Supplementary File

SUPPLEMENTARY APPENDIX

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Table S1. Characteristics of the studies included in the meta-analysis.

Author	Year	Country	Data source	Design	Setting	Enroll period	summary of followup	Group	No. patients	Age (years), mean (SD)	White, %	Smoker, %	BMI category	Hypertension, %	Dyslipidemia, %	socioeconomic status	education level	parity	Pre-eclampsia or eclampsia, %
Carr	2006	USA	GENetics of Non-Insulin dependent Diabetes (GENNID) study	retrospective cohort	multicenter	1993-2001	NR	GDM women	332	52.4±0.6	30.5	41%	33.7 ± 0.6	46.8	33.9		beyond high school 31.7%		
								control women	653	48.6±0.7	25	43.80 %	34.4 ± 1.2	37	26.3		beyond high school 36.3%		
Kessous	2013	Israel	Soroka University Medical Center	retrospective cohort	monocenter	1988-1999	0.1% death	GDM women	4928	32.4±6	Jewish67.7 Bedouin 32.3	NA	NA	NA	NA				
								control women	42981	29.4 ±6	Jewish72.6 Bedouin 27.4	NA	NA	NA	NA				
Fadl	2014	Sweden	National Swedish registry	retrospective case-control	nationwide	1991-2008	0% lost follwup	CVD women	2639	40.7±7.3	85.8	35.30 %	<18.5 2.3%, 18.5–24 55.7%, 25–29 26%, >30 16%	2.1	NA		lower education level 23.4%	2.44±1.2	mediating factor and therefore data are not shown in the analysis
								control women	133310	40.7±7.3	88.6	18.10 %	<18.5 2.5%, 18.5–24 67.2%, 25-29, 22.4%, >30 7.9%	0.3	NA		lower education level 15.1%	2.62±1.2	
Savitz	2014	USA	New York City administrative databases	retrospective cohort	multicenter	1995-2004	NR	GDM women	43169	NA	NA	NA	NA	NA	NA				
								control	8064	NA	NA	NA	NA	NA	NA				

								women	70									
Kaul	2015	Canada	Alberta provincial administrative databases	retrospective cohort	multicenter	1999-2010	8.5% lost to followup due to migration	GDM women	8731	31.8±5.46	70.3	16.6	Overweight: 16.0%	0	NA	Q1 24.55%		Nulliparity 58.1%	3.7
								control women	213765	28.6±5.58	83.5	19.8	Overweight: 7.6%	0	NA	Q1 26.15%		Nulliparity 64.9%	2.2
Gouesland	2016	France	French administrative databases	retrospective cohort	nationwide	2007-2008	NR	GDM women	62958	age 20-39 91.16%	NA	NA	obesity （BMI≥30） 12.9%	7.68	NA				
								control women	1452429	age20-39 93.87%	NA	NA	obesity （BMI≥30） 3.87%	2.89	NA				
Retnakaran	2017	Canada	Ontario provincial administrative databases	retrospective cohort	multicenter	1994-2014	no loss to follow-up	GDM women	56884	32 (29-36)	NA	NA	NA	5	4.2	lowest 26.4%			
								control women	1408798	30 (26-34)	NA	NA	NA	2	1.8	lowest 28.2%			
Tobias	2017	USA	Nurses' Health	prospective cohort	nationwide	1989	more than 90% of eligible participants complete follow-up	GDM women	78751	33.8±4.4	89	34	Normal weight (<25.0) 88% ; Overweight/ obese (≥25.0) 12% Baseline BMI : Normal weight (<25.0) 55% ; Overweight: 25%	21	NA			1.8±1.1	

			Study II										Obese: 20%					
								control women	958775	34.9±4.7	92	34	prepregnancy BMI : Normal weight (<25.0) 92% ; Overweight/ obese (≥25.0) 8% Baseline BMI : Normal weight (<25.0) 71% ; Overweight （25-29.9） 19% ; obese (≥30) 10%	10	NA			1.9±1.2	
Daly	2018	UK	primary-care database	retrospective cohort	nationwide	1990-2016	NR	GDM women	9112	33±5.4	30.7	35	BMI < 25 26%; 25–30 24%; >30 39%	2.54	NA	economically deprived （Q4 + Q5 ） 20%+17%			
								control women	37277	33±5.4	40	36	BMI < 25 50%; 25–30 21%; >30 14%	1.16	NA	economically deprived （Q4 + Q5 ） 18%+13%			
McKenzie-Sampson	2018	Canada	Quebec provincial registry	retrospective cohort	multicenter	1989-2003	4701 deaths during the study	GDM women	67356	age 20-29 59.5% age 30-39 33.1%	NA	NA	NA	NA	NA	disadvantage 18.7%	NA	1 45.4% 2 40.1% > 2 14.5%	5.5
								control women	1003311		NA	NA	NA	NA	NA				

Kabootari	2019	Iran	the Tehran Lipid and Glucose Study	prospective cohort	multicenter	1999-2001	Response rate of 85.8%	GDM women	477	45.3±9.4	NA	5.5	30.5 ± 4.9	28.5	64.6	NA	lower education level 47.8%	4(3–5)	0.0
								control women	3831	40.8±11.2	NA	4.8	28.0 ± 4.7	19.7	55.4	NA	lower education level 38.6%	3(2–4)	0.0
Echoufo-Tcheugui	2021	Canada	Ontario provincial administrative databases	retrospective cohort	multicenter	2007-2018	no loss to follow-up	GDM women	50193	32.32±5.28	Chinese 9.4% General population 81.5% South Asian 9.0%	NA	NA	4.8	NA	1 27.4% 2 21.9% 3 20.5% 4 17.9% 5 11.9%		0 60.9% 1:23.5% >=2 15.7%	Preeclampsia 10.0%
								control women	856126	29.59±5.56	Chinese 5.7% General population 90% South Asian 4.3%	NA	NA	2	NA	1 22.7% 2 20.5% 3 20.4% 4 20.4% 5 15.7%		0 66.0% 1 21.9% >=2 12.1%	Preeclampsia 5.7%
Sun	2021	Korea	reimbursement claims database of Korea's National Health Insurance Service	prospective cohort	nationwide	NA	6374 deaths during the study	GDM women	159066	age 20-29 45.5% age 30-39 53.1%	yellow race dominated	Non-smokers 91.96% Past smokers 2.39% Current smokers 2.33% Missing 3.32%	Underweight 15.57% Normal 64.94% Overweight 11.14% Obese 8.31% Missing 0.04%	7.34	11.53	low income 22.7%		1 85.5% 2 14.3%	Preeclampsia or hypertension 7.34%
								control women	1341102	age 20-29 50.1% age 30-39 48.8%	yellow race dominated			4.56	7.48	low income 22.9%		1 85/6% 2 14.31%	Preeclampsia or hypertension 4.56%
Yu	2021	Denmark	Danish national registry	prospective cohort	nationwide	1978-2016	censored due to noncardiovascular death	GDM women	21353	age 20-29 60% age 30-34 25%	dominantly	17%	Pre-pregnancy Obesity 18%	NA	NA		lower education level 25%	1 24% 2 45% > 2 31%	

							(n = 9,989) or emigration (n =27,350).	control women	981133	age 20-29 69% age 30-34 20%	dominantly	18%	Pre-pregnancy Obesity 4%	NA	NA		lower education level 25%	1 28% 2 50% > 2 23%	
Lee	2022	UK	UK Biobank	prospective cohort	nationwide	2006-2010	NR	GDM women	219330	NA	NA	NA	NA	NA	NA				
								control women		NA	NA	NA	NA	NA	NA				

Table S2. Risk-of-bias summary for the studies included in the meta-analysis, using Cochrane risk-of-bias tool ROBINS-I.

Study	**Bias due to confounding**	**Bias due to selection of participants**	**Bias due to exposure assessment**	**Bias due to misclassification during follow-up**	**Bias due to missing data**	**Bias due to measurement of the outcome**	**Bias due to selective reporting of the results**	**Overall judgement**
Carr, 16	Serious	Serious	Serious	No information	No information	Serious	Moderate	Serious
Kessous, 17	Serious	Moderate	Low	No information	No information	Moderate	Low	Serious
Fadl, 18	Moderate	Low	Low	No information	Moderate	Moderate	Low	Moderate
Savitz, 19	Moderate	Low	Moderate	No information	No information	Moderate	Low	Moderate
Kaul, 20	Moderate	Serious	Low	No information	Low	Moderate	Low	Serious
Goueslard, 21	Serious	Low	Moderate	No information	Moderate	Moderate	Low	Serious
Retnakaran, 7	Serious	Low	Moderate	No information	Low	Moderate	Low	Serious
Tobias, 22	Moderate	Low	Moderate	No information	Moderate	Moderate	Low	Moderate
Daly, 23	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
McKenzie-Sampson, 24	Serious	Low	Moderate	No information	No information	Moderate	Low	Serious
Kabootari, 25	Serious	Low	Serious	No information	Low	Moderate	Low	Serious
Echouffo-Tcheugui, 26	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
Sun, 27	Serious	Low	Moderate	No information	Low	Moderate	Low	Serious
Yu, 28	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate
Lee, 29	Moderate	Low	Moderate	No information	Low	Moderate	Low	Moderate

Table S3. Certainty of evidence and summary effect estimates assessed by GRADE (grading of recommendations, assessment, development, and evaluation) of the study outcomes.

Outcomes	Summary of findings		Quality assessment					Certainty of evidence[#]
	No. studies	RR (95%CI)	Study design*	Inconsistency†	Indirectness‡	Imprecision§	Other consideration	
Overall cardiovascular and cerebrovascular diseases	14	1.45 (1.36, 1.53)	serious	not serious	not serious	not serious	attenuation of the pooled RR by stratifying overt diabetes development	⊕⊕OO LOW
cardiovascular diseases	12	1.72 (1.40, 2.11)	serious	serious	not serious	not serious	none	⊕OOO VERY LOW
coronary artery diseases	4	1.40 (1.18, 1.65)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
myocardial infarction	6	1.74 (1.37, 2.20)	serious	serious	not serious	not serious	none	⊕OOO VERY LOW
angina pectoris	3	2.27 (1.79, 2.87)	serious	serious	not serious	not serious	large effect size (RR > 2)	⊕OOO VERY LOW
heart failure	6	1.62 (1.29, 2.05)	serious	serious	not serious	not serious	none	⊕OOO VERY LOW
cardiovascular procedures	4	1.87 (1.34, 2.62)	serious	serious	not serious	not serious	none	⊕OOO VERY LOW
cerebrovascular diseases	9	1.40 (1.29, 1.51)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
overall stroke	6	1.45 (1.29, 1.63)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
ischemic stroke	5	1.49 (1.29, 1.71)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
hemorrhagic stroke	2	1.44 (1.16, 1.78)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW
venous thromboembolism	4	1.28 (1.13, 1.46)	serious	not serious	not serious	not serious	none	⊕OOO VERY LOW

*Downgraded by one level if >25% of participants in this comparison were from studies at high risk of bias.
†Downgraded by one level if heterogeneity (I^2) >50%.

‡Downgraded by one level if >25% of included studies were monocenter-based.

§Downgraded by one level if the limits of the 95% CI for risk estimates are wide or cross a minimally important difference of 10% for outcomes (RR 0.9-1.1).

#High quality: very confident that the true effect lies close to that of the estimate of the effect; moderate quality: moderately confident in the effect estimate, and the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; low quality: confidence in the effect estimate is limited, and the true effect could be substantially different from the estimate of the effect; very low quality: very little confidence in the effect estimate, and the true effect is likely to be substantially different from the estimate of effect.

Table S4. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular diseases, according to study characteristics.

Study characteristics	**No. study**	**Risk ratio (95%CI)**	**I^2 (%)**	**τ^2**	**P for within groups**	**P for between groups**
All studies	12	1.72 (1.40, 2.11)	91	0.1029	/	/
Year of publication						
before 2017	4	1.72 (1.48, 2.00)	0	0	<0.0001	0.912
after 2017	8	1.74 (1.32, 2.29)	94	0.1266		
Study location						
North America	5	1.75 (1.41, 2.17)	54	0.0286	<0.0001	0.464
Europe	4	2.00 (1.31, 3.08)	94	0.1637		
Asia	3	1.40 (1.10, 1.79)	62	0.0291		
Study design						
retrospective	7	1.94 (1.74, 2.16)	14	0.0034	<0.0001	0.406
prospective	5	1.54 (1.01, 2.36)	96	0.2226		
Source of data						

local	6	1.73 (1.41, 2.12)	59	0.0335	<0.0001	0.951
nationwide	6	1.74 (1.21, 2.51)	95	0.1846		
Follow-up duration						
>10 years	6	1.64 (1.21, 2.21)	96	0.1303	<0.0001	0.543
≤ 10 years	5	1.79 (1.54, 2.09)	0	0		
Method of ascertainment of GDM						
diagnostic code	8	1.82 (1.40, 2.36)	93	0.1113	<0.0001	0.596
self-report	3	1.41 (1.15, 1.72)	0	0		
OGTT	1	1.58 (1.31, 1.92)	/	/		
Method of ascertainment of CVD						
diagnostic code	9	1.83 (1.44, 2.32)	93	0.1056	<0.0001	0.344
others	3	1.41 (1.15, 1.72)	0	0		
Sample size						
≥100,000	7	1.76 (1.34, 2.31)	94	0.1127	<0.0001	0.782
<100,000	5	1.60 (1.30, 1.96)	28	0.0153		
Number of events						
≥2,500	6	1.80 (1.34, 2.42)	95	0.1157	<0.0001	0.625
<2500	6	1.57 (1.33, 1.84)	11	0.0047		
ROBINS-I						
moderate	5	1.82 (1.20, 2.78)	93	0.1971		

serious	7	1.65 (1.31, 2.08)	84	0.0672	<0.0001	0.696

Table S5. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular diseases, according to a variety of adjustments.

Adjustment	**No. study**	**Risk ratio (95%CI)**	**I^2 (%)**	**τ^2**	**P for within groups**	**P for between groups**
All studies	12	1.72 (1.40, 2.11)	91	0.1029	/	/
Race						
Yes	5	1.47 (1.29, 1.67)	0	0	<0.0001	0.332
No	7	1.87 (1.41, 2.48)	94	0.1106		
Smoking						
Yes	5	1.82 (1.20, 2.78)	93	0.1971	<0.0001	0.686
No	7	1.65 (1.31, 2.08)	84	0.0672		
Body mass index						
Yes	6	1.72 (1.17, 2.52)	93	1967	<0.0001	0.950
No	6	1.72 (1.35, 2.21)	86	0.0679		
Socio-economic status						
Yes	3	1.71 (1.08, 2.72)	94	0.13	<0.0001	0.974
No	9	1.73 (1.33, 2.25)	90	0.1332		
Education level						
Yes	2	2.09 (1.14, 3.82)	91	0.1733	<0.0001	0.218
No	10	1.62 (1.35, 1.95)	82	0.0596		
Parity						
Yes	6	1.68 (1.25, 2.26)	95	0.1239		

No	6	1.68 (1.40, 2.02)	41	0.0191	<0.0001	0.809
Comorbidities						
Yes	5	1.70 (1.08, 2.67)	96	0.2365	<0.0001	0.482
No	7	1.81 (1.58, 2.07)	38	0.0109		
Pregnancy complications						
Yes	4	1.56 (1.12, 2.16)	92	0.078	<0.0001	0.715
No	8	1.83 (1.36, 2.46)	90	0.1388		

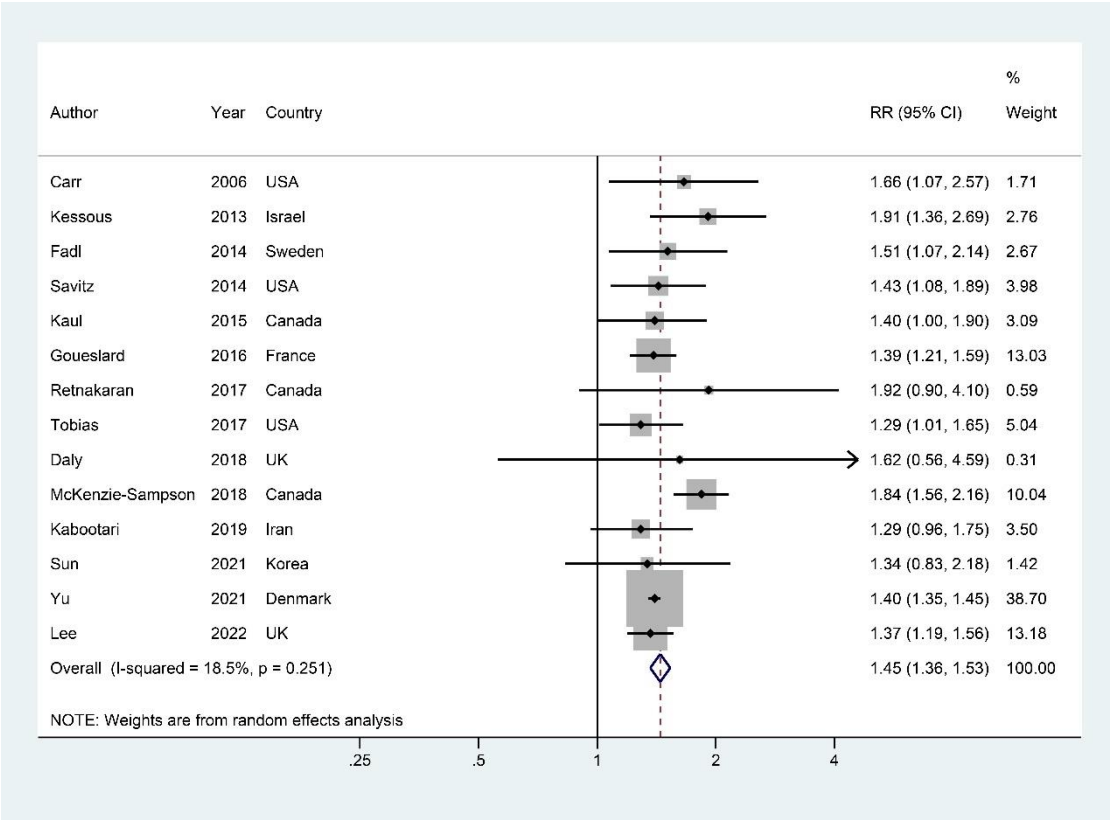


Figure S1. Forest plot of risk ratio of overall cardiovascular and cerebrovascular diseases in women with a history of gestational diabetes mellitus.

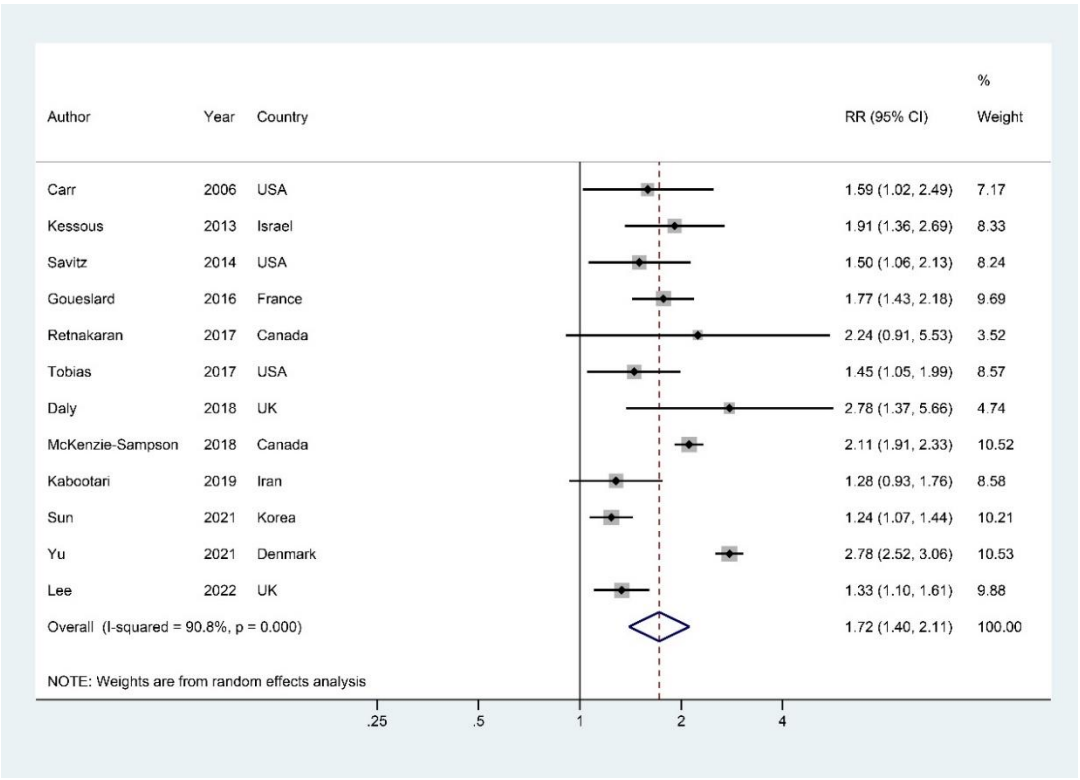


Figure S2. Forest plot of risk ratio of cardiovascular diseases in women with a history of gestational diabetes mellitus.

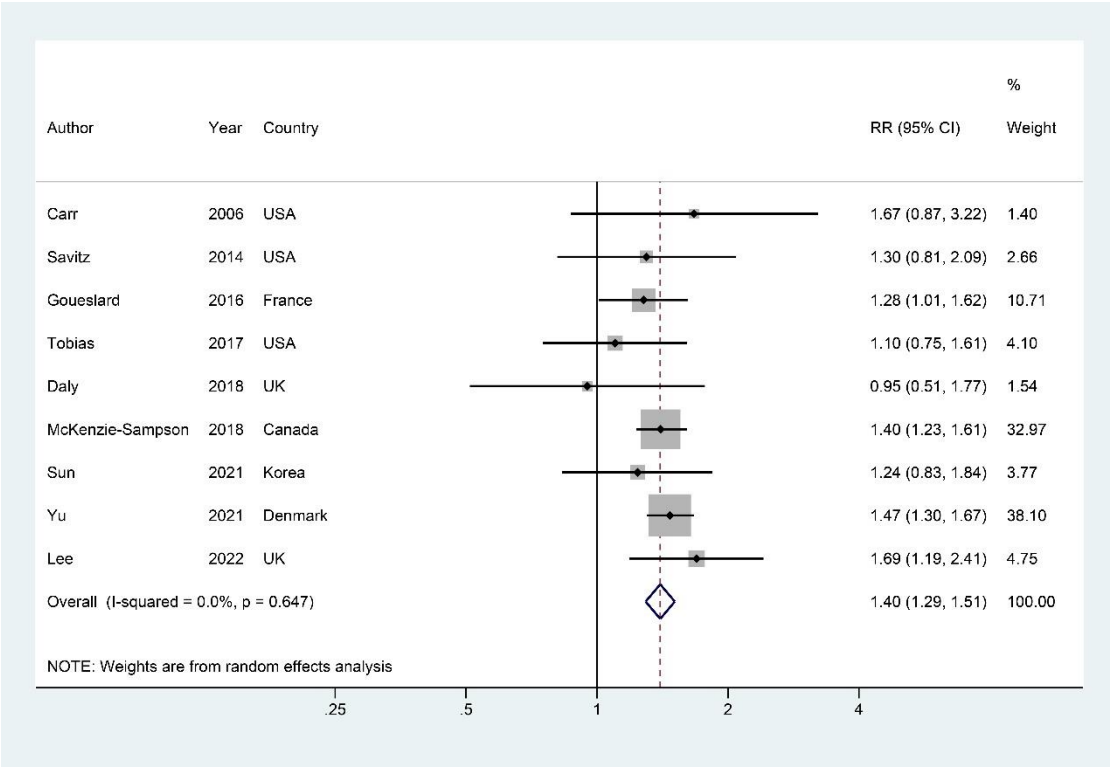
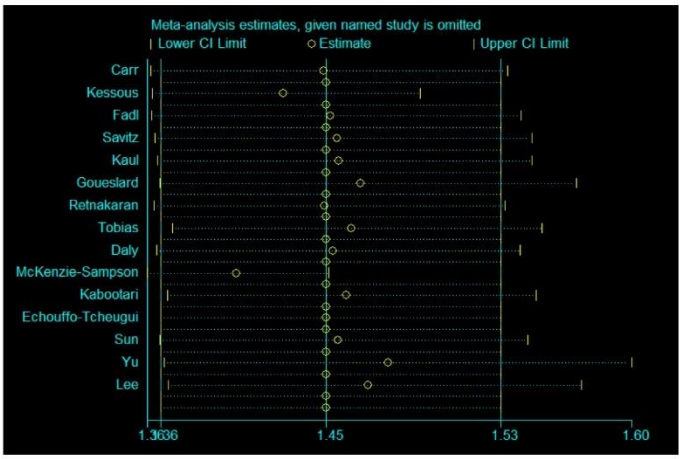
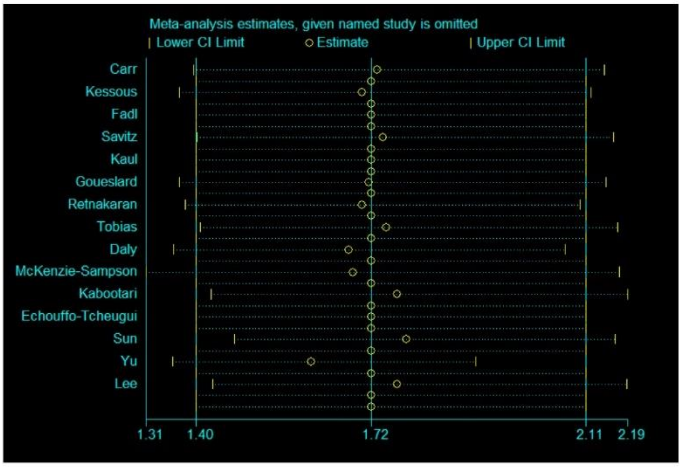


Figure S3. Forest plot of risk ratio of cerebrovascular diseases in women with a history of gestational diabetes mellitus.

A



B



C

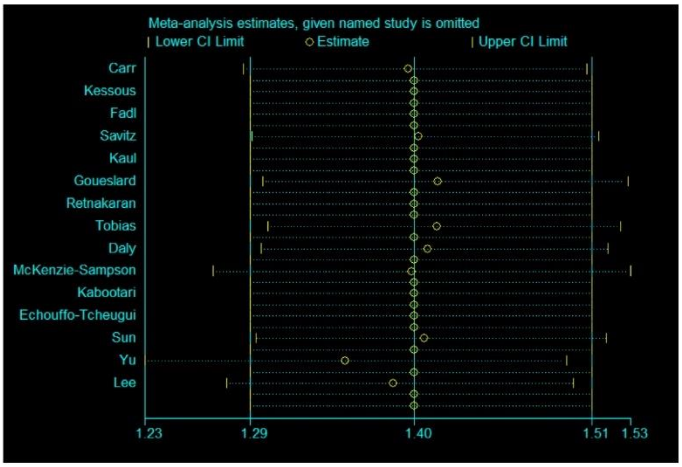


Figure S4. Sensitivity analysis using the jackknife approach, (A) overall cardiovascular and cerebrovascular diseases, (B) cardiovascular diseases, (C) cerebrovascular diseases.

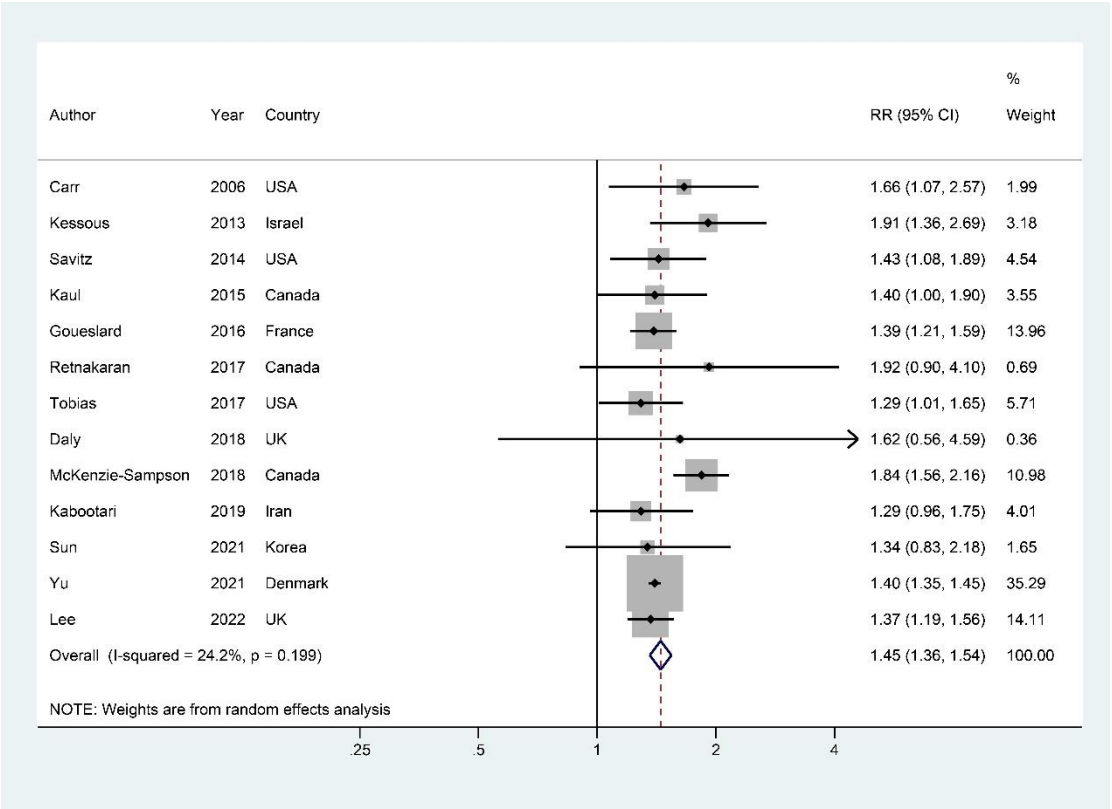


Figure S5. Sensitivity analysis after excluding the case-control study for the outcome of overall cardiovascular and cerebrovascular diseases.

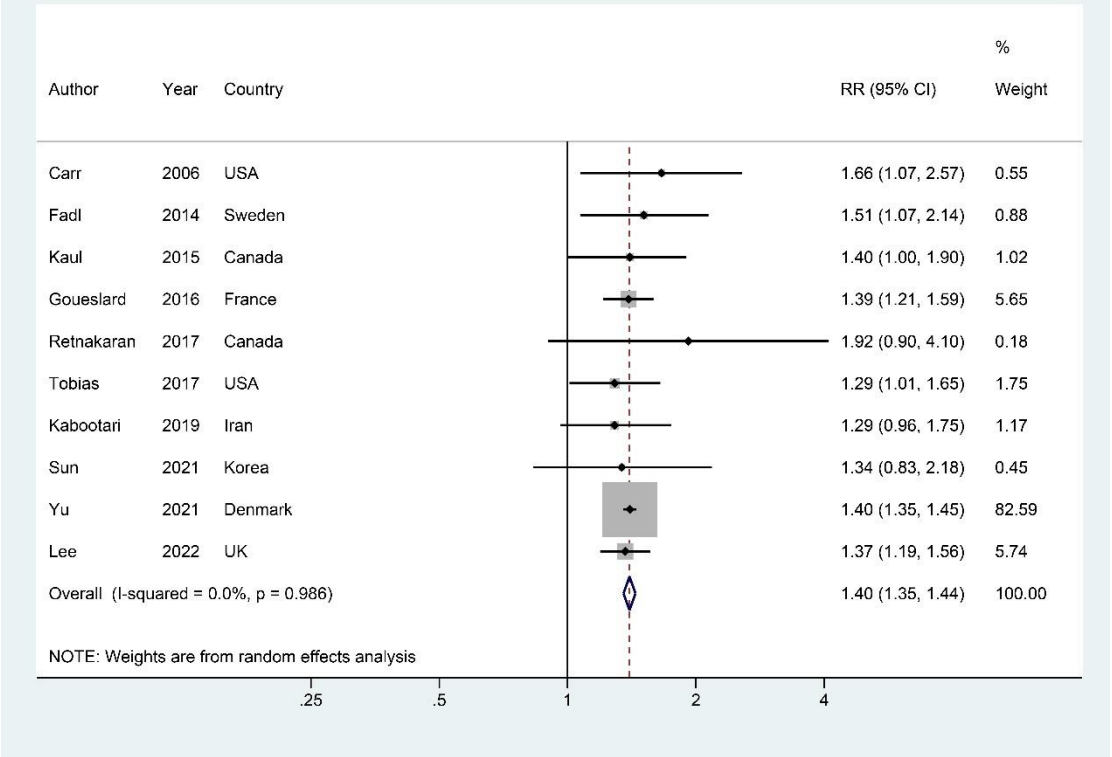


Figure S6. Sensitivity analysis after excluding the studies without direct information on the risk estimates for the outcome of overall cardiovascular and cerebrovascular diseases.

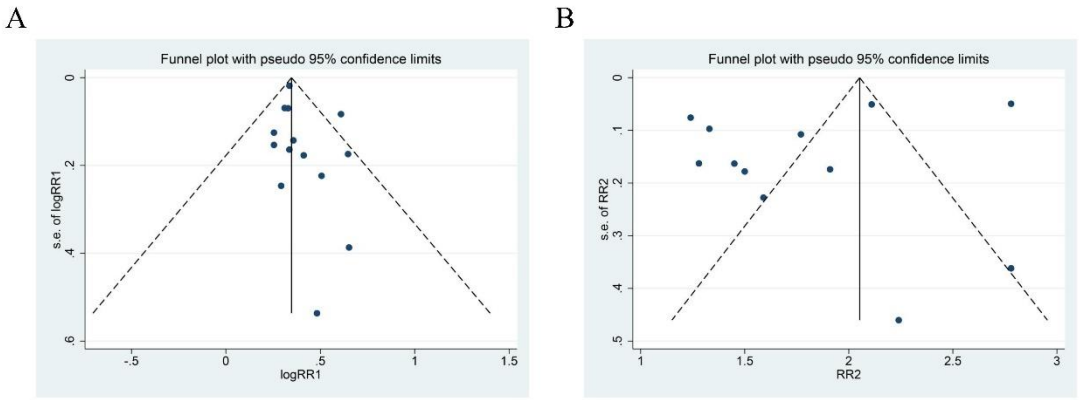


Figure S7. Funnel plot, (A) overall cardiovascular and cerebrovascular diseases, (B) cardiovascular diseases.

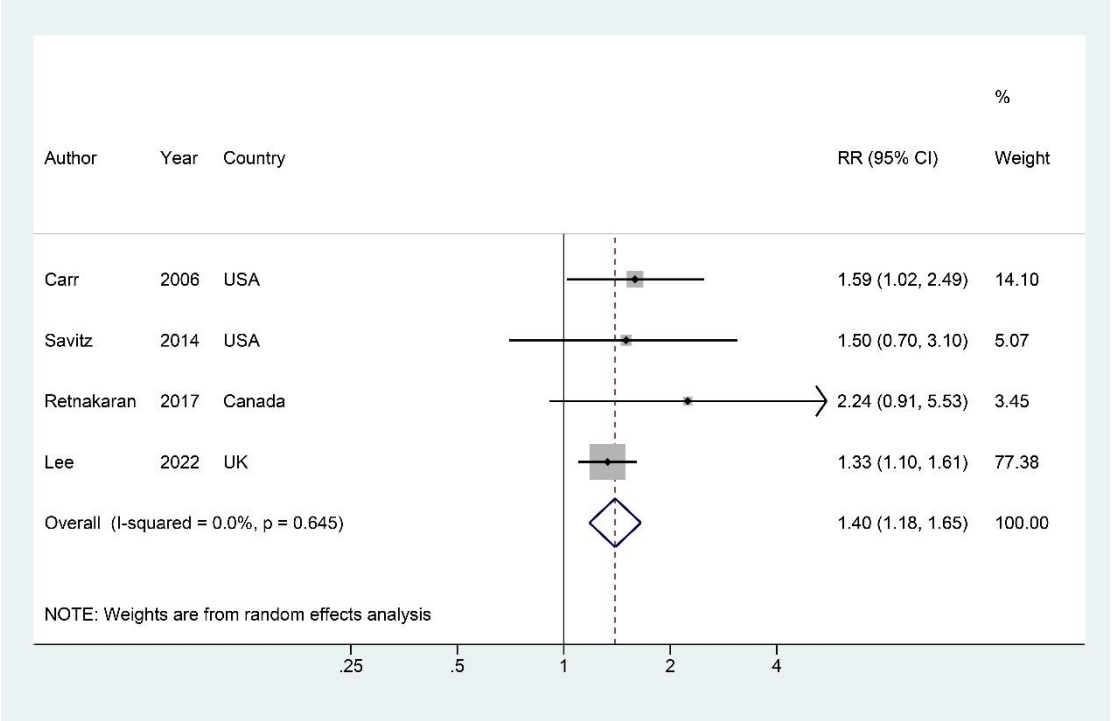


Figure S8. Forest plot of risk ratio of coronary artery diseases in women with a history of gestational diabetes mellitus.

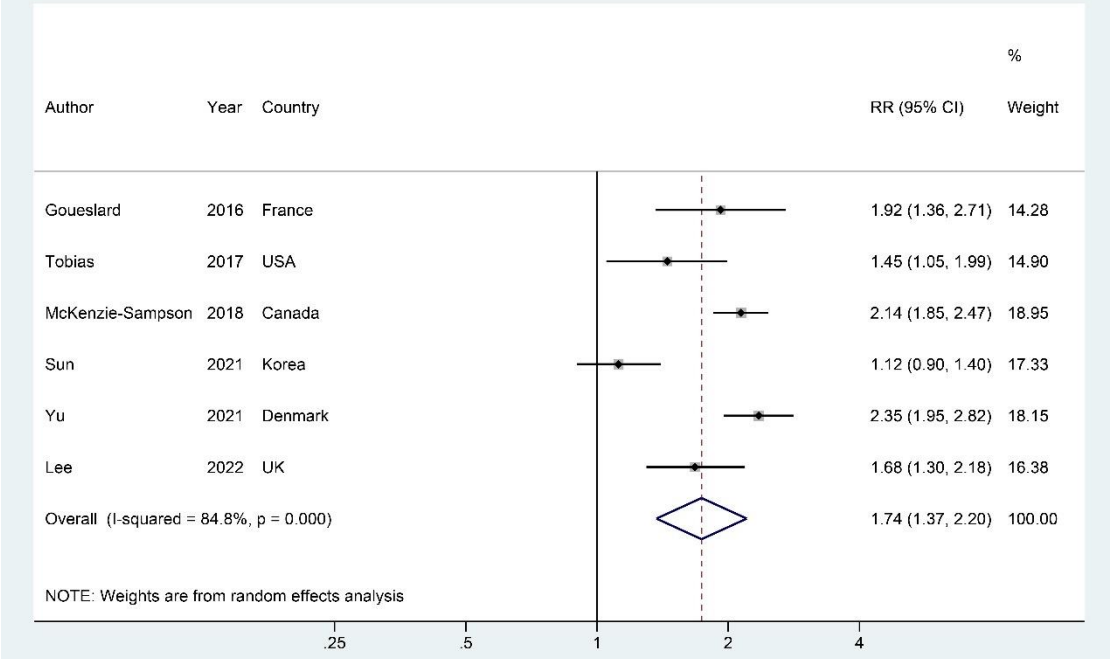


Figure S9. Forest plot of risk ratio of myocardial infarction in women with a history of gestational diabetes mellitus.

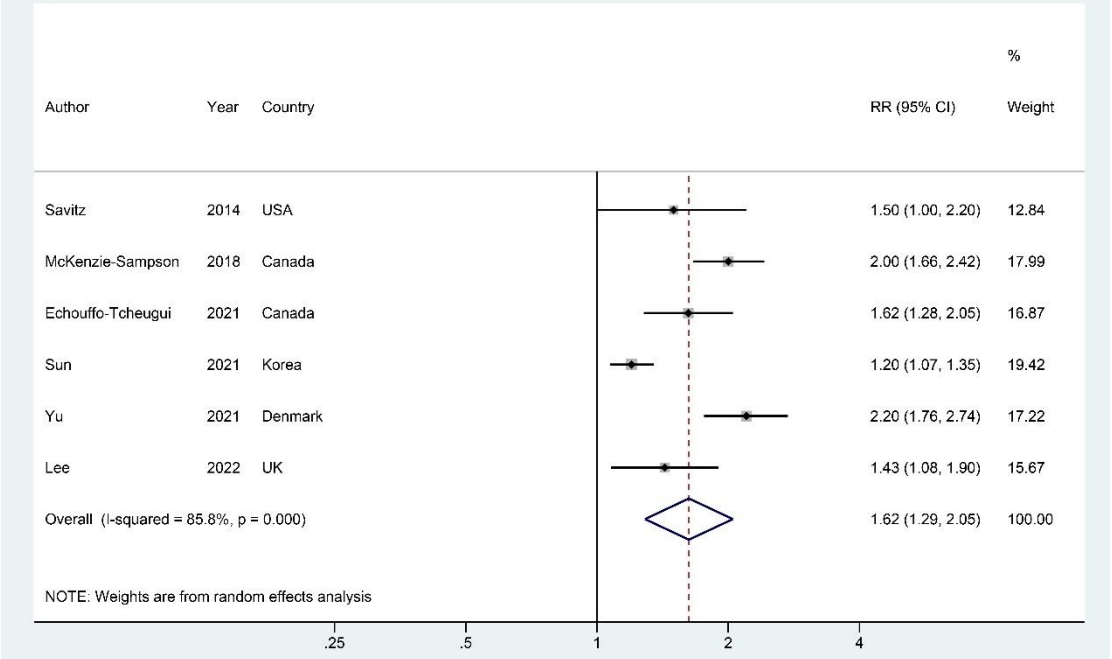


Figure S10. Forest plot of risk ratio of heart failure in women with a history of gestational diabetes mellitus.

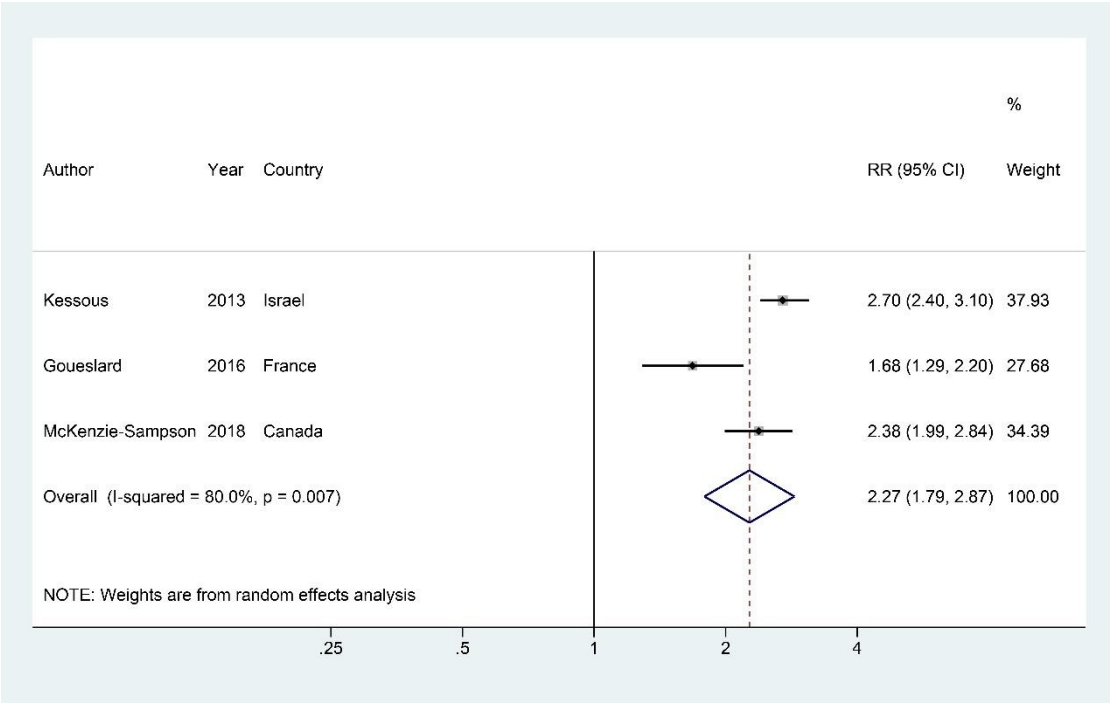


Figure S11. Forest plot of risk ratio of angina pectoris in women with a history of gestational diabetes mellitus.

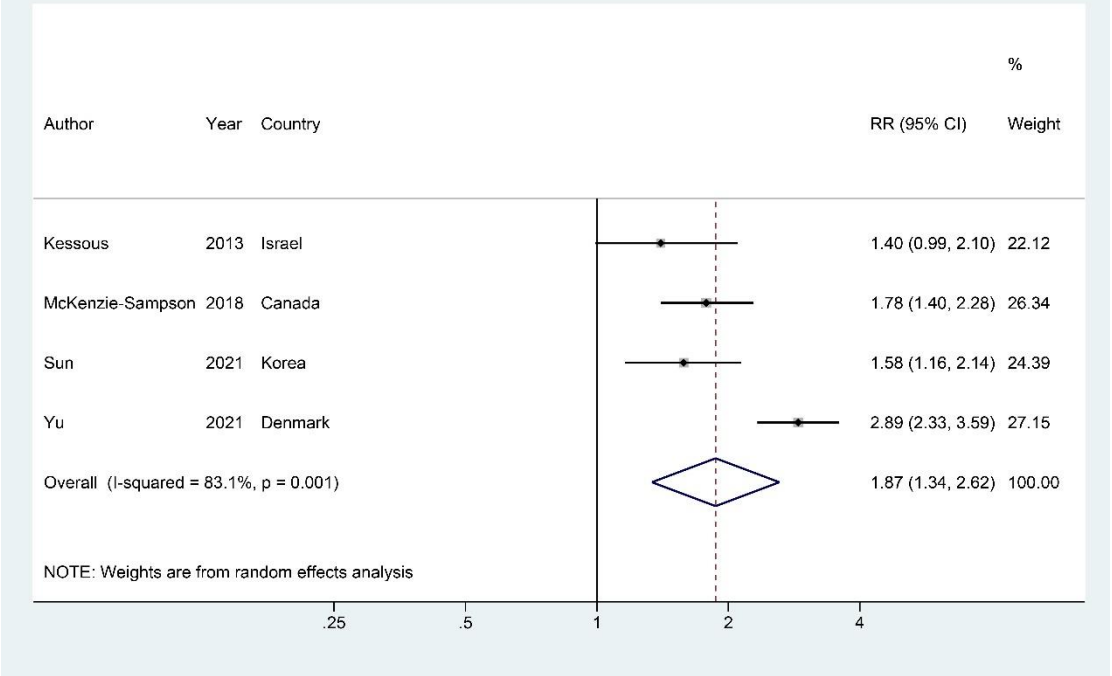


Figure S12. Forest plot of risk ratio of cardiovascular procedures in women with a history of gestational diabetes mellitus.

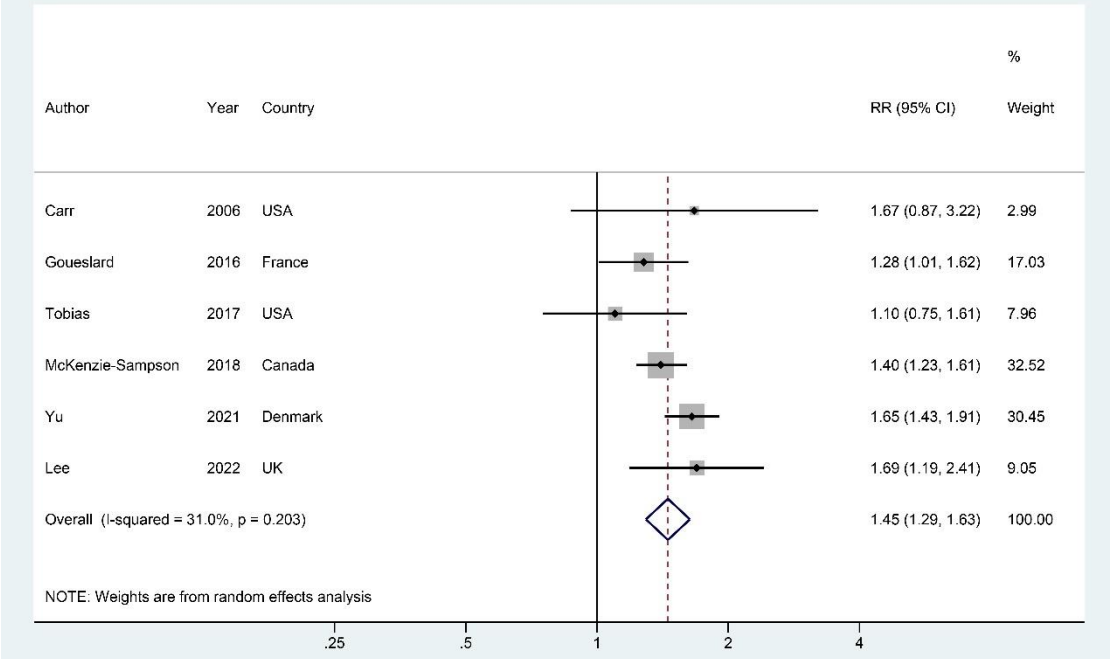


Figure S13. Forest plot of risk ratio of overall stroke in women with a history of gestational diabetes mellitus.

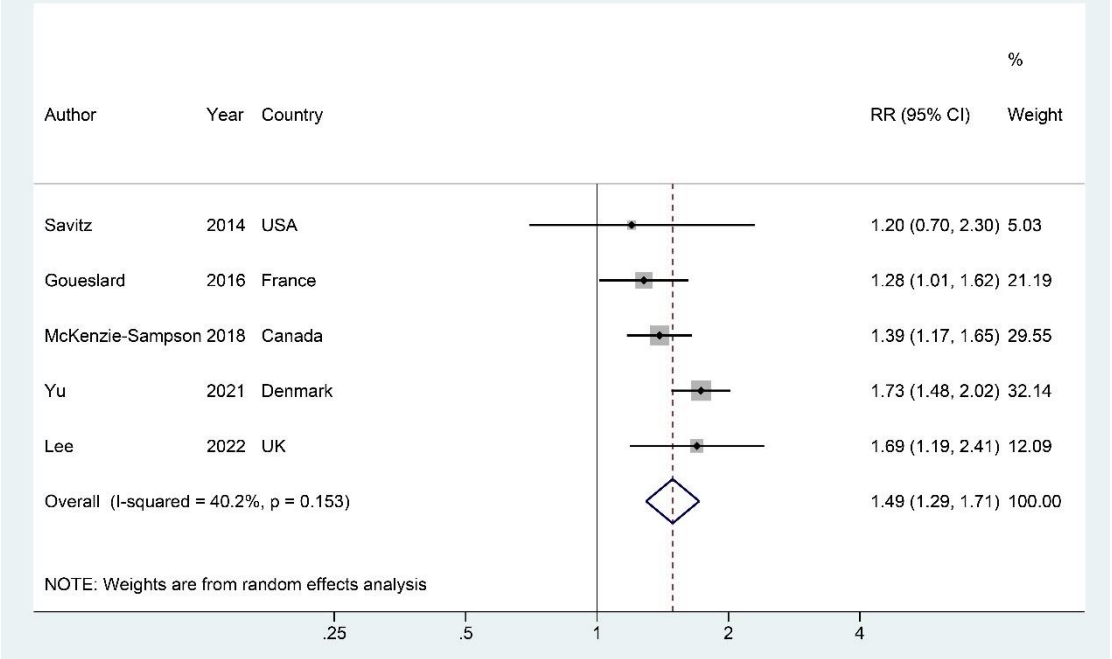


Figure S14. Forest plot of risk ratio of ischemic stroke in women with a history of gestational diabetes mellitus.

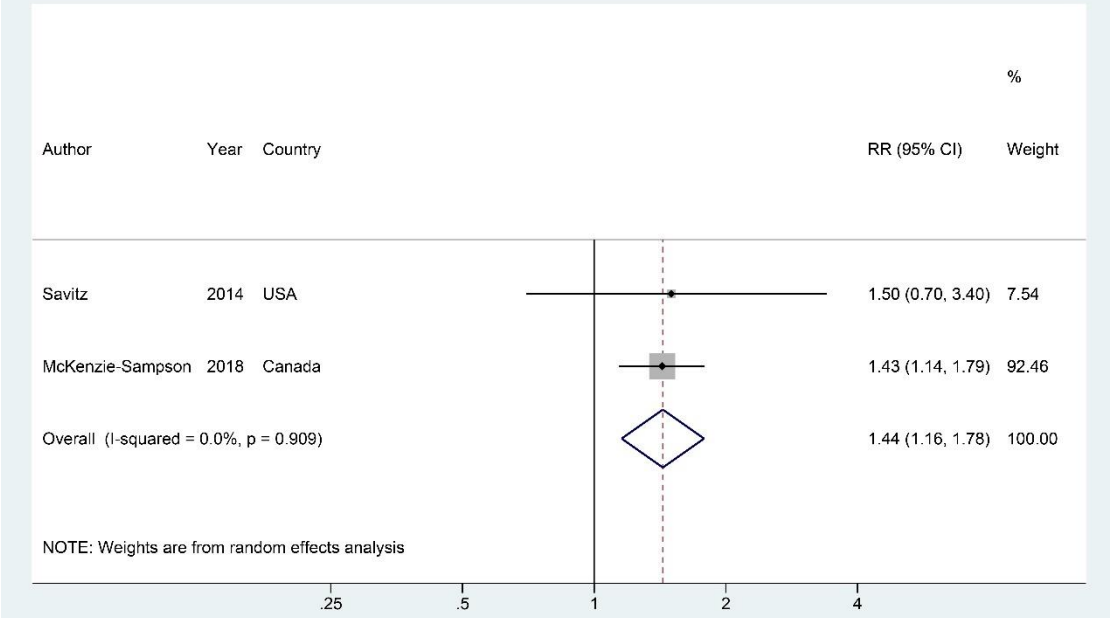


Figure S15. Forest plot of risk ratio of hemorrhagic stroke in women with a history of gestational diabetes mellitus.

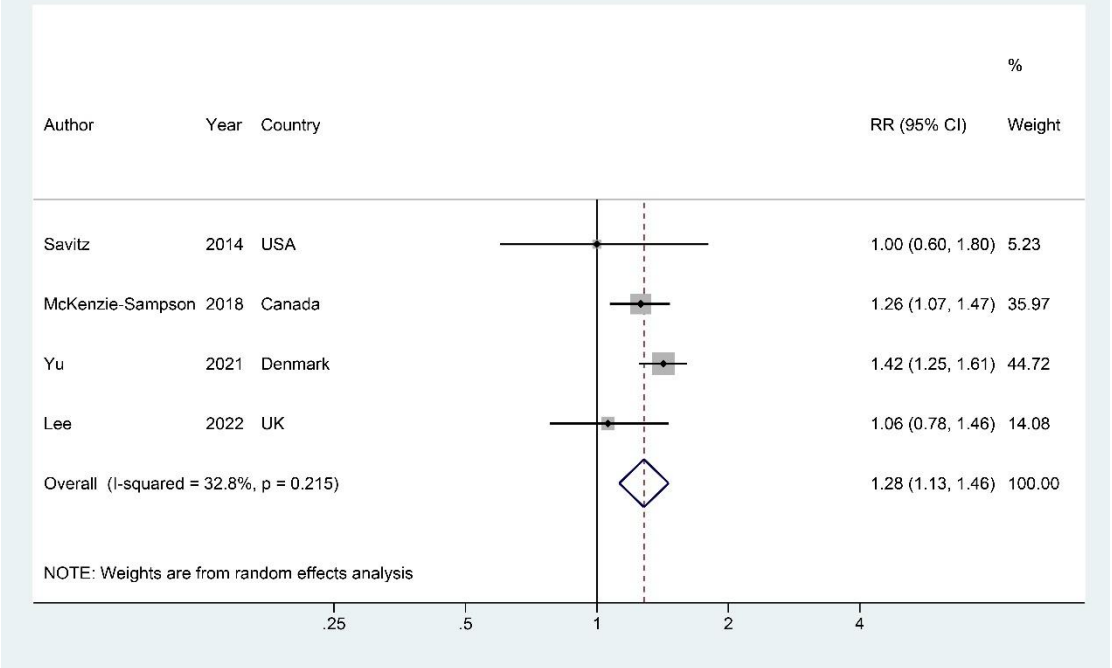


Figure S16. Forest plot of risk ratio of venous thromboembolism in women with a history of gestational diabetes mellitus.

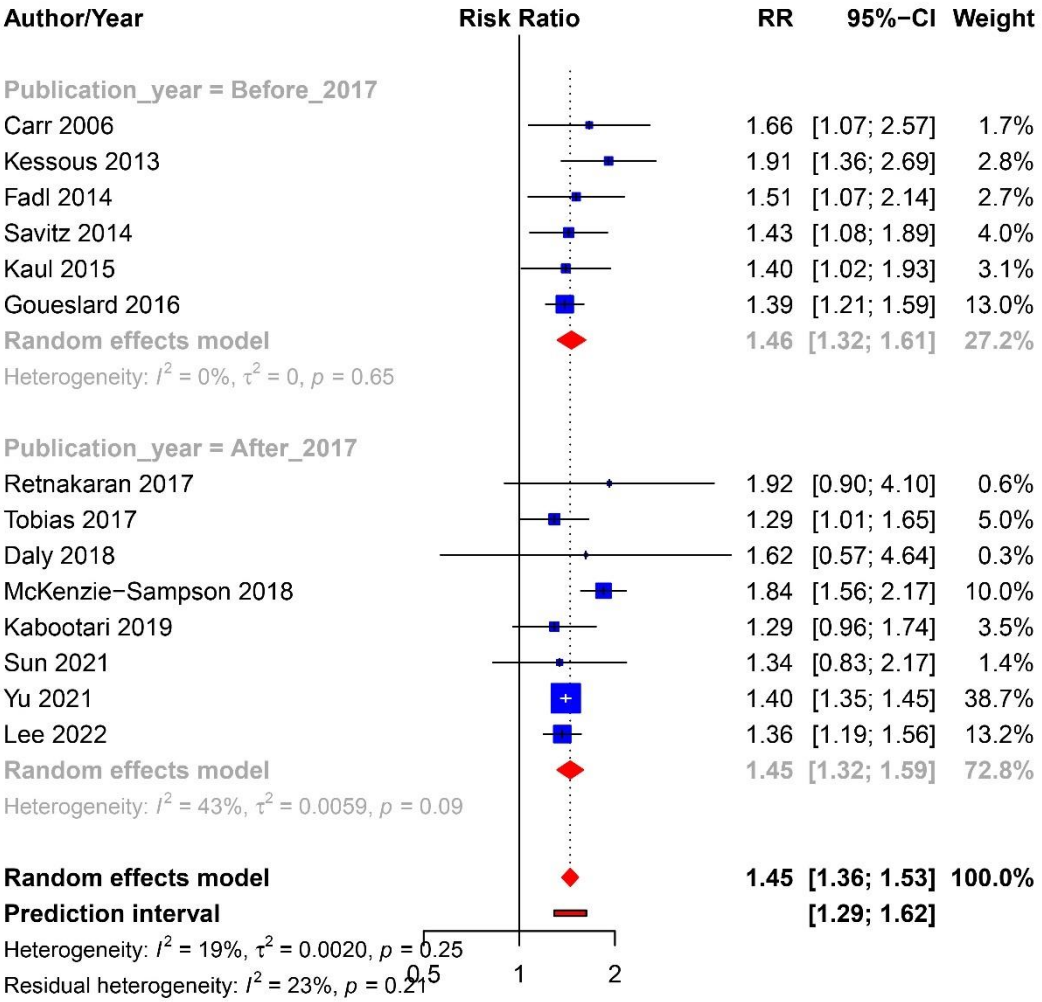


Figure S17. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to year of publication.

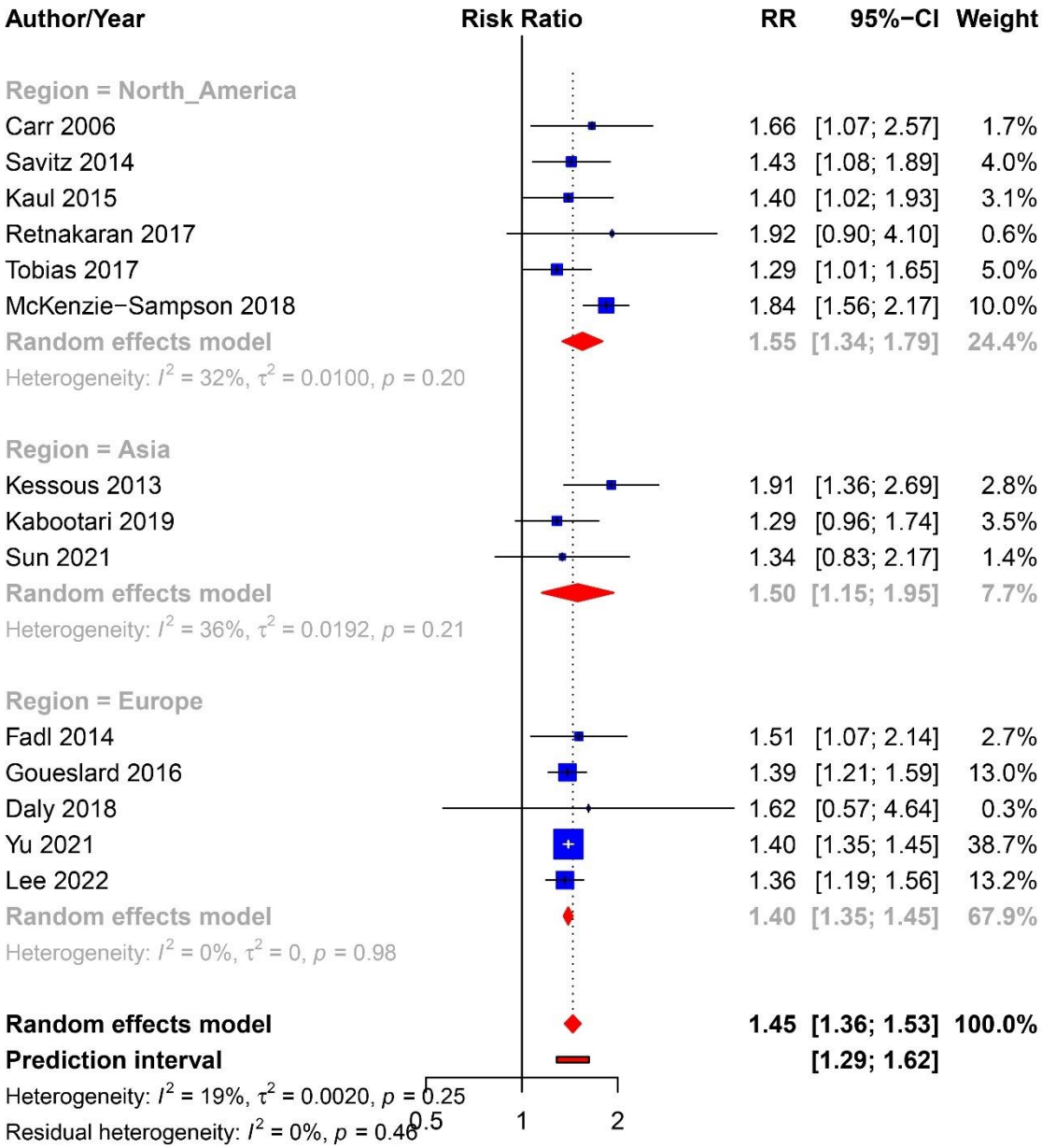


Figure S18. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to study location.

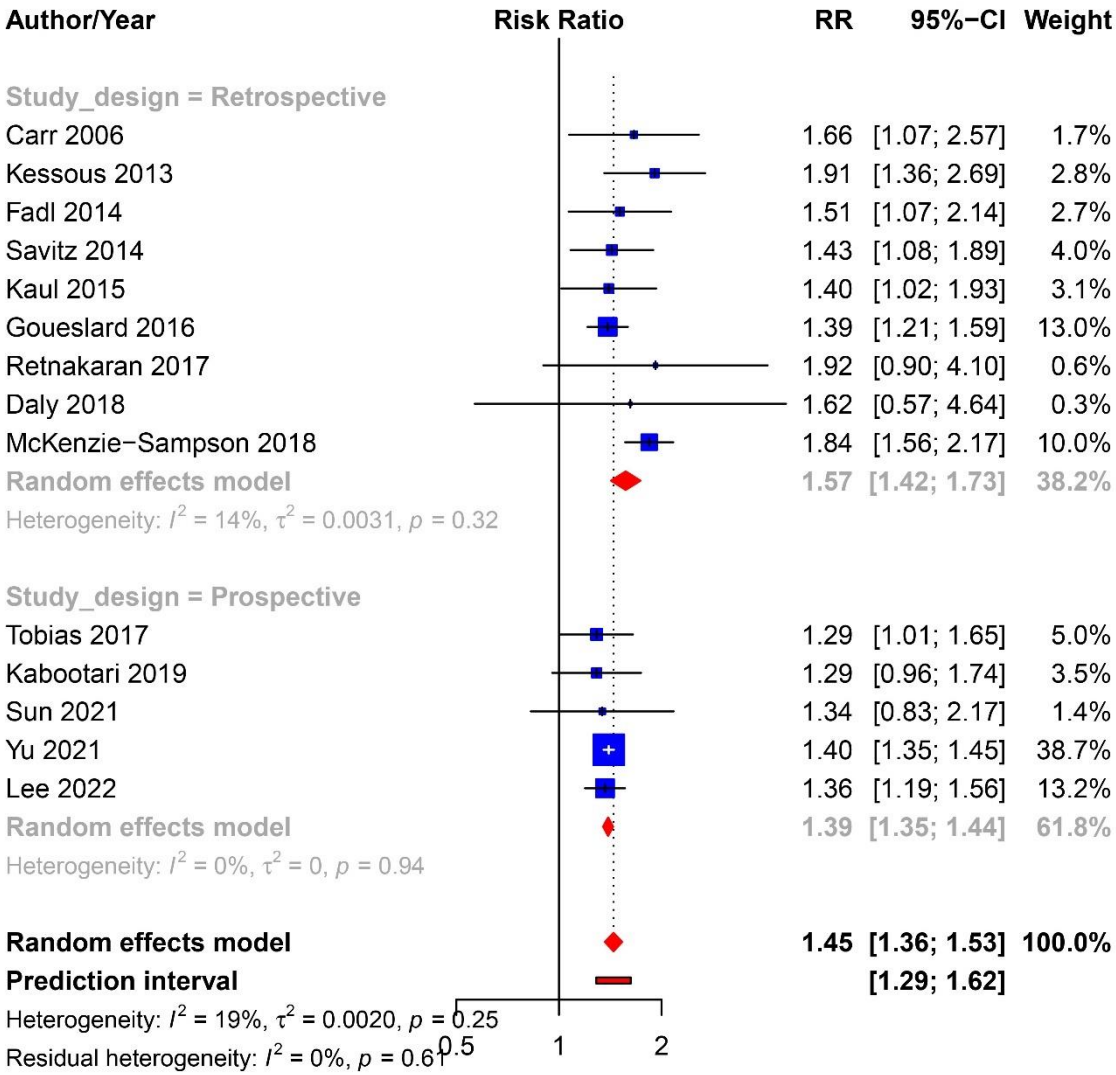


Figure S19. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to study design.

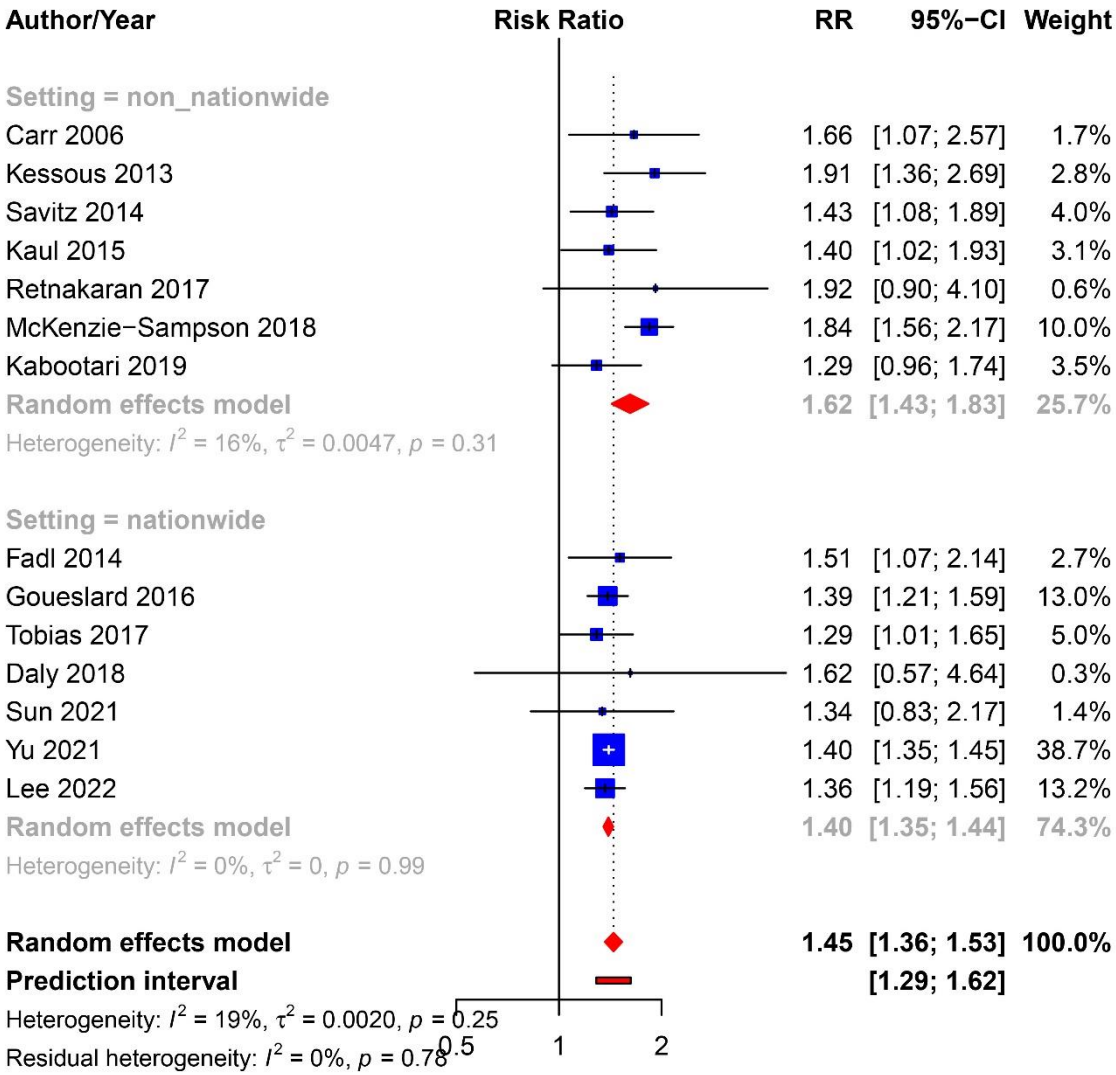


Figure S20. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to source of data.

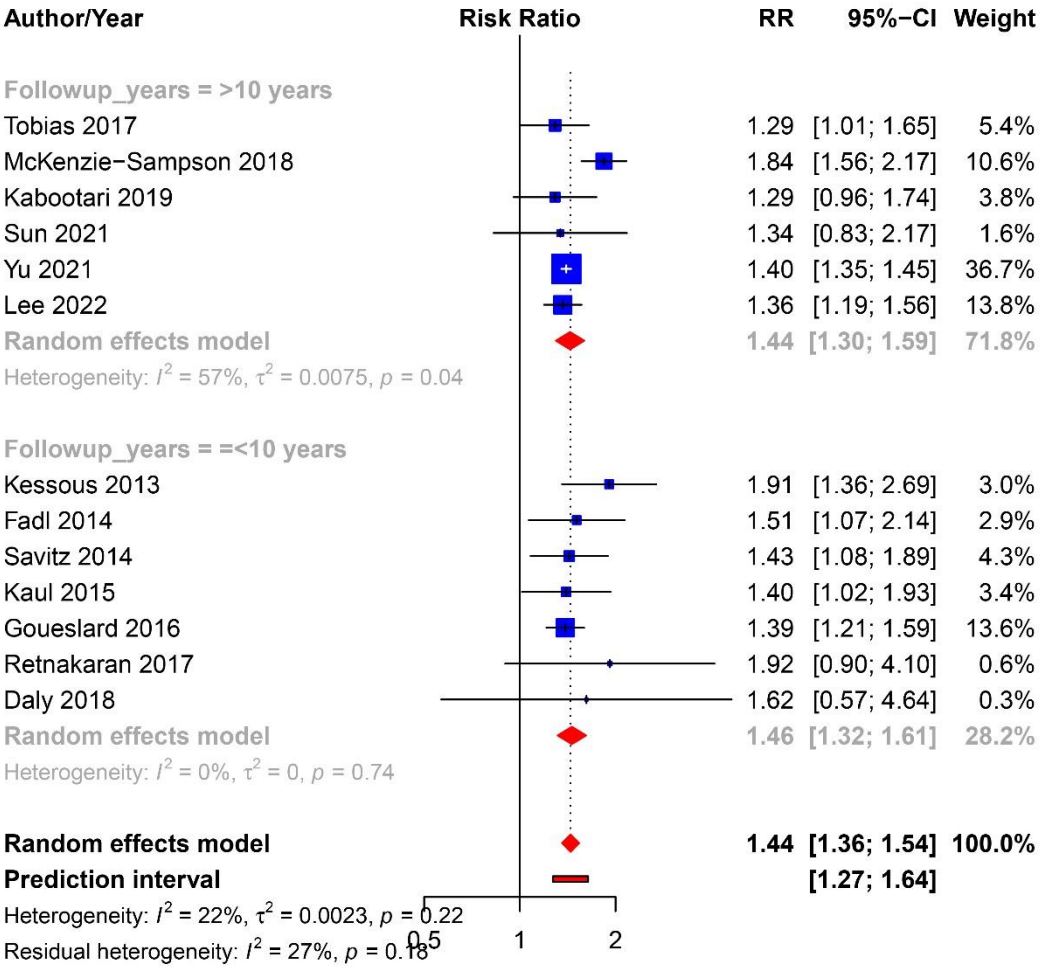


Figure S21. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to follow-up duration.

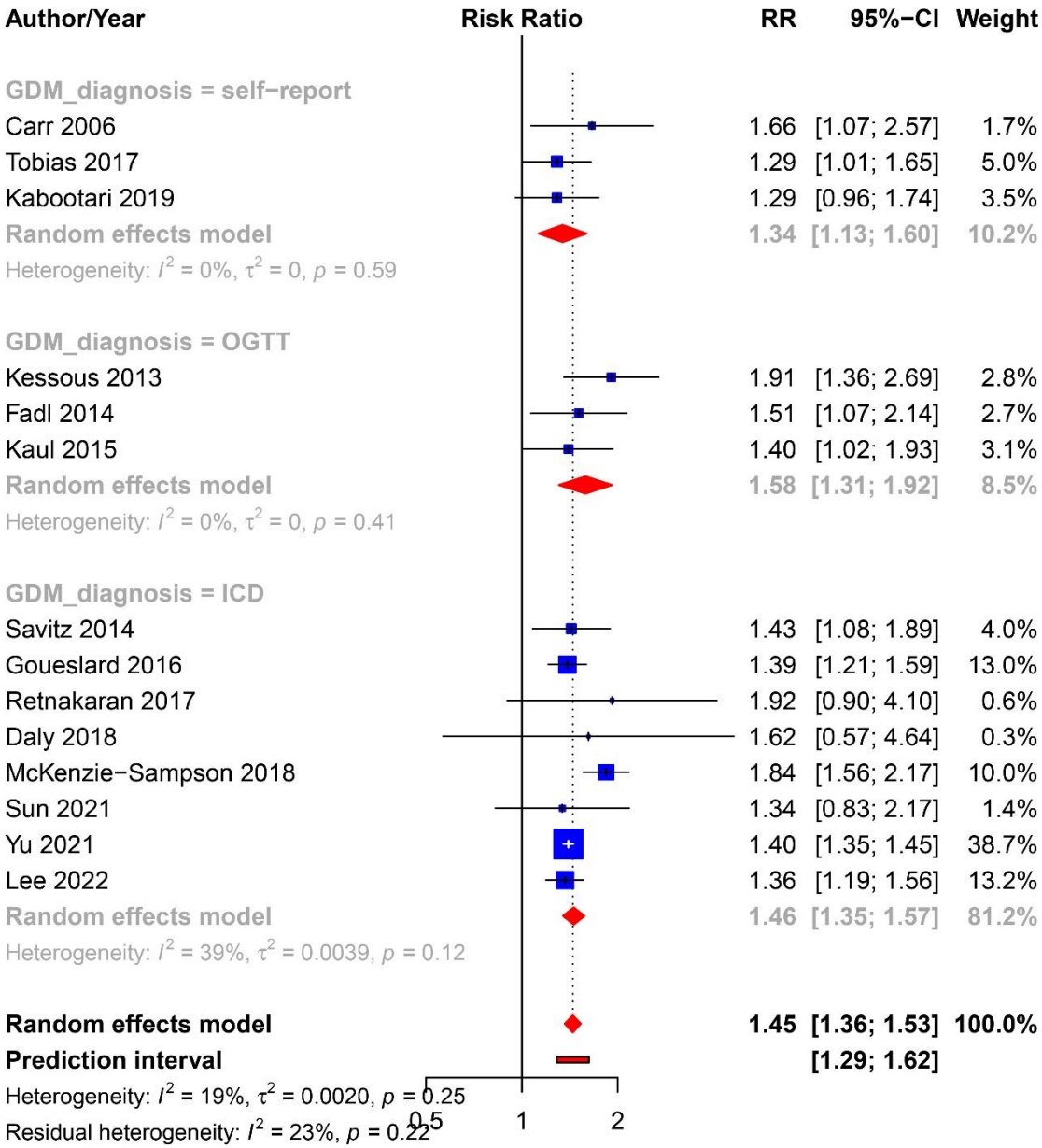


Figure S22. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to method of ascertainment of gestational diabetes mellitus.

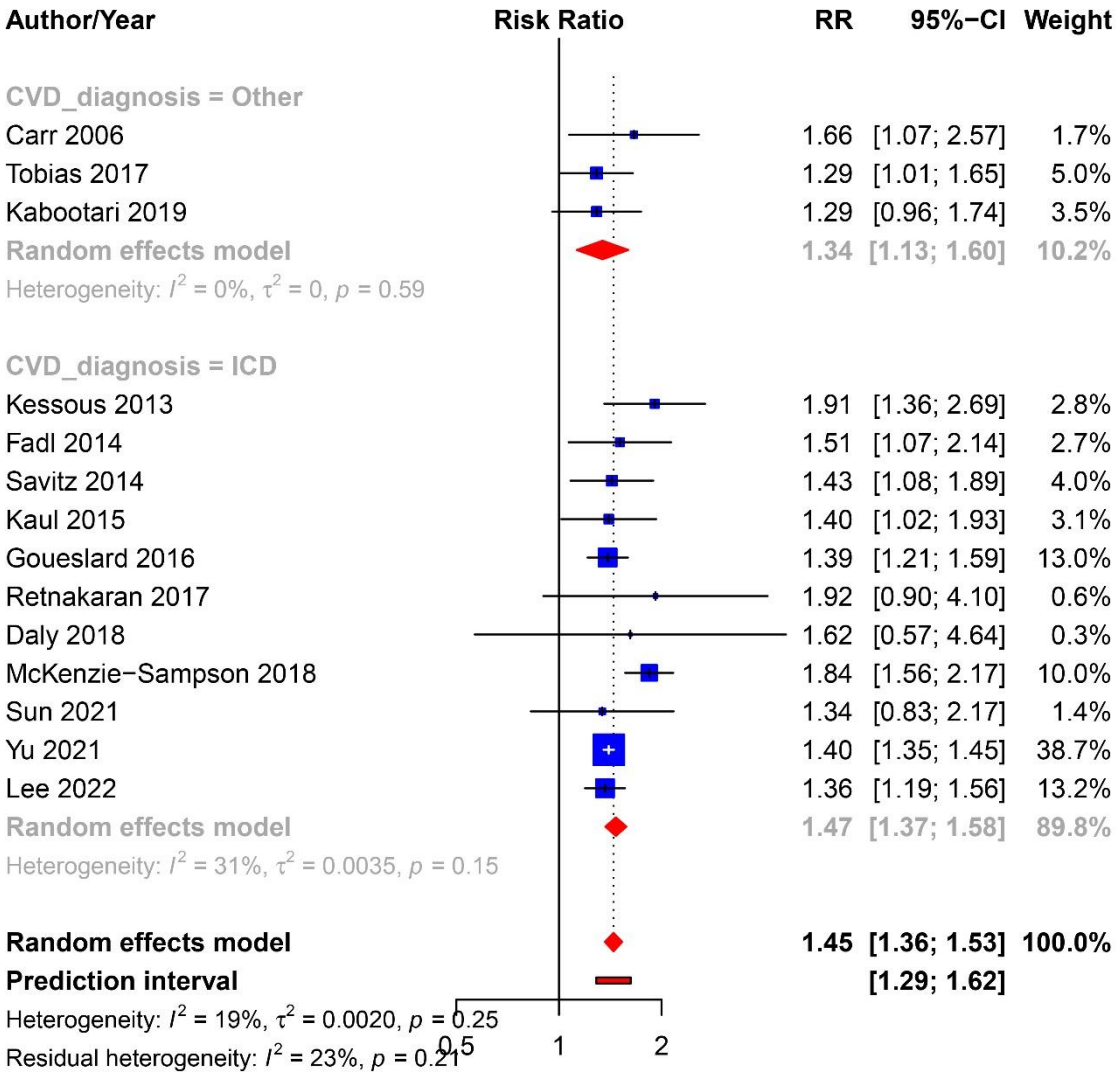


Figure S23. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to method of ascertainment of cardiovascular and cerebrovascular diseases.

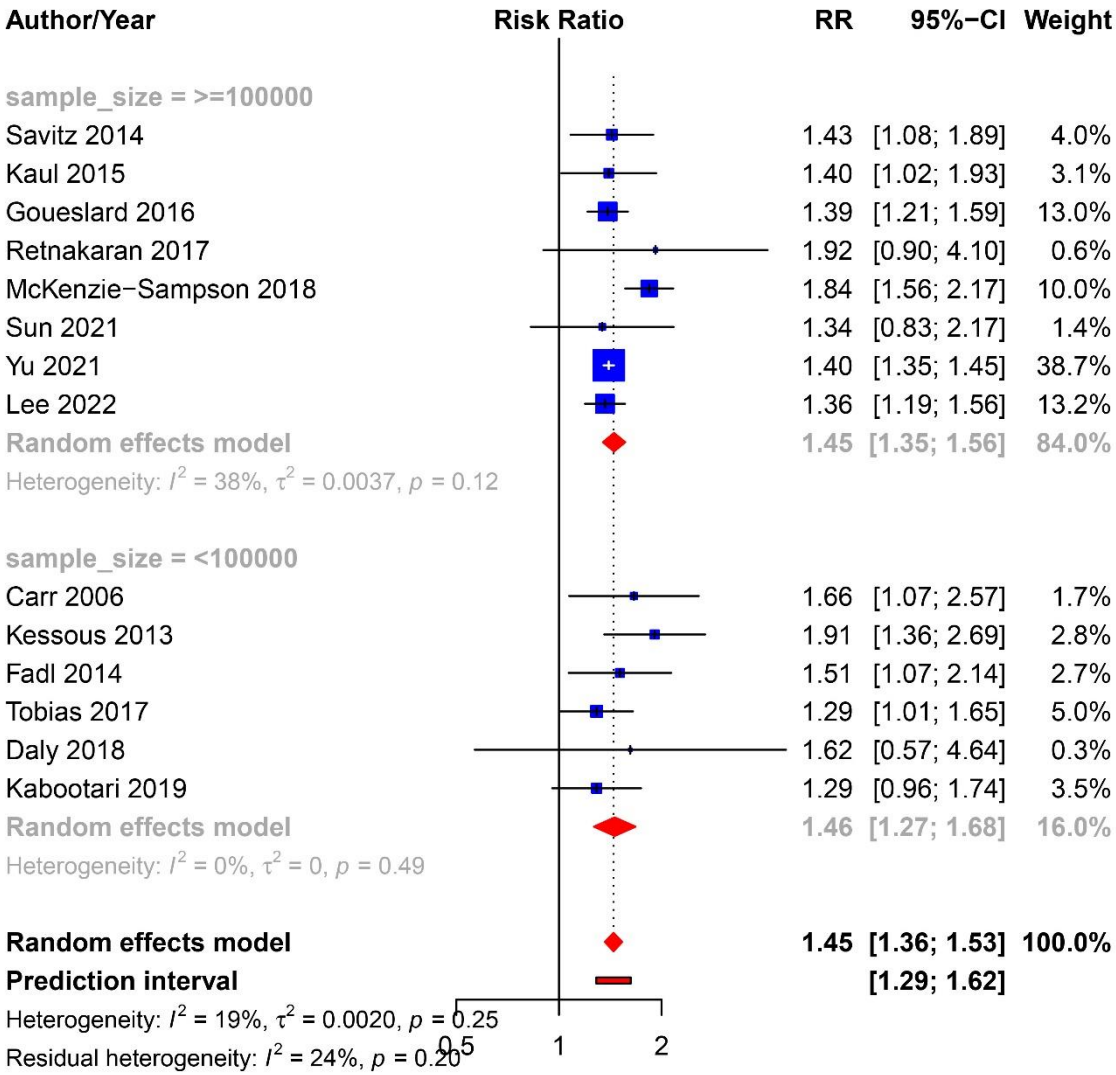


Figure S24. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to sample size.

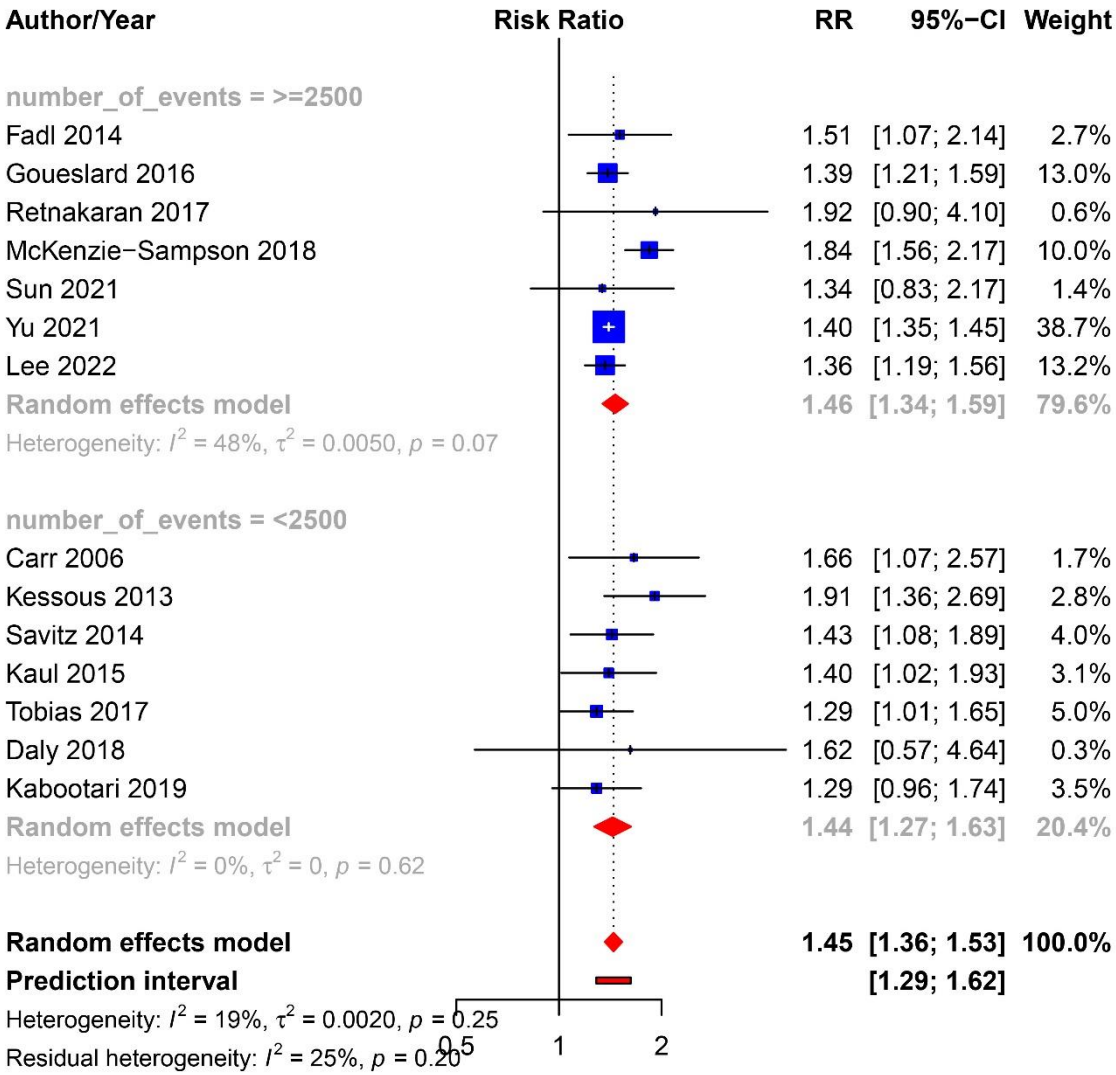


Figure S25. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to number of events.

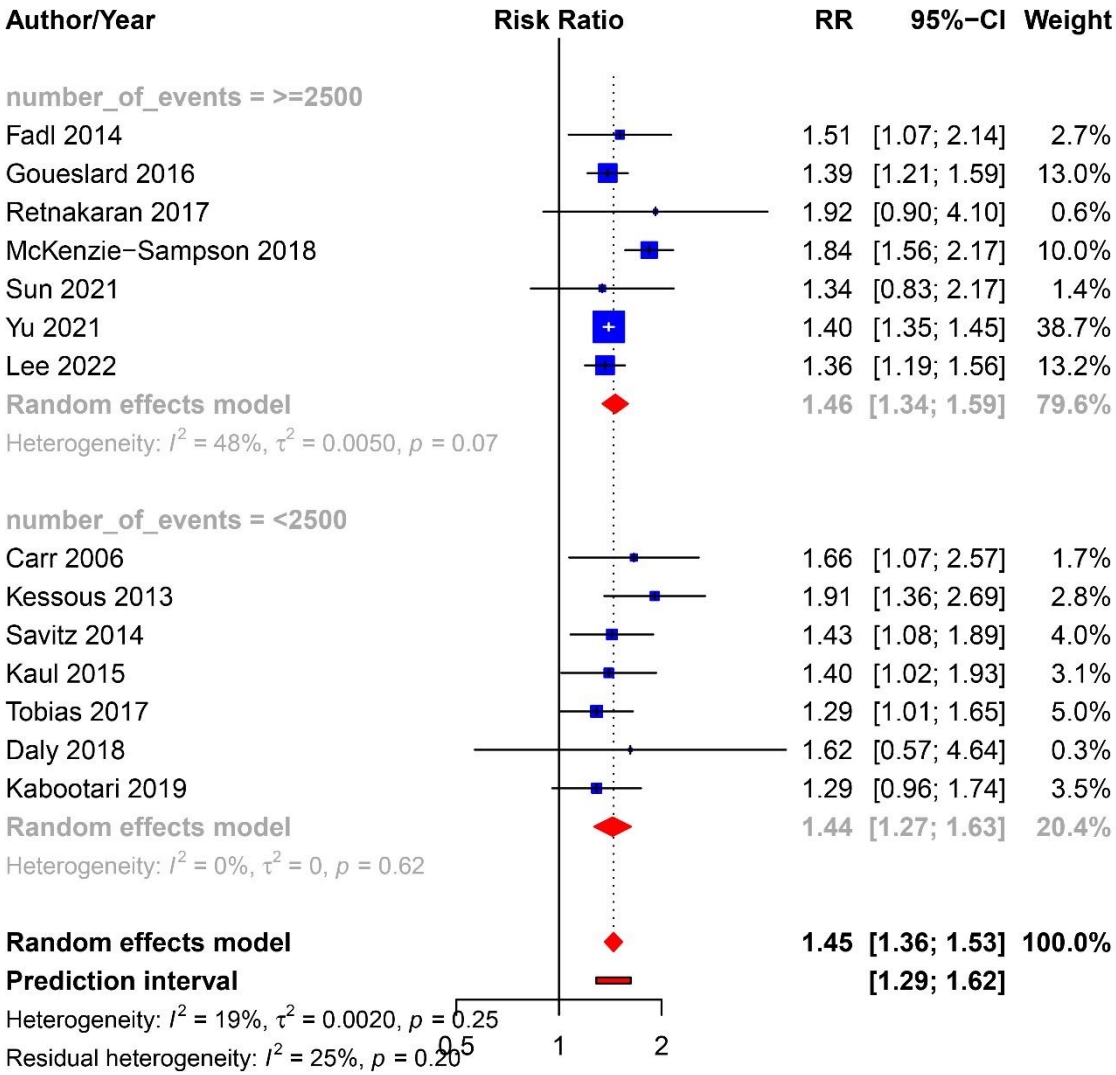


Figure S26. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to risk-of-bias (ROBINS-I).

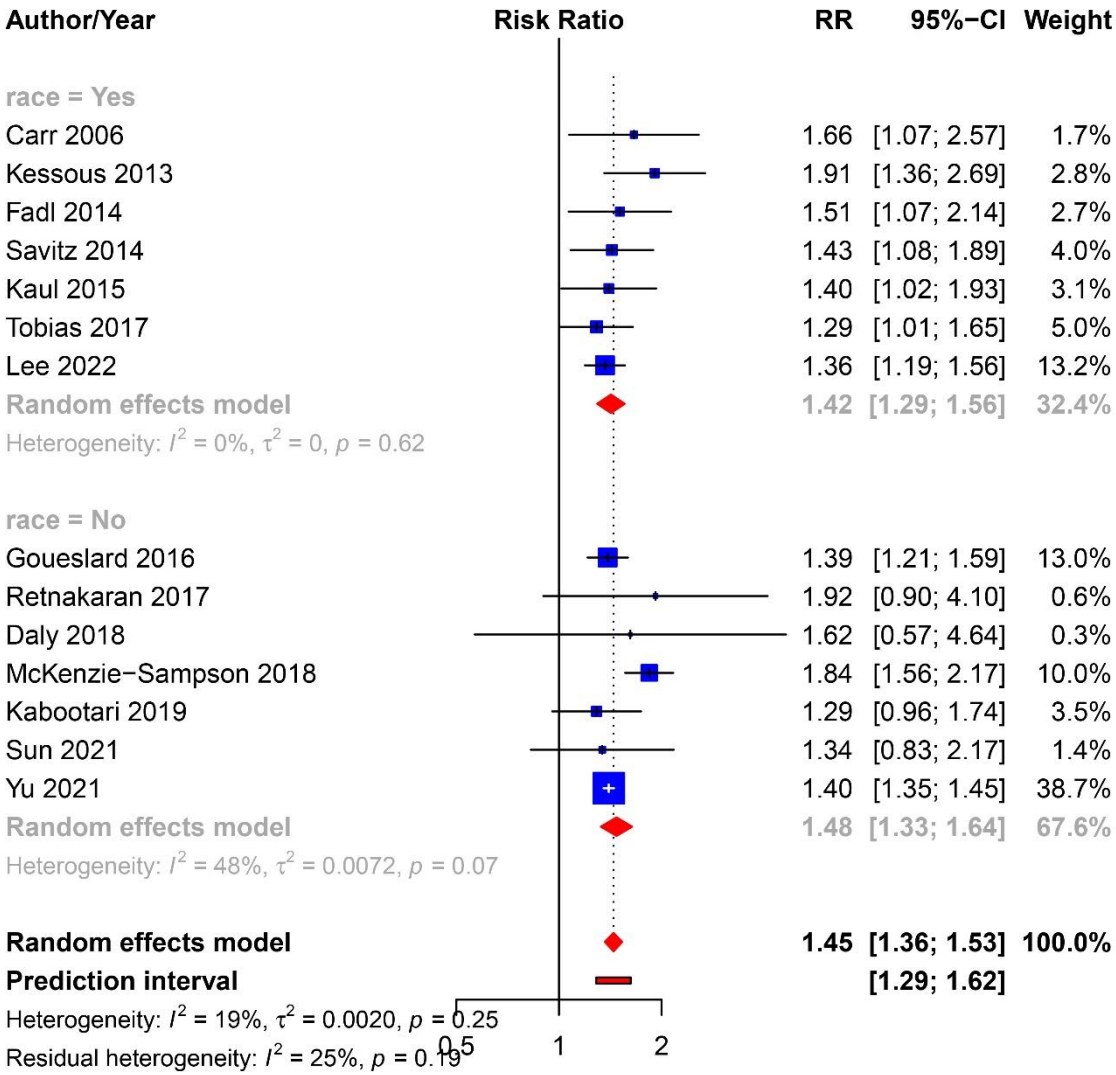


Figure S27. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of race.

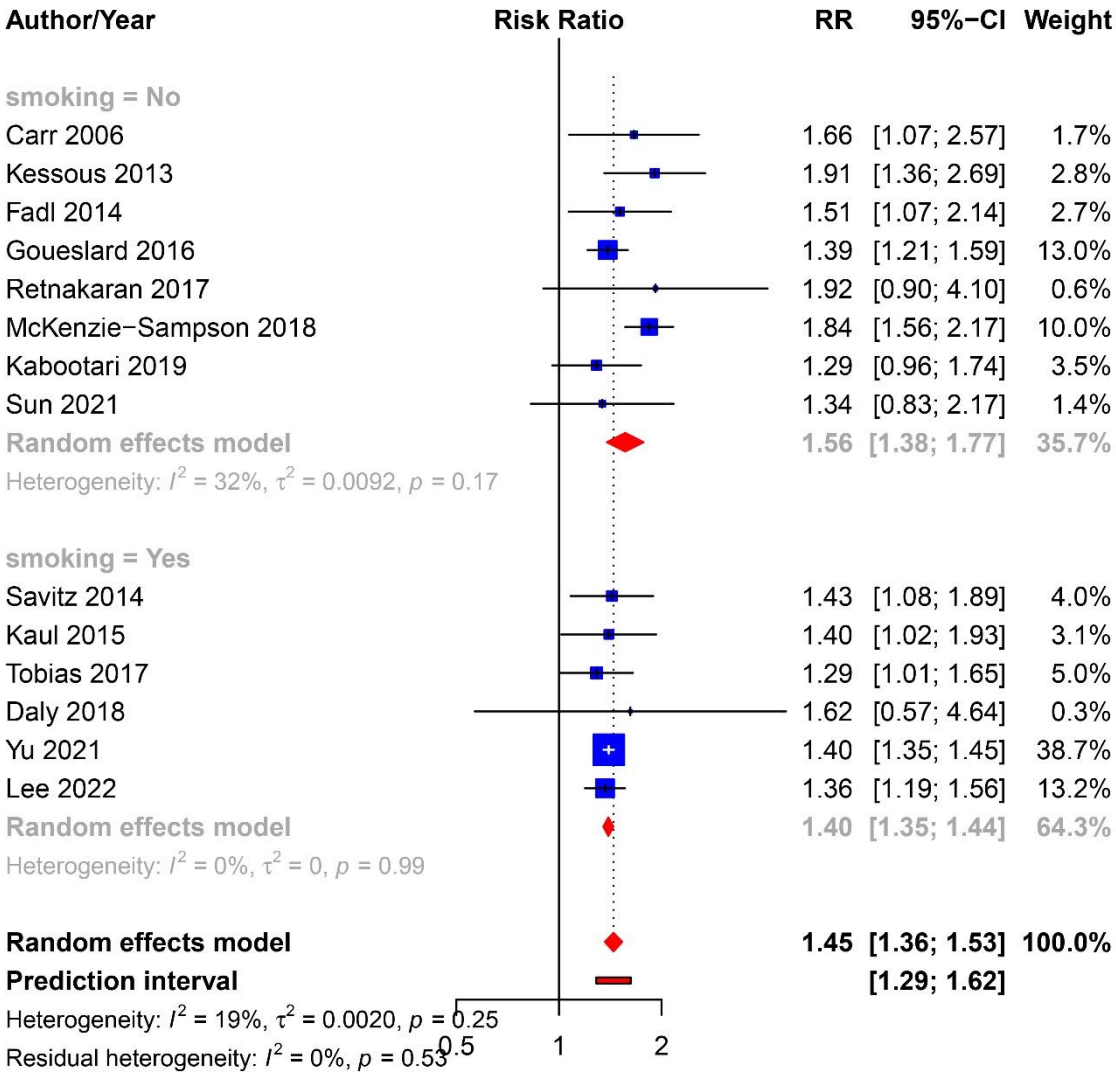


Figure S28. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of smoking.

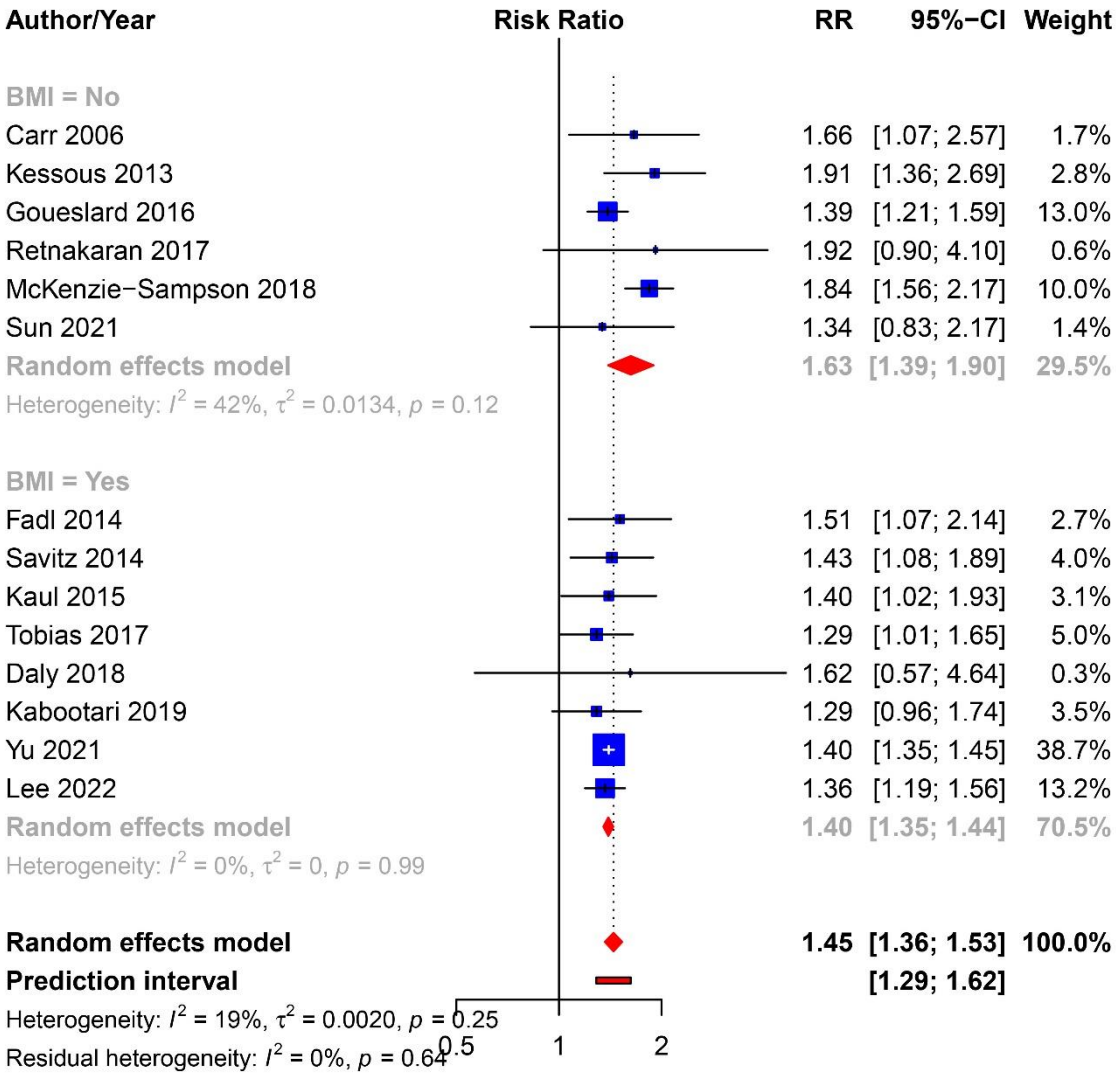


Figure S29. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of body mass index.

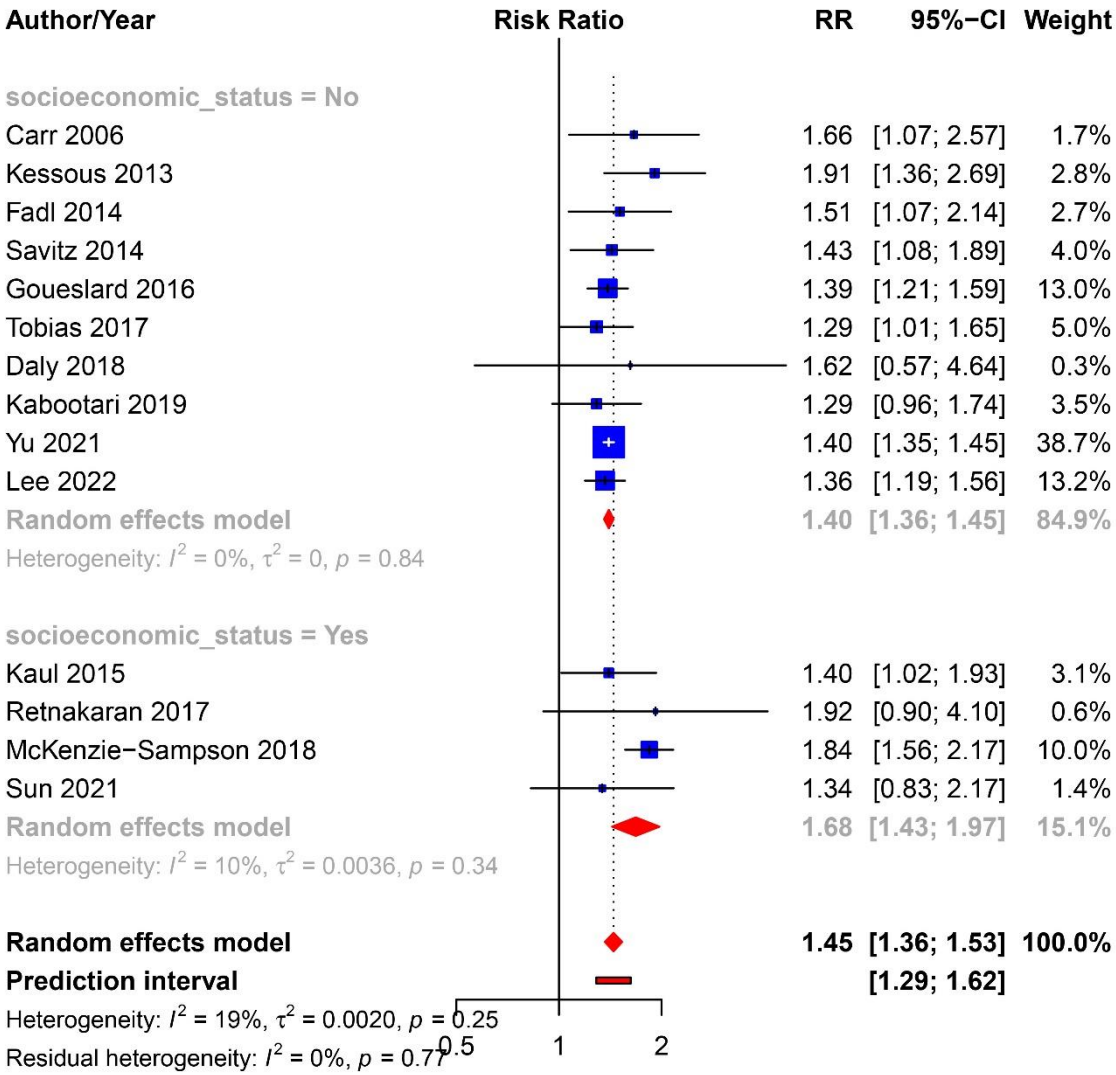


Figure S30. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of socio-economic status.

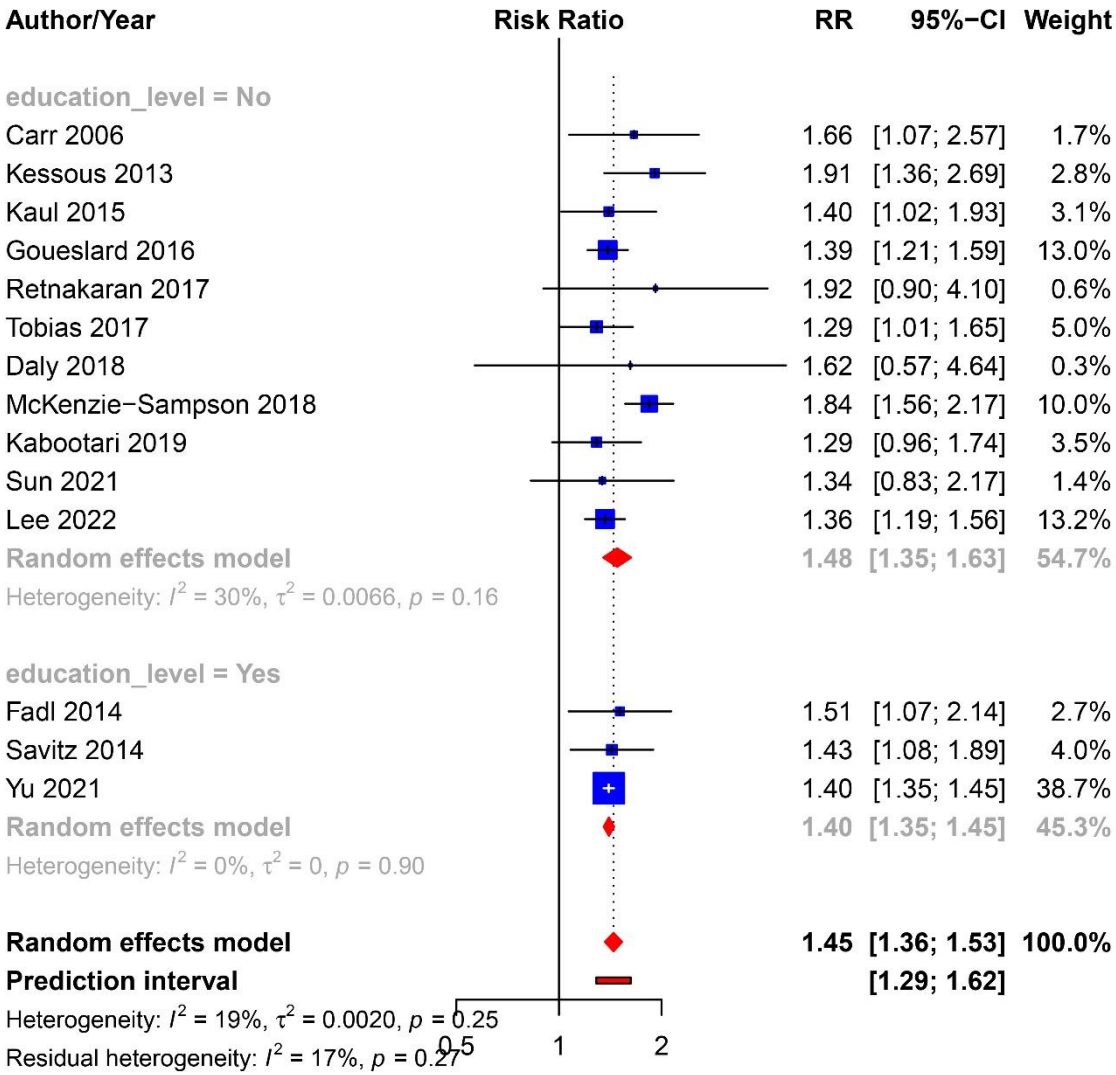


Figure S31. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of education level.

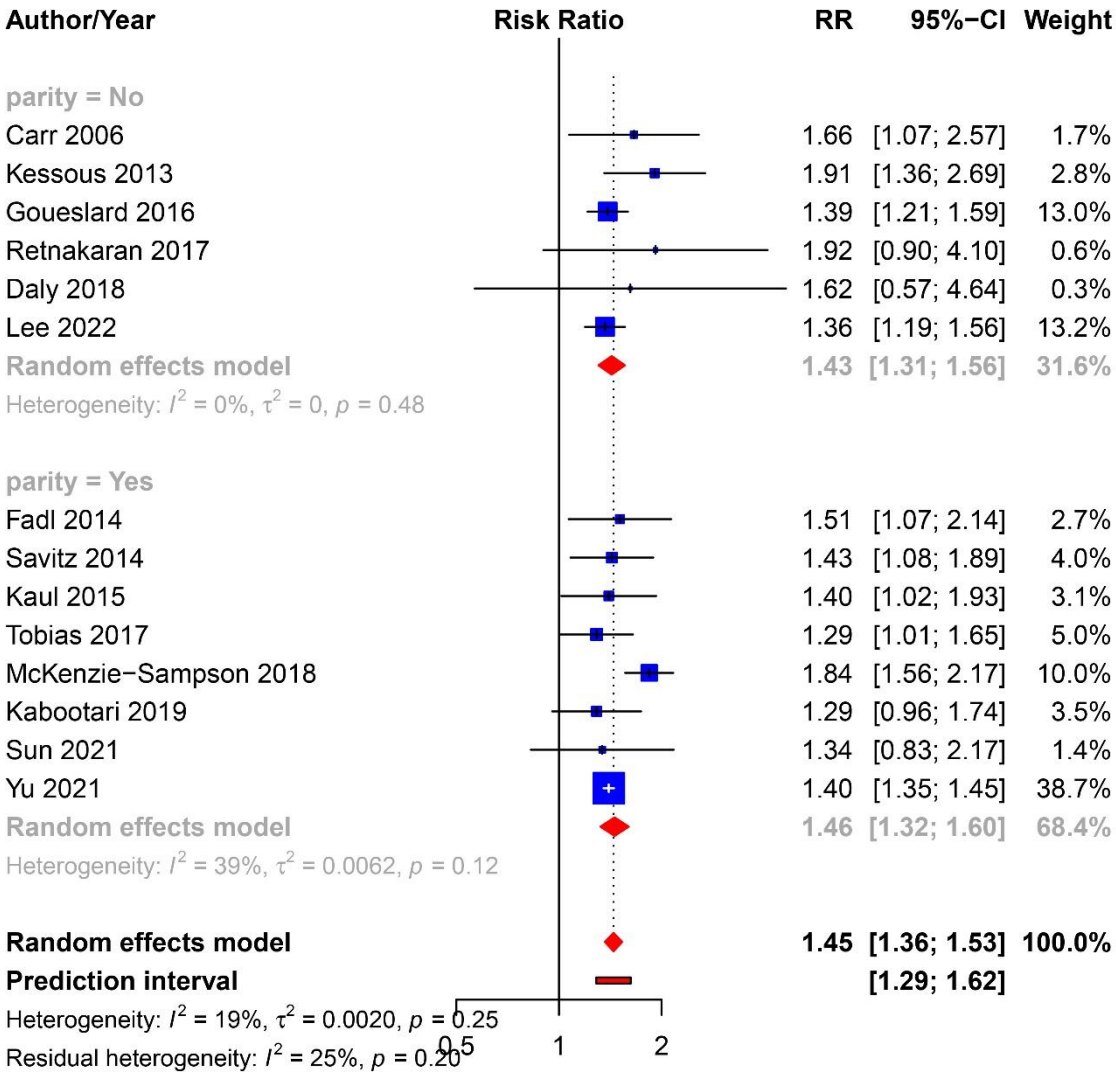


Figure S32. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of parity.

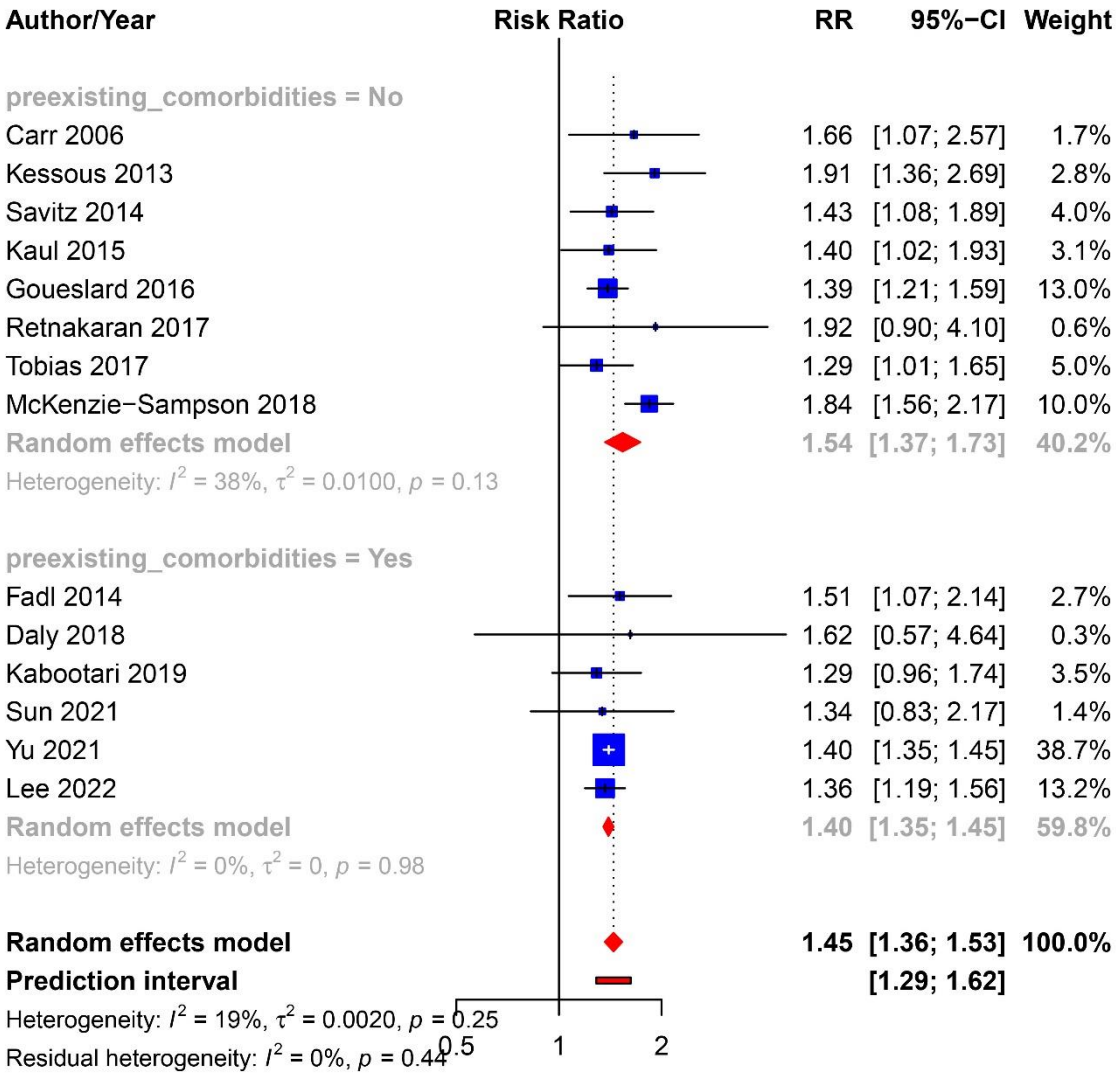


Figure S33. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of comorbidities.

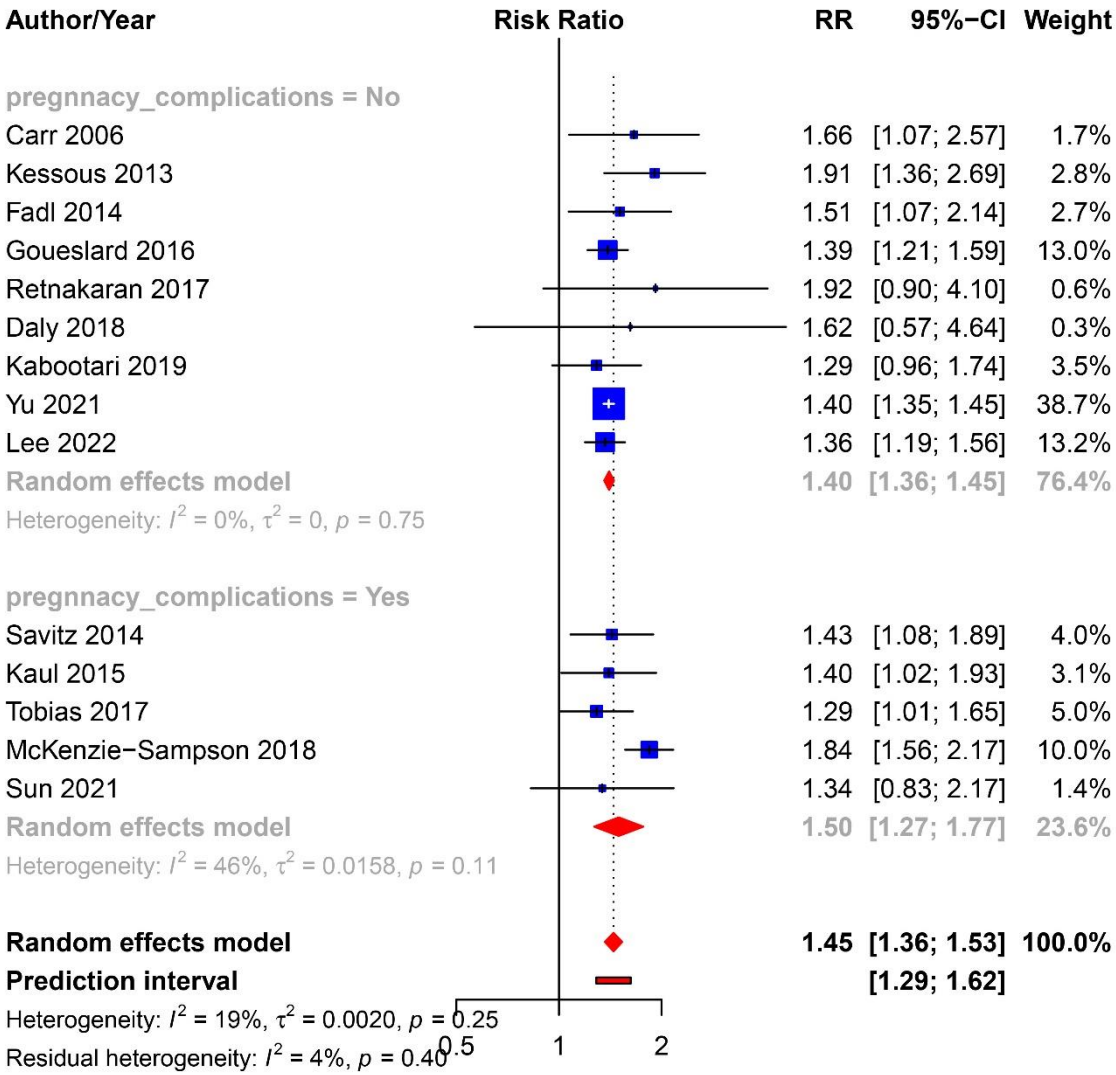


Figure S34. Subgroup analyses of the association between gestational diabetes mellitus and overall cardiovascular and cerebrovascular diseases, according to adjustment of pregnancy complications.

Appendix S1. Updated Study protocol

Title

Association of Gestational Diabetes Mellitus with Overall and Type-Specific Cardiovascular and cerebrovascular Diseases: Systematic Review with Meta-Analysis Involving Over 8 Million Participants

Review question

The risk of overall and type-specific cardiovascular and cerebrovascular diseases (CCVD) as well as venous thromboembolism in women with a history of gestational diabetes mellitus (GDM).

Searches

EMBASE, PubMed, and Cochrane library from inception to from database inception to 1 November 2021 and updated on 26 May 2022 were performed.

URL to search strategy.

(gestational diabetes OR gestational diabetes mellitus OR pregnancy diabetes OR pregnancy diabetes mellitus) AND (cardiovascular diseases OR cerebrovascular disorders OR venous thromboembolism OR cardiovascular OR cerebrovascular OR coronary artery disease* OR coronary heart disease* OR cardiac OR ischemic heart disease* OR cardiovascular and cerebrovascular OR myocardial infarction OR heart failure OR angina pectoris OR cerebral OR stroke OR transient ischemic attack OR pulmonary embolism OR deep vein thrombosis)

Condition or domain being studied.

Overall and Type-Specific Cardiovascular and cerebrovascular Diseases

Participants/population

Cohort studies, case-control studies, reporting the relationship between GDM and incident CVD. Studies will be excluded as follows:

1) Replicated publications from the same cohort
2) Insufficient data
3) Case report, editorial, review
4) Nonhuman studies

Intervention(s), exposure(s)

Our intervention of interest is the risk of overall and type-specific cardiovascular and cerebrovascular diseases.

Comparator(s)/control

Control without GDM.

Types of study to be included.

retrospective or prospective cohort studies, or case-control studies.

Context

Main outcome(s)

1) The primary outcome was the association of GDM with all CVD, cardiovascular and cerebrovascular diseases.

2) The secondary outcomes were the association of GDM with type-specific cardiovascular, cerebrovascular diseases as well as VTE (including deep vein thrombosis and pulmonary embolism).

Measures of effect

Pooled risk ratio

Additional outcome(s).

Not applicable.

Data extraction (selection and coding)

The following data will be independently extracted by two authors by two reviewers (WX and YW) on an excel sheet

1) First author, publication year, country/countries, study design, data sources.
2) Sample size and time period of observations in the study,
3) patients' demographics and clinical characteristics.
5) Study outcomes including number of patients developing CVD.

Risk of bias (quality) assessment

The risk of bias of selected studies was assessed independently by 2 reviewers (WX and YW)

according to the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool. In brief, this tool consists of the following seven domains: (1) bias due to confounding; (2) bias due to selection of participants; (3) bias due to exposure assessment; (4) bias due to misclassification during follow-up; (5) bias due to missing data; (6) bias due to outcome assessment; and (7) bias due to selective reporting. For each domain, the reviewer's judgments were rated as low risk, moderate risk, serious risk, critical risk, and no information. Any discrepancies were handled by a senior investigator (ZZ).

Strategy for data synthesis.

Extracted data for meta-analysis was performed with Stata Statistical Software version 13.0 and RR statistical language version R 3.6.0. The P-values were two sided with significant level a=0.05. Pooled RRs with 95% CIs were calculated as an effect measure using the random effect models (DerSimonian and Laird method) for determining the relationship between GDM and developing cardiovascular and cerebrovascular events. The HR and IRR were used as good estimators of RR to carry out the statistical estimations. Because the occurrence of CCVD in GDM patients was relatively low, the OR mathematically approximates the RRs. We selected risk estimates from the multivariate models that were fully adjusted for confounders. For the studies that only reported the risk estimates for type-specific CCVD however with absence of an overall CCVD, we summarized type-specific risk estimates by either fixed-effects or random-effects model based on the level of heterogeneity to obtain a combined risk estimates of the study, which was finally entered into the main pooled analysis [15]. The heterogeneity across studies was quantify by I^2 statistic (0-25% represents low heterogeneity, 25-50% moderate heterogeneity, 50-75% substantial heterogeneity, 75-100% high heterogeneity). Potential publication bias was assessed by visualization of funnel plot (≥10 included studies) in combination with both Egger's test and Begg's test.

Analysis of subgroups or subsets.

To identify the subgroup differences and potential sources of the observed heterogeneity, subgroup analyses were carried out after stratifying for median year of publication (before 2017 vs after 2017), study location (North America vs Europe vs Asia), study design (prospective vs retrospective), source of data (nationwide vs non-nationwide), median follow-up duration (>10 years vs ≤ 10 years), method of ascertainment of GDM (diagnostic code vs. self-report vs. oral glucose tolerance test [OGTT]), method of ascertainment of CCVD (diagnostic code vs. others), median sample size (≥100,000 vs < 100,000), number of CCVD events (≥2,500 vs < 2,500), and quality of study (moderate vs serious risk of bias). Meanwhile, to explore whether the association of GDM with CCVD was influenced by potential confounders, we performed additional analyses, stratified by a variety of adjustments, including race, smoking, body mass index, socio-economic status, education level, parity, preexisting comorbidities, the presence of pregnancy complications. A difference between the estimates of these subgroups was considered significant for a P-value less than <0.10. In addition, to assess the role of subsequent diabetes in the association between GDM and CCVD, we further analyzed the risk estimate for CCVD in all GDM patients and GDM patients who did not develop future overt diabetes. To evaluate the robustness of pooled results, sensitivity analyses were conducted by excluding each study one by one, excluding the case-control study and exclusively including the studies with direct risk estimates for overall CCVD.

Type and method of review

Meta-analysis, Systematic review

Language

No restriction

Appendix 2. Protocol deviations

Section	Previous Protocol	Publication
Title	Association of Gestational Diabetes Mellitus with Overall and Type-Specific Cardiovascular and cerebrovascular Diseases: Systematic Review with Meta-Analysis	Association of Gestational Diabetes Mellitus with Overall and Type-Specific Cardiovascular and cerebrovascular Diseases: Systematic Review with Meta-Analysis Involving Over 8 Million Participants
Authors	Wenhui Xie, Yu Wang, Shiyu Xiao, Lin Qiu, Yang Yu	Wenhui Xie, Yu Wang, Shiyu Xiao, Lin Qiu, Yang Yu, Zhuoli Zhang
Literature search	A literature search was performed using the electronic databases PubMed, EMBASE and the Cochrane Library from database inception to from inception to 1 November 2021	EMBASE, PubMed, and Cochrane library from inception to from database inception to 1 November 2021 and updated on 26 May 2022 were performed.
Risk of bias appraisal	The Newcastle-Ottawa Scale	Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool
Strategy for data synthesis	/	For the studies that only reported the risk estimates for type-specific CCVD however with absence of an overall CCVD, we summarized type-specific risk estimates by either fixed-effects or random-effects model based on the level of heterogeneity to obtain a combined risk estimates of the study, which was finally entered into the main pooled analysis
Strategy for data synthesis	Extracted data for meta-analysis was performed with Stata Statistical Software version 13.0	Extracted data for meta-analysis was performed with Stata Statistical Software version 13.0 and RR statistical language version R 3.6.0.
Analysis of subgroups or subsets	Subgroup analyses were carried out by year of publication, study location, study design, source of data, follow-up duration, diagnosis of GDM, diagnosis	To identify the subgroup differences and potential sources of the observed heterogeneity, subgroup analyses were carried out after stratifying for median

	of CVD, sample size and study quality. Moreover, to explore whether the association of GDM with CVD was influenced by potential confounders, we performed additional analyses, stratified by the adjustments, including race, smoking, body mass index, socio-economic status, education level, parity, preexisting comorbidities, the presence of pregnancy complications.	year of publication (before 2017 vs after 2017), study location (North America vs Europe vs Asia), study design (prospective vs retrospective), source of data (nationwide vs non-nationwide), median follow-up duration (>10 years vs ≤ 10 years), method of ascertainment of GDM (diagnostic code vs. self-report vs. oral glucose tolerance test [OGTT]), method of ascertainment of CCVD (diagnostic code vs. others), median sample size (≥100,000 vs < 100,000), number of CCVD events (≥2,500 vs < 2,500), and quality of study (moderate vs serious risk of bias). Meanwhile, to explore whether the association of GDM with CCVD was influenced by potential confounders, we performed additional analyses, stratified by a variety of adjustments, including race, smoking, body mass index, socio-economic status, education level, parity, preexisting comorbidities, the presence of pregnancy complications. A difference between the estimates of these subgroups was considered significant for a P-value less than <0.10.

Appendix S3. Search strategy

(gestational diabetes OR gestational diabetes mellitus OR pregnancy diabetes OR pregnancy diabetes mellitus) AND (cardiovascular diseases OR cerebrovascular disorders OR venous thromboembolism OR cardiovascular OR cerebrovascular OR coronary artery disease* OR coronary heart disease* OR cardiac OR ischemic heart disease* OR cardiovascular and cerebrovascular OR myocardial infarction OR heart failure OR angina pectoris OR cerebral OR stroke OR transient ischemic attack OR pulmonary embolism OR deep vein thrombosis)

Pubmed 2022-5-26 11305

("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields]) OR ("diabetes, gestational"[MeSH Terms] OR ("diabetes"[All Fields] AND "gestational"[All Fields]) OR "gestational diabetes"[All Fields] OR ("gestational"[All Fields] AND "diabetes"[All Fields] AND "mellitus"[All Fields]) OR "gestational diabetes mellitus"[All Fields]) OR ("pregnancy in diabetics"[MeSH Terms] OR ("pregnancy"[All Fields] AND "diabetics"[All Fields]) OR "pregnancy in diabetics"[All Fields] OR ("pregnancy"[All Fields] AND "diabetes"[All Fields]) OR "pregnancy diabetes"[All Fields]) OR ("pregnancy in diabetics"[MeSH Terms] OR ("pregnancy"[All Fields] AND "diabetics"[All Fields]) OR "pregnancy in diabetics"[All Fields] OR ("pregnancy"[All Fields] AND "diabetes"[All Fields] AND "mellitus"[All Fields]) OR "pregnancy diabetes mellitus"[All Fields])) AND ("cardiovascular diseases"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "diseases"[All Fields]) OR "cardiovascular diseases"[All Fields] OR ("cerebrovascular disorders"[MeSH Terms] OR ("cerebrovascular"[All Fields] AND "disorders"[All Fields]) OR "cerebrovascular disorders"[All Fields]) OR ("venous thromboembolism"[MeSH Terms] OR ("venous"[All Fields] AND "thromboembolism"[All Fields]) OR "venous thromboembolism"[All Fields]) OR ("cardiovascular system"[MeSH Terms] OR ("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields]) OR "cerebrovascular"[All Fields] OR (("coronary vessels"[MeSH Terms] OR ("coronary"[All Fields] AND "vessels"[All Fields]) OR "coronary vessels"[All Fields] OR ("coronary"[All Fields] AND "artery"[All Fields]) OR "coronary artery"[All Fields]) AND "disease*"[All Fields]) OR (("coronaries"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "coronary"[All Fields]) AND ("heart"[MeSH Terms] OR "heart"[All Fields] OR "hearts"[All Fields] OR "heart s"[All Fields]) AND "disease*"[All Fields]) OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields]) OR (("ischaemics"[All Fields] OR "ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischaemic"[All Fields] OR "ischemic"[All Fields] OR "ischemical"[All Fields] OR "ischemically"[All Fields] OR "ischemics"[All Fields] OR "ischemized"[All Fields]) AND ("heart"[MeSH Terms] OR "heart"[All Fields] OR "hearts"[All Fields] OR "heart s"[All Fields]) AND "disease*"[All Fields]) OR "cardiovascular and cerebrovascular"[All Fields] OR ("myocardial infarction"[MeSH Terms] OR ("myocardial"[All Fields] AND "infarction"[All Fields]) OR "myocardial infarction"[All Fields]) OR ("heart failure"[MeSH Terms] OR ("heart"[All Fields] AND "failure"[All Fields]) OR "heart failure"[All Fields]) OR ("angina pectoris"[MeSH Terms] OR ("angina"[All Fields] AND "pectoris"[All Fields]) OR "angina pectoris"[All Fields]) OR ("cerebrally"[All Fields] OR "cerebrum"[MeSH Terms] OR "cerebrum"[All Fields] OR "cerebral"[All Fields] OR "brain"[MeSH Terms] OR "brain"[All Fields]) OR ("stroke"[MeSH Terms] OR "stroke"[All Fields] OR "strokes"[All Fields] OR "stroke s"[All Fields]) OR ("transient ischaemic attack"[All Fields] OR "ischemic attack, transient"[MeSH Terms] OR ("ischemic"[All Fields] AND "attack"[All Fields] AND "transient"[All Fields]) OR "transient ischemic attack"[All Fields] OR ("transient"[All Fields] AND "ischemic"[All Fields] AND "attack"[All Fields])) OR ("pulmonary embolism"[MeSH Terms] OR ("pulmonary"[All Fields] AND "embolism"[All Fields]) OR "pulmonary embolism"[All Fields]) OR ("venous thrombosis"[MeSH Terms] OR ("venous"[All Fields] AND "thrombosis"[All Fields]) OR "venous thrombosis"[All Fields] OR ("deep"[All Fields] AND "vein"[All Fields] AND "thrombosis"[All Fields]) OR "deep vein thrombosis"[All Fields]))

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('gestational diabetes'/exp OR 'gestational diabetes' OR (gestational AND ('diabetes'/exp OR diabetes)) OR 'gestational diabetes mellitus'/exp OR 'gestational diabetes mellitus' OR (gestational AND ('diabetes'/exp OR diabetes) AND mellitus) OR 'pregnancy diabetes'/exp OR 'pregnancy diabetes' OR (('pregnancy'/exp OR pregnancy) AND ('diabetes'/exp OR diabetes)) OR 'pregnancy diabetes mellitus'/exp OR 'pregnancy diabetes mellitus' OR (('pregnancy'/exp OR pregnancy) AND ('diabetes'/exp OR diabetes) AND mellitus)) AND ('cardiovascular diseases'/exp OR 'cardiovascular diseases' OR (('cardiovascular'/exp OR cardiovascular) AND ('diseases'/exp OR diseases)) OR 'cerebrovascular disorders'/exp OR 'cerebrovascular disorders' OR (cerebrovascular AND ('disorders'/exp OR disorders)) OR 'venous thromboembolism'/exp OR 'venous thromboembolism' OR (venous AND ('thromboembolism'/exp OR thromboembolism)) OR 'cardiovascular'/exp OR cardiovascular OR cerebrovascular OR 'coronary artery'/exp OR 'coronary artery' OR (coronary AND ('artery'/exp OR artery) AND disease*) OR 'coronary heart' OR (coronary AND ('heart'/exp OR heart) AND disease*) OR cardiac OR 'ischemic heart'/exp OR 'ischemic heart' OR (ischemic AND ('heart'/exp OR heart) AND disease*) OR 'cardio cerebrovascular' OR 'myocardial infarction'/exp OR 'myocardial infarction' OR (myocardial AND ('infarction'/exp OR infarction)) OR 'heart failure'/exp OR 'heart failure' OR (('heart'/exp OR heart) AND ('failure'/exp OR failure)) OR 'angina pectoris'/exp OR 'angina pectoris' OR (('angina'/exp OR angina) AND pectoris) OR cerebral OR 'stroke'/exp OR stroke OR 'transient ischemic attack'/exp OR 'transient ischemic attack' OR (transient AND ischemic AND attack) OR 'pulmonary embolism'/exp OR 'pulmonary embolism' OR (pulmonary AND ('embolism'/exp OR embolism)) OR 'deep vein thrombosis'/exp OR 'deep vein thrombosis' OR (deep AND ('vein'/exp OR vein) AND ('thrombosis'/exp OR thrombosis)))

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(gestational diabetes OR gestational diabetes mellitus OR pregnancy diabetes OR pregnancy diabetes mellitus) AND (cardiovascular diseases OR cerebrovascular disorders OR venous thromboembolism OR cardiovascular OR cerebrovascular OR coronary artery disease* OR coronary heart disease* OR cardiac OR ischemic heart disease* OR cardiovascular and cerebrovascular OR myocardial infarction OR heart failure OR angina pectoris OR cerebral OR stroke OR transient ischemic attack OR pulmonary embolism OR deep vein thrombosis)

Appendix S4. Description and decision criteria for each domain in ROBINS-I

Domain	Explanation	Judgments
Bias due to confounding	• Is there potential for confounding of the effect of exposure in this study? • Did the authors use a multivariable-adjusted analysis method that controlled at least for age, sex, smoking, physical activity, and body mass index? • Did the authors avoid adjusting for post-exposure variables? \	Low risk of bias: No bias expected due to confounding, including time-varying confounding. Moderate risk of bias: Confounding is expected: including at least 5 factors of the following factors: age, smoking, body mass index (alternatively weight), comorbidities, maternal parity, race/ethnicity, others (socio-economic status, maternal education) and have been appropriately controlled for in a multivariable-adjusted analysis. Serious risk of bias: 3-4 above-mentioned factors were measured or appropriately controlled for. Critical risk of bias: less than 3 above-mentioned factors were measured or appropriately controlled for No information: No information on which confounders have been controlled for.
Bias due to selection of participants	• Was the selection of participants into the study based on participant's characteristics observed after the start of the study/exposure assessment? • Do the start of follow-up and the start of exposure coincide for most participants? Were methods used that are likely to correct for the presence of selection biases?	Low risk of bias: All participants who would have been eligible for the target study were included in the study (e.g. population-based study without special exclusion criteria). Moderate risk of bias: Selection into the study may have been related to exposure and outcome, e.g., inclusion of GDM women with a family history of type 2 diabetes only; or exclusion of women with maternal risk factors (e.g. hypertension, heart disease, renal disease); *and* the authors used appropriate methods to correct for the selection bias; Serious risk of bias: Selection into the study was related to exposure and outcome (e.g., only participants at higher risk of CCVD were included in the analysis); *and* this could not be corrected for in the analyses; *or* the start of follow-up and start of exposure do not coincide *and* the rate ratio is not constant over time. Critical risk of bias: over half of included GDM patients having CCVD at baseline; No information: No information is reported about selection of participants into the study.
Bias due to exposure assessment	• Were exposure groups clearly defined and adequately assessed? • Was the information used to define the exposure groups based on reasonable a priori data?	Low risk of bias: GDM was well defined, according to OGTT or relevant guideline *and* no measurement error is expected in its assessment. Moderate risk of bias: Exposure status is defined by diagnostic code (e.g. ICD) or by self-reported but measured by validated tool with satisfactory accuracy (⩾90%) (e.g. validated questionnaire). Serious risk of bias: Exposure status is defined according to self-reported with unsatisfied accuracy (50-90%). Critical risk of bias: Exposure status is defined according to self-reported with poor accuracy (less than 50%). No information: No definition of exposure or no explanation of the source of information about

		exposure status is reported.
Bias due to misclassification during follow-up	• Were there deviations from the exposure beyond what would be expected in usual practice? • Were these deviations unbalanced between groups and likely to have affected the outcome?	Low risk of bias: Repeated measurements of the exposure status during follow-up are available. No or only slight changes in fat intake were observed and the changes were considered in the analysis. Moderate risk of bias: Repeated measurements of the exposure are not available, but high changes are not expected during follow-up (compare notes) or repeated measurements of the exposure status during follow-up are available and some changes in lifestyle factors were observed. The analysis was appropriate to estimate the effect of changes in lifestyle factors, allowing for deviations that were likely to impact the outcome; Serious or critical risk of bias: Exposure status is measured during follow-up and high changes in lifestyle factors have been observed, and the analysis was not appropriate to estimate the effect of changes in lifestyle factors, allowing for deviations that were likely to impact the outcome. No information: No information on deviations from the exposure is reported.
Bias due to missing data	• Were there missing outcome data? • Were participants excluded due to missing data on exposure status? • Were participants excluded due to missing data on other variables needed for analysis?	Low risk of bias: Little loss-to-follow-up (<20%) and data on exposure and other variables were reasonably complete (<10% missing data) and was unlikely to introduce bias; *or* the analysis addressed missing data and is likely to have removed any risk of bias. Moderate risk of bias: There is a proportion of missing data in the original cohort or a high proportion of loss-to-follow-up; *and* the analysis is unlikely to have removed the risk of bias arising from the missing data (e.g., using logistic regression). Serious or critical risk of bias: High proportions (>50%) of missing data; *and* the analysis is unlikely to have removed the risk of bias arising from the missing data; *or* missing data were addressed inappropriately in the analysis; *or* the nature of the missing data means that the risk of bias cannot be removed through appropriate analysis. No information: No information is reported about missing data or the potential for data to be missing.
Bias due to measurement of the outcome	• Could the outcome measure have been influenced by knowledge of the exposure status? • Were the methods of outcome assessment comparable across exposure groups? • Was any systematic error in the measurement of the outcome related to exposure status?	Low risk of bias: The methods of outcome assessment were comparable across exposure groups; *and* the outcome measure was unlikely to be influenced by knowledge of the exposure status of study participants; *and* any error in measuring the outcome is unrelated to exposure status (i.e., objective measures such as confirmed medical records, record linkage). Moderate risk of bias: The methods of outcome assessment were comparable across exposure groups; *and* any error in measuring the outcome may be minimally related to exposure status *or* if the outcome measure was not reliable measured (i.e. confirmed records are not available for the whole study population). Serious or critical risk of bias: The methods of outcome assessment were not comparable across exposure groups; *or* the outcome measure was subjective (i.e., self-report of type 2 diabetes by study participants); *and* error in measuring the outcome was related to exposure status.

		No information: No information is reported about the methods of outcome assessment.
Bias due to selective reporting of the results	• Is the reported effect estimate likely to be selected from multiple analyses of the exposure-outcome relationship? • Is the reported effect estimate likely to be selected from different subgroups?	Low risk of bias: There is a clear description of all analyses and the analyses are consistent and all reported results correspond to all intended outcomes, analyses and sub-cohorts. Moderate risk of bias: The analyses are clearly defined; *and* there is an indication of selection of the reported analysis from among multiple analyses; *and* there is an indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results (e.g., estimates not shown for all analyses). Serious or critical risk of bias: There is a high risk of selective reporting from among multiple analyses; *or* the cohort or subgroup is selected from a larger study for analysis and appears to be reported based on the results. No information: There is too little information to make a judgment.
Overall judgment	Low risk of bias	The study is judged to be at a low risk of bias for all domains.
	Moderate risk of bias	The study is judged to be at low or moderate risk of bias for all domains.
	Serious risk of bias	The study is judged to be at serious risk of bias in at least one domain, but not at critical risk in any domain.

Appendix S5. List of excluded studies

Ineligible population (n= 21)

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11. Yefet E, Schwartz N, Sliman B, Ishay A, Nachum Z. Good glycemic control of gestational diabetes mellitus is associated with the attenuation of future maternal cardiovascular risk: a retrospective cohort study. Cardiovasc Diabetol. 2019 Jun 5;18(1):75. doi: 10.1186/s12933-019-0881-6.
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No outcome of interest (n= 16)

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Duplicate population (n= 15)

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No eligible control (n= 10)

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Insufficient data (n= 8)

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