

Low-carbohydrate diet and risk of cardiovascular disease, all-cause, cardiovascular and cancer mortality: a systematic review and meta-analysis of cohort studies

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Supplementary Table 1 Systematic literature review search terms and strategy

Search terms for PubMed (n=12444), until 26 July 2023
#1 (“Diet, Carbohydrate-Restricted”[Mesh] OR “Diet, High-Protein Low-Carbohydrate”[Mesh] OR “Diet, High-Protein” OR “dietary carbohydrate”[Mesh] OR “Diet, Ketogenic”[Mesh] OR “Diet, Diabetic”[Mesh] OR “low-carbohydrate-diet”[Title/Abstract] OR “Diet, Carbohydrate-Restricted”[Title/Abstract] OR “carbohydrate”[Title/Abstract] OR "ketogenic diet"[Title/Abstract] OR “Atkins diet”[Title/Abstract] OR “diabetic diet” [Title/Abstract] OR "high-protein diet"[Title/Abstract])
#2 (“cerebrovascular disorders” [Mesh] OR “Cardiovascular Diseases”[Mesh] OR “cerebrovascular disorders” [Title/Abstract] OR “cardiovascular disease” [Title/Abstract] OR “cardiovascular diseases” [Title/Abstract] OR “CVD” [Title/Abstract] OR “coronary disease” [Title/Abstract] OR “coronary artery disease” [Title/Abstract] OR “coronary heart disease” [Title/Abstract] OR “CHD” [Title/Abstract] OR “ischemic heart disease” [Title/Abstract] OR “ischaemic heart disease” [Title/Abstract] OR “stroke” [Title/Abstract] OR “cerebrovascular disease” [Title/Abstract] OR “cerebrovascular disorders” [Title/Abstract] OR “heart disease” [Title/Abstract] OR “myocardial infarction” [Title/Abstract] OR “MI” [Title/Abstract] OR “heart failure” [Title/Abstract] OR “cerebral vascular accident” [Title/Abstract] OR “CVA” [Title/Abstract] OR “cardiovascular” [Title/Abstract] OR “coronary” [Title/Abstract] OR “myocardial” [Title/Abstract])
#3 (“mortality” [Mesh] OR “death” [Mesh] OR “survival” [Mesh] OR “mortality” [Title/Abstract] OR “death*” [Title/Abstract] OR “fatal” [Title/Abstract] OR “surviv*” [Title/Abstract])
#4 (#2 OR #3)
#1 AND #4
Search terms for Embase (n=13031), until 26 July 2023
#1 carbohydrate-restricted.mp. or high-protein.mp. or protein diet/ or dietary carbohydrate.mp. or ketogenic diet/ or low-carbohydrate-diet.mp. or low-carbohydrate diet.mp. or carbohydrate intake/ or carbohydrate diet/ or diabetic diet/
#2 cerebrovascular disorders.mp. OR cerebrovascular disease/ or cardiovascular diseases.mp. or cardiovascular disease/ or coronary heart disease.mp. or heart disease.mp. or heart disease/ or ischemic heart disease.mp. or ischaemic heart disease.mp. or ischemic heart disease/ or ischemic heart disease/

or coronary artery disease/ or CHD.mp. or myocardial infarction.mp. or heart infarction/ or stroke.mp.
or cerebrovascular accident/ or ischemic stroke.mp. or brain ischemia/ or haemorrhagic stroke.mp. or
brain hemorrhage/ or hemorrhagic stroke.mp. or brain hemorrhage/ or CVD.mp. or coronary
disease.mp. or heart failure.mp. or heart failure/ or cerebral vascular accident.mp. or cerebrovascular
accident/ or cardiovascular.mp. or coronary.mp. or myocardial.mp.

#3 mortality/ or death/ or survival/ or mortality.mp. or death.mp. or deaths.mp. or fatal.mp. or
survival.mp. or survive.mp.

#4 (#2 OR #3)

#1 AND #4

Search terms for Web of Science (n= 17646), until 26 July 2023

TS= (“Diet, Carbohydrate-Restricted” OR “Diet, High-Protein Low-Carbohydrate” OR “Diet, High-
Protein” OR “dietary carbohydrate” OR “Diet, Ketogenic” OR “Diet, Diabetic” OR “low-
carbohydrate-diet” OR “carbohydrate” OR "ketogenic diet"OR “Atkins diet” OR “diabetic diet” OR
"high-protein diet") AND ((“cerebrovascular disorders” OR “cerebrovascular disease” OR
“cardiovascular disease” OR “cardiovascular disease” OR “coronary heart disease” OR “heart disease”
OR “heart disease” OR “ischemic heart disease” OR “ischaemic heart disease” OR “ischemic heart
disease” OR “ischemic heart disease” OR “coronary artery disease” OR “CHD” OR “myocardial
infarction” OR “heart infarction” OR stroke OR “cerebrovascular accident” OR “ischemic stroke” OR
“brain ischemia” OR “haemorrhagic stroke” OR “brain hemorrhage” OR “hemorrhagic stroke” OR
“brain hemorrhage” OR “CVD” OR “coronary disease” OR “heart failure” OR “heart failure” OR
“cerebral vascular accident” OR “cerebrovascular accident”) OR (“mortality” OR “death” OR “deaths”
OR “survival” OR “fatal” OR “survive”))

Supplementary Table 2 Quality assessment of included studies in the meta-analysis of low carbohydrate diet score

First author (year)	Study Selection				Comparability of cohorts		Outcome			Total
	a	b	c	d	e	f	g	h	i	
CVD										
Zhao (2023)	0	1	0	1	1	1	1	1	1	7
Wang (2023)	1	1	1	1	1	1	1	1	1	9
McKenzie (2022)	1	1	0	1	0	1	1	1	1	7
Sun (2022)	0	1	1	1	0	1	1	1	1	7
Oh (2022)	1	1	1	1	1	1	1	1	1	9
Akter (2020)	1	1	0	1	1	1	1	1	1	8
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Nakamura (2014)	1	1	1	1	1	0	0	1	1	7
Fung (2010) NHS	0	0	1	1	1	1	1	1	1	7
Fung (2010) HPFS	0	0	1	1	1	1	1	1	1	7
Lagiou (2007)	1	1	0	1	0	0	1	1	1	6
Farhadnejad (2020)	1	1	1	1	1	1	1	1	1	9
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Lagiou (2012)	1	1	0	1	0	0	1	1	1	6
Halton (2006)	0	1	0	1	1	1	1	1	1	7
CHD										
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Lagiou (2012)	1	1	0	1	0	0	1	1	1	6
Halton (2006)	0	1	0	1	1	1	1	1	1	7
Stroke										
Wang (2023)	1	1	1	1	1	1	1	1	1	9
Lagiou (2012)	1	1	0	1	0	0	1	1	1	6
Cardiovascular mortality										
Zhao (2023)	0	1	0	1	1	1	1	1	1	7
Sun (2022)	0	1	1	1	0	1	1	1	1	7
Oh (2022)	1	1	1	1	1	1	1	1	1	9
Mazidi (2019)	1	1	1	1	1	1	1	1	1	9
Akter (2020)	1	1	0	1	1	1	1	1	1	8
Nakamura (2014)	1	1	1	1	1	0	0	1	1	7
Fung (2010) NHS	0	0	1	1	1	1	1	1	1	7
Fung (2010) HPFS	0	0	1	1	1	1	1	1	1	7
Lagiou (2007)	1	1	0	1	0	0	1	1	1	6
All-cause mortality										
Zhao (2023)	0	1	0	1	1	1	1	1	1	7
Zhang (2022)	0	1	1	1	1	1	1	1	1	8
Sun (2022)	0	1	1	1	0	1	1	1	1	7
Oh (2022)	1	1	1	1	1	1	1	1	1	9
McKenzie (2022)	1	1	0	1	0	1	1	1	1	7
Shan (2020)	1	1	1	1	1	0	1	1	1	8
Akter (2020)	1	1	0	1	1	1	1	1	1	8

Nakamura (2014)	1	1	1	1	1	0	0	1	1	7
Nilsson (2012)	1	1	1	1	1	0	1	1	1	8
Sjogren (2010)	1	1	1	1	1	0	1	1	1	8
Fung (2010) NHS	0	0	1	1	1	1	1	1	1	7
Fung (2010) HPFS	0	0	1	1	1	1	1	1	1	7
Lagiou (2007)	1	1	0	1	0	0	1	1	1	6

CVD, cardiovascular disease; CHD, coronary heart disease

a. Representativeness of the exposed cohort;

b. Selection of the non-exposed cohort;

c. Ascertainment of exposure;

d. Demonstration that outcome of interest was not present at start of study;

e. Comparability of cohorts on the basis of the design or analysis (adjusted for the most important factor);

f. Comparability of cohorts on the basis of the design or analysis (adjusted for a second important factor);

g. Assessment of outcome;

h. Was follow-up long enough for outcomes to occur;

i. Adequacy of follow-up of cohorts.

Supplementary Table 3 The definition of LCD score

Study	LCD score definition
Zhao (2023) USA	<p>To calculate the overall LCD score, we divided the percentages of energy from total fat, total carbohydrates, and total protein into 11 strata. For total carbohydrates, participants in the lowest stratum received 10 points, participants in the next stratum received 9 points, and so on, up to participants in the highest stratum receiving 0 points. For total fat and total protein, the orders of the strata were reversed. The three macronutrient scores were summed to obtain the overall LCD score, ranging from 0 to 30, with a higher overall LCD score indicating greater adherence to a general LCD.</p>
Wang (2023) China	<p>All study participants were divided into 11 strata according to their carbohydrate, protein, and fat intakes. Each stratum of macronutrient intake was expressed as proportion of energy intake [23]. For fat and protein, participants in the highest stratum received 10 points for that macronutrient, participants in the next stratum received 9 points, and so on, down to participants in the lowest stratum, who received 0 points. For carbohydrates including good and bad carbohydrates, the order of the strata was reversed. Those with the lowest carbohydrate intake received 10 points and those with the highest carbohydrate intake received 0 points. The points for each dietary macronutrient were then summed to yield an overall diet score, which ranged from 0 (the lowest fat and protein intake and the highest carbohydrate intake) to 30 (the highest protein and fat intake and the lowest carbohydrate intake) points. The higher the score, the more closely the participant's diet followed the pattern of LCD.</p>
Zhang (2022) USA	<p>For carbohydrate, the order of the strata was reversed; those with the lowest carbohydrate intake received 10 points, and those with the highest carbohydrate intake received 0 points. The points for each of the three macronutrients were then summed to create the overall diet score, which ranged from 0 (the lowest fat and protein intake and the highest carbohydrate intake) to 30 (the highest protein and fat intake and the lowest carbohydrate intake).</p>
Sun (2022) China	<p>Percentages of energy from carbohydrate, fat, and protein for each participant were each calculated and used to rank the participants into 11 strata. For carbohydrates, participants in the lowest group received 10 points and those in the highest group received 0 points. The order of the strata for fat and protein was reversed. The scores of the three macronutrients were summed to create an overall LCD score, which ranged from 0 to 30.</p>
Oh (2022) USA	<p>We divided the participants into 11 strata, with fat, protein, and carbohydrate intake expressed as a percentage of total energy intake. For fat and protein intake, participants in the highest stratum received 10 points; those in the second-highest stratum received 9 points, and so on down to participants in the lowest stratum, who received 0 points. The lowest stratum received 10 points for carbohydrates, and the highest received 0 points. Three LCD scores were obtained. The overall LCD score was calculated as the sum of the points for total carbohydrate, fat, and protein.</p>
McKenzie (2022) UK	<p>Dietary characteristics of clusters: up(low PUFA, low protein)=Energy:9460.86(kJ/d); Carbohydrate(CHO):52.19%; Sugar:25.96%;Fibre:1.32%; Fat:32.31%; Saturated fat(SFA):13.66%; Polyunsaturated fat(PUFA):5.03%; Protein:14.30%. cfP(low CHO low fat, high protein)=Energy:8173.76(kJ/d); Carbohydrate(CHO):45.06%; Sugar:20.23%;Fibre:1.41%; Fat:29.47%; Saturated fat(SFA):11.11%; Polyunsaturated fat(PUFA):5.27%; Protein:18.61%. cF(low CHO, and high fat)=Energy:9245.26(kJ/d); Carbohydrate(CHO):40.98%; Sugar:17.52%;Fibre:1.24%; Fat:39.45%; Saturated fat(SFA):15.77%; Polyunsaturated fat(PUFA):6.66%; Protein:16.27%.</p>

Shan (2020) USA	The participants were divided into 11 sex-specific strata each of percentage of energy from fat, protein, and carbohydrate. For fat and protein, individuals in the highest stratum received 10 points and those in the lowest stratum received 0 points. For carbohydrate, the order of the strata was reversed. The points for the 3 macronutrients were then summed to create the overall LCD score, which ranged from 0 to 30. Therefore, the higher the score, the more closely the participant's diet followed the pattern of an overall LCD.
Akter (2020) Japan	The participants were divided into 11 categories according to the percentage of energy from carbohydrate, protein, or fat with equal sample size. For carbohydrate, participants in the lowest through highest categories received points from 10 to 0. Meanwhile, for protein and fat, participants in the lowest through highest categories received points from 0 to 10. The LCD score was calculated as total score of carbohydrate, protein, and fat. The maximum score was 30, which represented the highest intake of protein and fat and the lowest intake of carbohydrate.
Farhadnejad (2020) Iran	To calculate LCD score, we divided the total population into quintiles of carbohydrate (Q1: ≤ 51.59, Q2: 51.60-55.84, Q3: 55.85-59.21, Q4: 59.22-63.30, and Q5: ≥ 63.31%), protein (Q1: ≤ 11.79, Q2: 11.80-12.94, Q3: 12.95-14.05, Q4: 14.06-15.40, and Q5: ≥ 15.41%), and fat (Q1: ≤ 25.72, Q2: 25.73-29.72, Q3: 29.73-32.87, Q4: 32.88-36.98, and Q5: ≥ 36.99%) intakes as percentage of energy intake. For carbohydrate, participants in the highest quintile received 0 points, individuals in the next quintile received 1 point, and so on, down to adults in the lowest quintile, who received 4 points. For protein and total fat, the order of the strata was reversed; those with the highest protein and fat intakes received 4 points and those with the lowest protein and fat intakes received 0 points. The scores for each macronutrient were then summed to calculate LCD score, which ranged from 0 (the lowest fat and protein intakes and the highest carbohydrate intakes) to 12 (the highest protein and fat intakes and the lowest carbohydrate intakes). Therefore, the higher LCD score shows higher adherence of individuals to the pattern of a low carbohydrate diet.
Nakamura (2014) Japan	Instead of calculating scores based on animal or vegetable fat, we used more specifically SFA or MUFA+PUFA values, because the harmful effects of SFA and the beneficial effects of MUFA+PUFA are known. Data are reported as a percentage of energy. Women and men were analysed separately, by dividing them into eleven strata each for fat, protein and carbohydrate intake. For fat and protein, the points ranged from 10, given to participants in the highest stratum, to 0, given to participants in the lowest stratum. For carbohydrate, the order of the strata was reversed. The points for each of the three macronutrients were then summed to obtain the overall diet score, which ranged from 0 to 30.
Nilsson (2012) Sweden	Sex- and FFQ-specific deciles of carbohydrate intake (descending) and protein intake (ascending) as energy-adjusted residuals, were added. Low carbohydrate high-protein scores thus ranged from 2 to 20, representing increasing proportions of protein and decreasing proportions of carbohydrates in the diet. The score was divided into three categories, low (2-8 points), medium (9-13 points) and high (14-20 points), with high scores representing the lowest carbohydrate and highest protein intakes.
Sjogren (2010) Sweden	The carbohydrate restricted diet score applied in our study distinguishes individuals according to their intake of energy-adjusted carbohydrates and proteins. The cohort was divided into deciles according to the carbohydrate and protein intakes, respectively, and the individuals were assigned a score from 1 to 10 due to decile participation. Increases in carbohydrate intake yielded a descending score (10 points to the lowest intake) and, inversely, increases in protein intake resulted in an ascending score (10 points to the highest intake). Consequently, the carbohydrate restricted score could take a value from 2 to 20 points.
Fung (2010) USA	Percentages of energy from fat, protein, and carbohydrate were divided into deciles. For fat and protein, participants in the highest decile received 10 points for that macronutrient, participants in the ninth decile received 9 points, and so forth. For carbohydrate, the lowest decile received 10 points, and the highest received 0 points. The fat, protein, and carbohydrate scores were summed to create the overall low carbohydrate diet score, which ranged from 0 to 30.

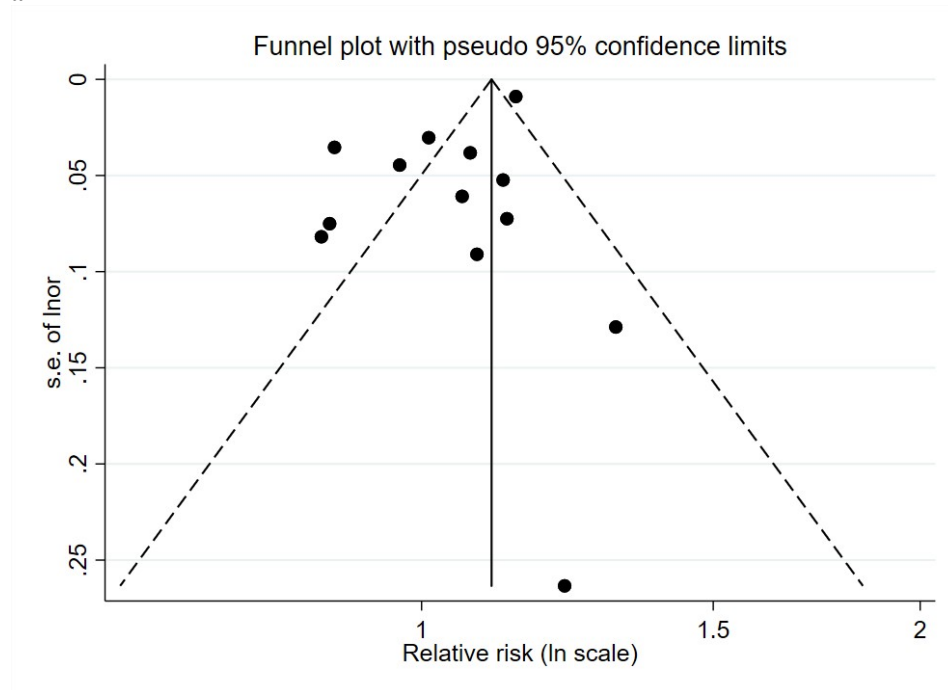
Lagiou (2007) Sweden	Women were then assigned a score from 1 (very low protein intake) to 10 (very high protein intake), according to their decile of energy-adjusted total protein intake. An inverse score, from 1 (very high carbohydrate intake) to 10 (very low carbohydrate intake) was also assigned according to the woman's decile of energy-adjusted total carbohydrate intake. The scores were studied both separately and after being added creating a composite additive score simultaneously assessing the position of each subject in terms of protein and carbohydrate intake. Thus, a woman with a score of 2 is one with very high consumption of carbohydrates and very low consumption of proteins, whereas a woman with a score of 20 is one with very low consumption of carbohydrates and very high consumption of proteins.
Mazidi (2019) USA	The carbohydrate categories were scored from 10 (lowest intake) to 0 (highest intake), whereas protein and fat categories were scored from 0 (lowest intake) to 10 (highest intake). Ranks were added to create a total score with a maximum value of 30, which represented the highest intake of total protein and total fat and the lowest intake of carbohydrate.
Nakamura (2014) Japan	Instead of calculating scores based on animal or vegetable fat, we used more specifically SFA or MUFA+PUFA values, because the harmful effects of SFA and the beneficial effects of MUFA/PUFA are known. Data are reported as a percentage of energy. Women and men were analyzed separately, by dividing them into eleven strata each for fat, protein and carbohydrate intake. For fat and protein, the points ranged from 10, given to participants in the highest stratum, to 0, given to participants in the lowest stratum. For carbohydrate, the order of the strata was reversed. The points for each of the three macronutrients were then summed to obtain the overall diet score, which ranged from 0 to 30.
Lagiou (2012) Sweden	For each woman, we assigned a score from 1 (very low protein intake) to 10 (very high protein intake), according to her tenth of energy adjusted total protein intake, and an inverse score from 1 (very high carbohydrate intake) to 10 (very low carbohydrate intake), according to her tenth of energy adjusted total carbohydrate intake. We studied the scores for high protein and low carbohydrate intake both separately and after adding them together to create a composite low carbohydrate-high protein score (ranging from 2 to 20), which simultaneously assessed the position of each woman in terms of protein and carbohydrate intake. Thus, a woman with a score of 2 was one with very high consumption of carbohydrates and very low consumption of proteins, whereas a woman with a score of 20 was one with very low consumption of carbohydrates and very high consumption of proteins.
Halton (2006) USA	We divided the study participants into 11 strata each of fat, protein, and carbohydrate intake, expressed as a percentage of energy. For fat and protein, women in the highest stratum received 10 points for that macronutrient, women in the next stratum received 9 points, and so on down to women in the lowest stratum, who received 0 points. For carbohydrate, the order of the strata was reversed; those with the lowest carbohydrate intake received 10 points and those with the highest carbohydrate intake received 0 points. The points for each of the three macronutrients were then summed to create the overall diet score, which ranged from 0 (the lowest fat and protein intake and the highest carbohydrate intake) to 30 (the highest protein and fat intake and the lowest carbohydrate intake).

Supplementary Table 4 Sensitivity analysis of low carbohydrate diet score and risk of cardiovascular disease and all-cause mortality for the highest versus lowest meta-analysis

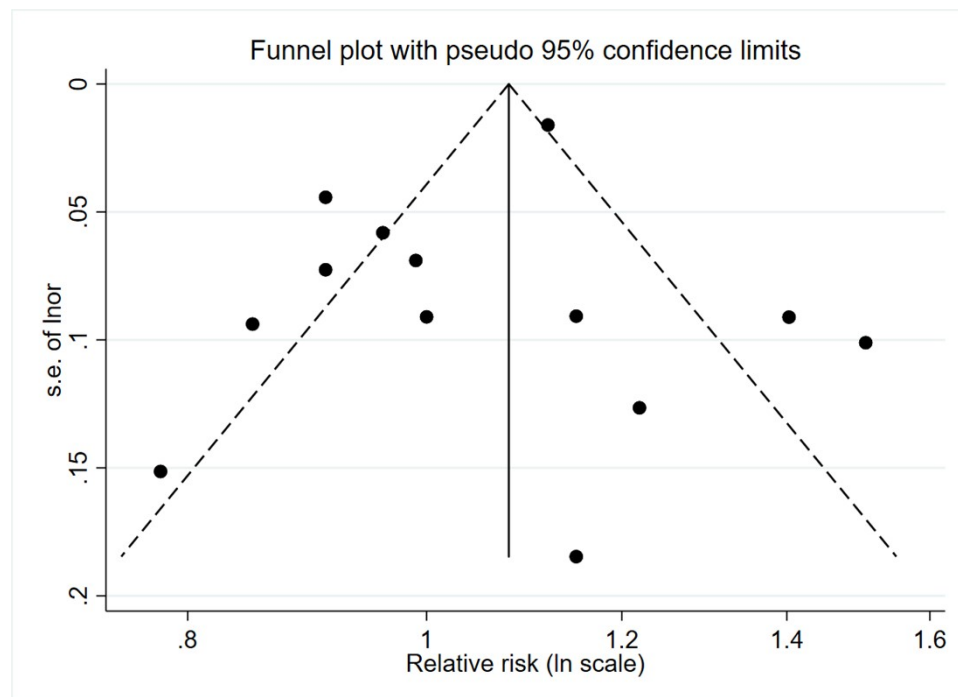
Study omitted	RR	95% CI	
CVD			
Zhao (2023)	1.04	0.94	1.15
Wang (2023)	1.06	0.97	1.16
McKenzie (2022)	1.07	0.98	1.16
Sun (2022)	1.06	0.96	1.16
Oh (2022)	1.05	0.96	1.14
Akter (2020)	1.06	0.97	1.16
Farhadnejad (2020)	1.07	0.98	1.16
Mazidi (2019)	1.02	0.94	1.11
Nakamura (2014)	1.06	0.98	1.16
Lagiou (2012)	1.02	0.94	1.12
Fung (2010) NHS	1.04	0.95	1.14
Fung (2010) HPFS	1.05	0.96	1.15
Halton (2006)	1.04	0.95	1.14
CHD			
Mazidi (2019)	1.41	1.06	1.87
Lagiou (2012)	1.30	1.06	1.60
Halton (2006)	1.59	1.29	1.95
Stroke			
Wang (2023)	1.02	0.74	1.39
Lagiou (2012)	0.91	0.79	1.05
Cardiovascular mortality			
Zhao (2023)	1.09	0.96	1.23
Sun (2022)	1.11	1.00	1.22
Oh (2022)	1.08	0.99	1.19
Akter (2020)	1.11	1.01	1.23
Mazidi (2019)	1.07	0.98	1.17
Mazidi (2019)	1.05	0.97	1.15
Nakamura (2014)	1.11	1.01	1.21
Fung (2010) NHS	1.08	0.98	1.20
Fung (2010) HPFS	1.10	1.00	1.22
Lagiou (2007)	1.08	0.99	1.19
All-cause mortality			
Zhao (2023)	1.02	0.96	1.08
Zhang (2022)	1.02	0.96	1.10
Sun (2022)	1.04	0.97	1.11
Oh (2022)	1.03	0.96	1.10
McKenzie (2022)	1.05	0.99	1.11
Shan (2020)	1.04	0.98	1.12
Akter (2020)	1.03	0.96	1.11
Nakamura (2014)	1.04	0.98	1.12
Nilsson (2012)	1.03	0.96	1.10
Sjogren (2010)	1.03	0.96	1.10
Fung (2010) NHS	1.02	0.95	1.10
Fung (2010) HPFS	1.03	0.95	1.11
Lagiou (2007)	1.02	0.95	1.09

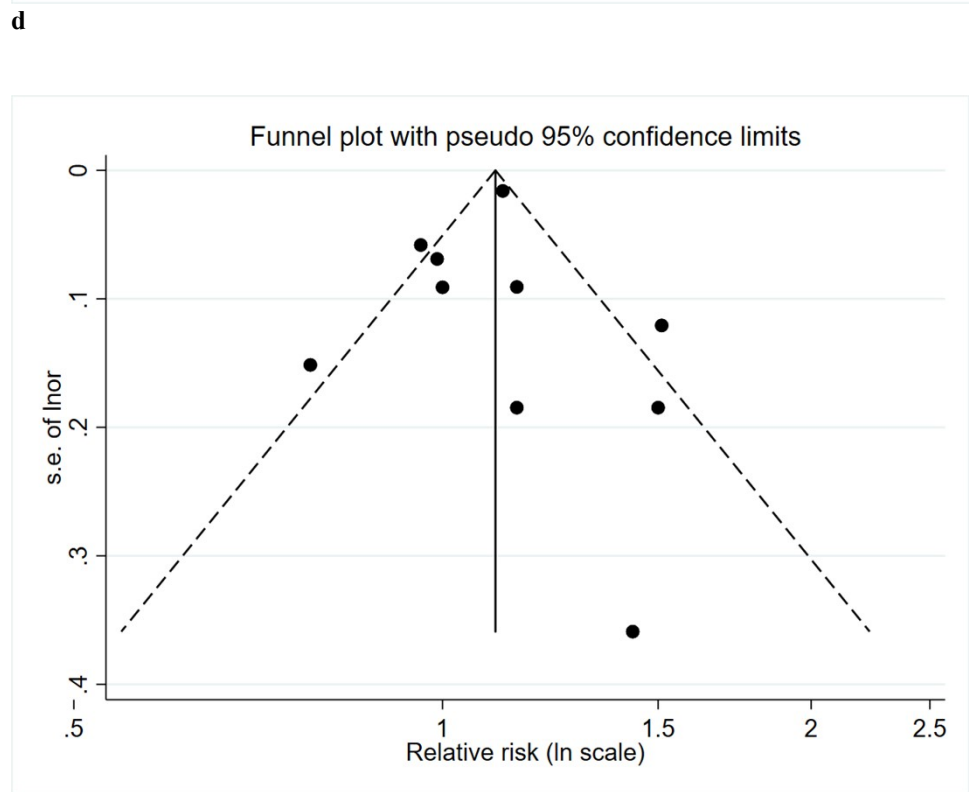
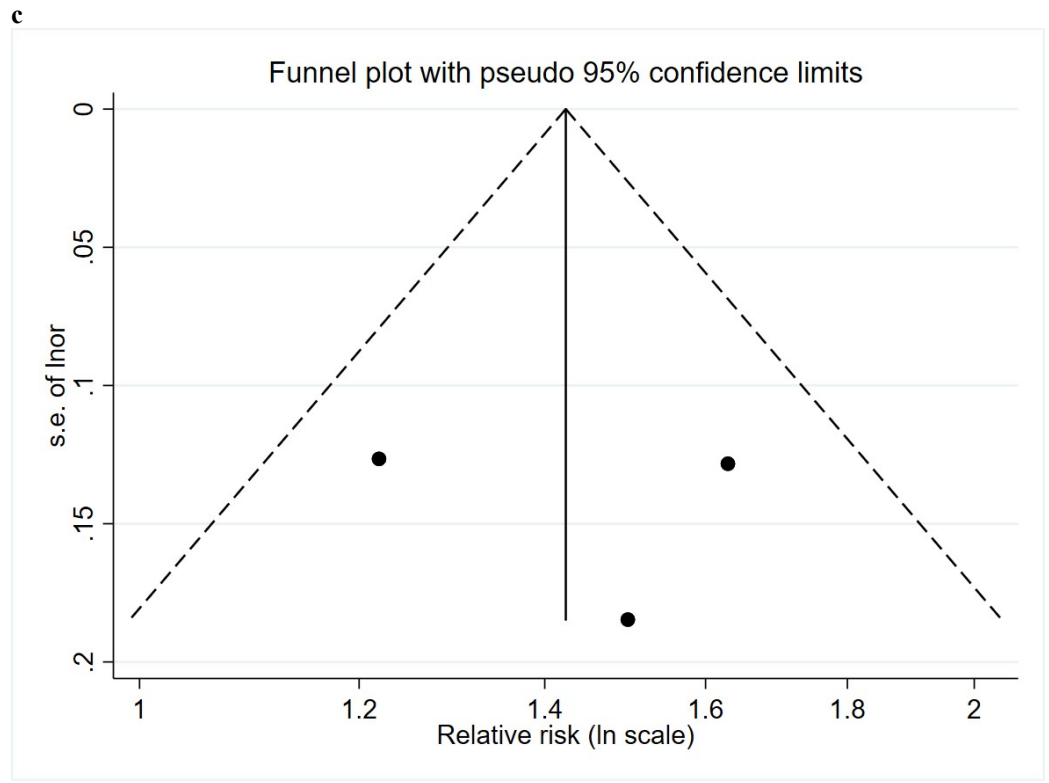
CVD, cardiovascular disease; CHD, coronary heart disease

a



b





Supplementary Fig.1 Funnel plots for detection of publication bias in the analysis of low carbohydrate diet score

a. all-cause mortality; b. cardiovascular disease; c. coronary heart disease;; d. cardiovascular mortality