1.16	0.60 to 2.21	0.06	-0.22 to 0.35	933
2	130	Austin <i>et al</i> <sup>60</sup>	Carbohydrate intake (% of energy)—NHANES I	0.99	0.95 to 1.04	0.00	-0.02 to 0.02	12276
2	130	Austin <i>et al</i> <sup>60</sup>	Carbohydrate intake (% of energy)—NHANES 2005/2006	0.99	0.95 to 1.03	0.00	-0.02 to 0.01	4057
2	782	Garaulet <i>et al</i> <sup>61</sup>	Carbohydrate intake (% of energy)	0.71	0.25 to 2.07	-0.15	-0.60 to 0.32	193
2	930	Hartline-Grafton <i>et al</i> <sup>62</sup>	Carbohydrate intake (% of energy)	0.83	0.54 to 1.29	-0.08	-0.27 to 0.11	373
2	1297	Langlois <i>et al</i> <sup>63</sup>	Carbohydrate intake (% of energy)	1.02	0.98 to 1.07	0.01	-0.01 to 0.03	6454
2	1410	Lyles III <i>et al</i> <sup>64</sup>	Carbohydrate dietary variety score	1.42	0.85 to 2.36	0.15	-0.07 to 0.37	74
2	1426	Ma <i>et al</i> <sup>65</sup>	Daily dietary glycemic index versus BMI continuous	2.12	1.23 to 3.67	0.33	0.09 to 0.56	641
2	1480	Maskarinec <i>et al</i> <sup>66</sup>	Carbohydrate (1 g/100 kcal)	1.08	1.04 to 1.12	0.03	0.02 to 0.05	101699
2	1557	Miller <i>et al</i> <sup>67</sup>	Lean vs obese subjects and energy derived from carbohydrates	0.87	0.67 to 1.13	-0.06	-0.18 to 0.05	216
2	1587	Mokhtar <i>et al</i> <sup>68</sup>	Carbohydrate mean daily energy intake	1.07	1.05 to 1.09	0.03	0.02 to 0.04	20080
2	2591	Yang <i>et al</i> <sup>69</sup>	Carbohydrate intakes (% of energy)	0.39	0.24 to 0.64	-0.41	-0.62 to -0.19	7828

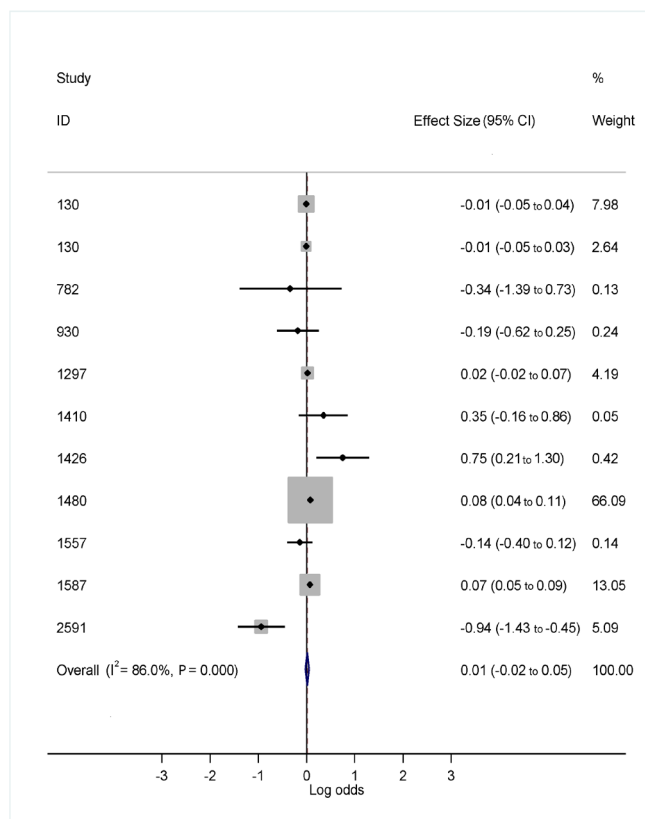
BMI, body mass index; NHANES, National Health and Nutrition Examination Surveys.



**Figure 4** Forest plot of association (logs OR) between high and low carbohydrate intake and obesity.

51.92% of the total pooled sample, showed an increased risk of obesity related to high-carbohydrate diets (ID 420, 2616), a high-carbohydrate rice-based diet (1206) and a high carbohydrate refined grains based diet (2226). Two studies in the South Western United States showed contrasting odds in the risk of obesity across two ethnic groups. In these two studies, Hispanic women indicated a reduced risk of obesity in relation to a high-carbohydrate diet, whereas white women indicated an increased risk of obesity. The highest odds of increased obesity were indicated in a Sri Lankan study involving high levels of inactivity, as well as a high-carbohydrate intake.

In strata 2, 11 adult-based studies investigated the relationship between total calorie intake of carbohydrates and the odds of obesity. Six studies showed a reduced risk and five an increased risk (figure 5), once more with a non-significant pooled OR of 0.984 (95% CI: 0.926 to 1.042), in opposite direction to results observed for stratum 1 (table 1). One study, involving multiple surveys of a multiethnic Hawaiian population (ID 1480), making up 66% of the total pooled sample, indicated a 7.7% increased risk of obesity in response to a higher percentage of total carbohydrate intake. Conversely, the three US-based National Health and Nutrition Examination Surveys (NHANES), making up 15.71% of the total pooled sample indicated no



**Figure 5** Forest plot of association (log OR) between percentage of total carbohydrate intake and obesity.

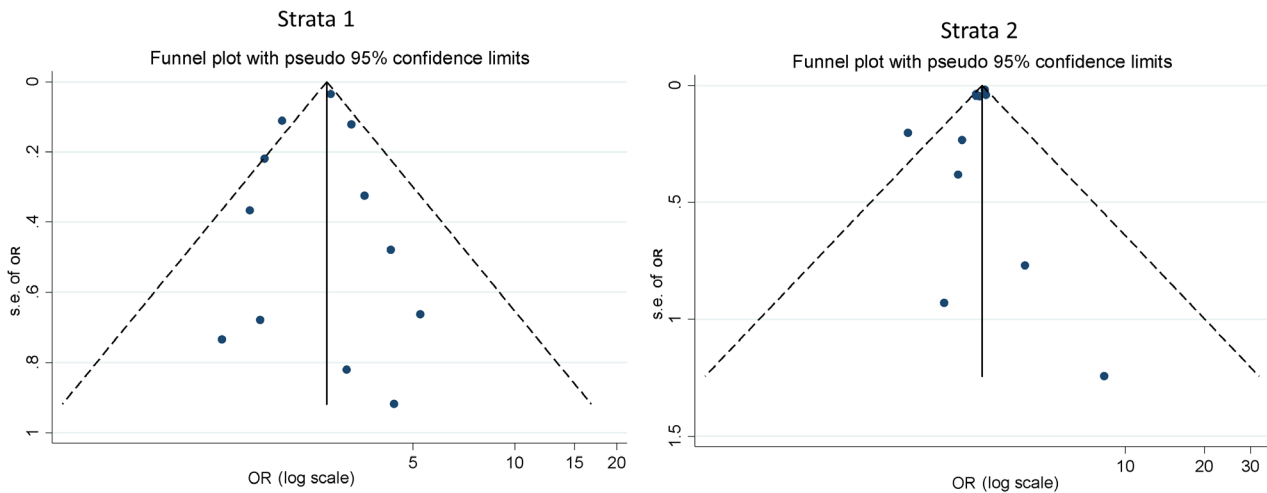
increased risk (ID 130, 130) or a reduced risk of obesity (ID 2591).

The results of the meta-analyses by strata both suggested prominent heterogeneity across individual studies (stratum 1  $I^2=85.4%$ ; strata 2  $I^2=86.1%$ ). Possible reasons for this are discussed under the limitations section.

Publication bias: the P-values from the Egger test for publication bias by strata both suggested no significant publication bias (stratum 1  $P=0.691$ ; strata 2  $P=0.199$ ). A visualisation based on funnel plots (figure 6) confirmed a likely lack of potential publication bias.

## DISCUSSION

The results of this systematic review/meta-analysis study, suggest that a higher proportion of carbohydrates in unrestricted diets do not increase obesity levels. Our paper, therefore, cannot contradict the assumption of the total energy intake/expenditure paradigm as the primary driver of body weight, modulated by an interaction of genetic, environmental and psychosocial factors.<sup>6-8</sup> Other studies, however, have indicated that certain dietary carbohydrates, like sugar sweetened beverages, have been shown to be positively associated with weight gain.<sup>11 19 20</sup>



**Figure 6** Funnel plots for assessment of publication bias by strata.

The results of a number of systematic reviews, investigating high versus low carbohydrate restricted calorie diets, are interesting. In terms of achieving weight loss on a restricted calorie diet, both high fat—low carbohydrate and low fat—high carbohydrate diets were equally effective although there were differences in serum lipid profiles.<sup>21–23</sup> Low carbohydrate restricted calorie diets (high fat) have shown that they induce at least the same level (or more) of weight loss than their low fat (high carbohydrate) counterpart diets.<sup>1 24 25</sup> Low-carbohydrate diets also substantially reduce body weight, BMI, abdominal circumference, systolic and diastolic BP and triglycerides, as well as fasting glucose, glycated haemoglobin, plasma insulin and plasma C reactive protein, as well as increasing high-density lipoprotein.<sup>26</sup> From a physiological perspective, low-carbohydrate diets may decrease calorie intake because they increase demands on protein and amino acid turnover for gluconeogenesis which has a high energy cost. Alternatively, low-carbohydrate diets may induce weight loss due to reducing insulin concentrations, thus promoting free fatty acid mobilisation from body fat storage.<sup>27</sup> Low-carbohydrate diets are also related to weight loss because of increased levels of satiety thus positively re-enforcing reduced calorie intake.<sup>28 29</sup>

The linkage between carbohydrates and obesity continues to be an intense debate with no clear resolution at this stage. A major issue that needs to be addressed is whether the opposing roles of carbohydrates in disease is paralleled by their role in obesity. The good and bad role of refined versus unrefined carbohydrates is well documented in disease.<sup>30–32</sup> Refined carbohydrates and sugars have long been labelled as the cause of ‘saccharine disease’ involving a wide variety of vascular disorders,<sup>9</sup> metabolic syndrome and type 2 diabetes,<sup>33</sup> cardiovascular and kidney disease.<sup>34</sup> Conversely, the protective role of unrefined carbohydrates is reflected in a ‘consistent, inverse association between dietary whole grains and the incidence of cardiovascular

disease’.<sup>30</sup> In general, moreover, pooled meta-analyses have indicated a protective effect from the consumption of coarse grains.<sup>35 36</sup> Interestingly, a recent projection of longevity in 35 industrialised countries reflects that carbohydrates are an integral aspect of the diets of the four leading countries.<sup>37–39</sup> The opposing roles of dietary carbohydrates and obesity is also supported in the literature that demonstrates bad carbohydrates (unrefined carbohydrates and sugar) promote obesity while unrefined carbohydrates may have the opposite effect.<sup>7 11 40</sup> However, the same evidence of good and bad carbohydrates in obesity is far from conclusive and the studies included in this paper provided insufficient evidence of the risk of obesity relating to different categories of carbohydrates as envisaged in our initial research protocol.

Many limitations persist to establish whether there is a direct link between high-carbohydrate intake and obesity. First, the non-standard nature of dietary records used across different settings make it difficult to compare the results in a meta study. In particular, the selected studies did not quantify different classes of carbohydrates.<sup>41 42</sup> This is further complicated by significant changes in carbohydrate type and proportion in the same population groups over time.<sup>43</sup> Finally, multiple confounding influences are nuanced across different populations, as well as age, gender and different ethnic groups in the same population, as well as differences across the urban–rural divide.<sup>6 44 45</sup>

A further limitation of our study was the concentration of a few countries in the two strata and the recognition that different populations/subpopulations consume varying proportions of different categories of carbohydrates in their daily diet.<sup>46</sup> This limitation is further nuanced by the nutrition transition experienced in industrialising countries in which higher a proportion of carbohydrates consumed consist of refined carbohydrates and sugars.<sup>47</sup> In the first stratum, the weighting of the pooled sample was largely made up of South Korean and United States

data. In the second stratum, the pooled sample was influenced by a large sample resulting from multiple surveys of a multiethnic Hawaiian population. A further limitation was the heterogeneity across studies as evidenced by the large  $I^2$  statistics. This was potentially due to the heterogeneity in the classification of dietary intake across the studies.

## CONCLUSION

Based on our findings it cannot be concluded that a high-carbohydrate diet, or increased percentage of total energy intake in the form of carbohydrates, increases the odds of being obese. Mounting evidence exists, however, to indicate that the obesity epidemic has occurred during the industrial food era that has promoted the increased intake of refined carbohydrates and sugars. Further studies are needed that specifically investigate obesity as a function of different carbohydrate groups including refined versus unrefined carbohydrate intake. In parallel, prospective studies are needed to ascertain the relationship between obesity and long term high fat, high unrefined carbohydrates–sugar diets. We, therefore, advise readers that the assumption that all carbohydrates are not linked to obesity, is potentially erroneous.

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**Contributors** All authors contributed to the conception and design of the systematic literature review, the collection and screening of publications. KS and BS contributed to the analysis and interpretation of the findings. KS and BS drafted the manuscript. TM and CS reviewed and provided input to revise the manuscript. All authors gave final approval for submission.

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**Data sharing statement** No additional data are available.

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