Supplementary Material

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Text S1. **The Danish national health registers.**

The Danish National Health Service provides tax-funded universal access to healthcare, guaranteeing free access to general practitioners and hospitals, and part reimbursement for prescribed drug treatment. All Danish residents are assigned a unique central personal register number (CPR), and individual data from national registries can be linked using the CPR (1,2).

The Danish Civil Registration System(2) contains data on vital statistics, emigration, sex, date and place of birth, place of residence, marriage, and linage to relatives.

The Danish Medical Birth Registry(3) was established in 1968. The Danish Medical Birth Registry includes various characteristics of the new-borns, such as the date of birth, sex, gestational age, birth weight, singleton or not, maternal smoking during pregnancy since 1991.

The Danish National Patient Register (4) contains hospital discharge diagnoses from 1977 and outpatient and emergency diagnoses are included since 1995. The diagnoses are classified according to the *International Classification of Disease* codes (ICD-8 codes during 1977-1993 and ICD-10 codes thereafter).

The Danish Register of Causes of Death(5) has been computerized since 1970 and contains information on the date and causes of death of all citizens in Denmark(ICD-8 codes during 1970-1993 and ICD-10 codes thereafter).

The Danish Integrated Database for Longitudinal Labour Market Research(6) contains information on education and personal labour market affiliation.

Text S2. **Detailed description of methods used to identify GDM and type 2 diabetes.**

Information on diagnoses of gestational diabetes (GDM) and type 2 diabetes was obtained from the Danish National Diabetes Register (1995-2016) (7), the Danish National Patient Registry (1977-2016) (8), and the Danish National Prescription Registry (1994-2016) (9) using *International Classification of Disease* codes (ICD-8 codes during 1970-1993 and ICD-10 codes since 1994) and *Anatomical Therapeutic Chemical* (ATC) classification codes.

The Danish National Diabetes Register contains information on diabetes since 1995, using the following criteria: #1. ICD-10 diagnosis code (not gestational diabetes), #2. ⩾2 redeemed prescriptions for insulin or oral antidiabetic drugs from the Register of Medicinal Product Statistics, #3. receipt of chiropody for diabetic patients, #4. five glucose measurements within one year or two blood glucose measurements per year during five consecutive years, as recorded in The National Health Insurance Service Registry. We did not use blood glucose measurements alone due to their poor validity. In addition to using criteria #1 (ICD-10 diagnosis code), we also used criteria # 2 (medication), and criteria #3 (chiropody) to identify diabetes. In addition, we classified women who redeemed two prescriptions for insulin within six months as having type 1 diabetes, and those with 2 redeemed prescriptions for oral antidiabetic medications within six months or chiropody for diabetic patients as having type 2 diabetes.

	ICD-8 codes	**ICD-10 codes**	**ATC Codes**
Gestational diabetes	634.74, Y6449	O24.4, O24.9	
Type 2 diabetes	250	E11, O24.1	A10B*

* Two redeemed prescriptions within six months

Because diabetes was recorded using a single code (250) from 1977 to 1986, two methods were used to distinguish between type 1 diabetes and type 2 diabetes during 1977-1986: 1) a specific code for type 1 diabetes or type 2 diabetes recorded later in time, 2) type 1 diabetes if age at diabetes onset < 30 years, otherwise type 2 diabetes (10-12).

Overall, ascertainment and verification of diabetes in Denmark are considered highly reliable and the estimated completeness (sensitivity) of diagnosed diabetes in the Danish National Diabetes Register is

93%-95% (1,13). Regarding the validation of diabetes in the Danish National Patient Registry, the number of reviewed records is small in most studies (see Table below). Two validation studies with over 1400 records suggest that type 1 diabetes diagnoses are of high quality (both PPV and sensitivity >91%).

Table-Validation studies of diabetes in the Danish National Patient Registry

Study	**Condition**	**Study period**	**ICD codes**	**Reviewed records**	**PPV; NPV; sensitivity (Se); specificity (Sp)**	**Reference standard**
Thygesen 2011[14]	Diabetes	1998–2007	E10.0, E10.1, E10.9, E11.0, E11.1, E11.9	50	PPV =96.0 (86.5–98.9)	Discharge summaries
Kristensen 2007[15]		1999–2003	E10–13, H36.0, O24, except O24.4	NA	PPV =64; Se =97	General practitioner verification
Thomsen 2004[16]		1992–2001	249–250, E10–E11, also prescription for insulin or an oral antidiabetic drug (A10A, A10B)	65	PPV=96.9 (89.5–99.2)	Medical records, Clinical Laboratory System Database
Atladottir 2009[17]	Diabetes in women	1977–2006	249; E10	40	PPV =95.0 (83.5–98.6)	Medical records
Svensson 2007[18]	Diabetes in children(<15 y)	1996–2002	E10–14	1479	PPV =95.9 (94.8–96.8); NPV =100(100–100); Se =97.9 (97.1–98.6); Sp =100 (100–100)	Medical records; Danish Registry for Child and Adolescent Diabetes
Svensson 2007[18]	Type 1 diabetes	1996–2002	E10–14	1479	PPV =94.3 (93.0–95.4); NPV =100(100–100); Se =98.0 (97.1–98.6); Sp =100 (100–100)	Medical records; Danish Registry for Child and Adolescent Diabetes
Nielsen 1996[19]	Type 1 diabetes	1987–1993	249	1722	PPV =96.3 (95.4–97.1); Se =91.0(89.6–92.2)	Medical records; Prescription Registry
Langhoff 2003[20]	Gestational diabetes	2001	O24	21	PPV =100 (84.5–100); NPV =99.7(99.2–99.9); Se =87.5(69.0–95.7); Sp =100 (99.7–100)	Medical records

Text S3. **Sensitivity analysis for violations of uncontrolled confounding assumptions in causal mediation analysis.**

The mediation analysis was conducted under strong assumptions of no uncontrolled confounding of the GDM–CVD (i.e. exposure–outcome) relationship and of the type 2 diabetes–CVD (i.e. mediator–outcome) relation. Under these assumptions as well as the assumptions of positivity, consistency, no other sources bias and no model misspecification, sensitivity analysis was performed to focus on the evaluation of the possible violations of the no uncontrolled mediator-outcome confounding assumptions only (13,14).

Specifically, we considered a binary unmeasured confounding variable *U* that is a common cause of type 2 diabetes and CVD (e. g., alcohol use, diet, or psychological stress). We assumed that the prevalence of *U* was 20% and 30% for women with and without GDM conditional on type 2 diabetes, respectively (Table S4). We also considered a simplified assumption that the prevalence of *U* was the same among women with and without GDM. For the magnitude of the association between U and CVD conditional on GDM and type 2 diabetes, we assessed the influence of unmeasured mediator-outcome confounding in two settings: (i) moderate confounding, where we assumed if *U* elevated CVD risk by a factor of 1.4; and (ii) strong confounding where we assumed if *U* elevated CVD risk by a factor of 2.

Under the simplified assumption that the prevalence of U was the same in women with and without GDM, the estimate of controlled direct effect (CDE) was unchanged. If the prevalence of U was assumed to be higher in women with GDM compared with those without GDM, the bias-adjusted CDE would be lower than the original CDE and the proportion eliminated would be higher. However, if the prevalence of U was assumed to be lower in women with GDM compared with those without GDM, the bias-adjusted CDE would be higher than the original CDE (Table S4).

References

1. Schmidt M, Schmidt SAJ, Adelborg K, Sundboll J, Laugesen K, Ehrenstein V, Sorensen HT. The Danish health care system and epidemiological research: from health care contacts to database records. Clin Epidemiol 2019;11:563-591
2. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. Eur J Epidemiol 2014;29:541-549
3. Knudsen LB, Olsen J. The Danish Medical Birth Registry. Dan Med Bull 1998;45:320-323
4. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. Scand J Public Health 2011;39:30-33
5. Helweg-Larsen K. The Danish Register of Causes of Death. Scand J Public Health 2011;39:26-29
6. Petersson F, Baadsgaard M, Thygesen LC. Danish registers on personal labour market affiliation. Scand J Public Health 2011;39:95-98
7. Carstensen B, Kristensen JK, Ottosen P, Borch-Johnsen K, Steering Group of the National Diabetes R. The Danish National Diabetes Register: trends in incidence, prevalence and mortality. Diabetologia 2008;51:2187-2196
8. Andersen TF, Madsen M, Jorgensen J, Mellemkjoer L, Olsen JH. The Danish National Hospital Register. A valuable source of data for modern health sciences. Dan Med Bull 1999;46:263-268
9. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. Scand J Public Health 2011;39:38-41
10. Feltbower RG, McKinney PA, Campbell FM, Stephenson CR, Bodansky HJ. Type 2 and other forms of diabetes in 0-30 year olds: a hospital based study in Leeds, UK. Arch Dis Child 2003;88:676-679
11. Oyen N, Diaz LJ, Leirgul E, Boyd HA, Priest J, Mathiesen ER, Quertermous T, Wohlfahrt J, Melbye M. Prepregnancy Diabetes and Offspring Risk of Congenital Heart Disease: A Nationwide Cohort Study. Circulation 2016;133:2243-2253
12. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sorensen HT, Qin G, Li J. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. BMJ 2019;367:l6398
13. Green A, Sortso C, Jensen PB, Emneus M. Validation of the danish national diabetes register. Clin Epidemiol 2015;7:5-15
14. Thygesen SK, Christiansen CF, Christensen S, Lash TL, Sørensen HT. The predictive value of ICD-10 diagnostic coding used to assess Charlson comorbidity index conditions in the population-based Danish National Registry of Patients. BMC Med Res Methodol 2011;11:1-6
15. Kristensen JK, Drivsholm TB, Carstensen B, Steding-Jensen M, Green A. Validation of methods to identify known diabetes on the basis of health registers. Ugeskr Laeger 2007;169:1687-1692
16. Thomsen RW, Hundborg HH, Lervang H-H, Johnsen SP, Sørensen HT, Schønheyder HC. Diabetes and outcome of community-acquired pneumococcal bacteremia: a 10-year population-based cohort study. Diabetes Care 2004;27:70-76
17. Atladóttir HÓ, Pedersen MG, Thorsen P, Mortensen PB, Deleuran B, Eaton WW, Parner ET. Association of family history of autoimmune diseases and autism spectrum disorders. Pediatrics 2009;124:687-694
18. Svensson J, Marinelli K, Eising S. Landspatientregisteret over for et specialespecifikt register for diabetes i barnealderen? Ugeskr Laeger 2007;169:122
19. Nielsen GL, Sørensen HT, Pedersen AB, Sabroe S. Analyses of data quality in registries concerning diabetes mellitus—a comparison between a population based hospital discharge and an insulin prescription registry. J Med Syst 1996;20:1-10
20. Langhoff-Roos J, Rasmussen S. Danish Health and Medicines Authority. [Validering af Landspatientregistret (LPR) mhp. obstetrisk forskning og kvalitetssikring] Copenhagen. 2003;

21. VanderWeele T. *Explanation in causal inference: methods for mediation and interaction*. Oxford University Press, 2015
22. VanderWeele TJ. Bias formulas for sensitivity analysis for direct and indirect effects. Epidemiology 2010;21:540-551

Table S1. Definition of cardiovascular disease*

	ICD-8	ICD-10	Procedure/Surgery Codes
Overall cardiovascular disease (CVD)	390-444.1, 444.3-458, 782.4	I00-I99	30350, 30354, 30240, KFNG, KFNF 30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200, KFNA-KFNE, KFNH20
Ischemic heart disease	410-414	I20-I25	
Myocardial infarction	410	I21	
Cerebrovascular disease	430-438	I60-I69	
Stroke	430-436	I61-I64	
Ischemic stroke	433-434	I63-I64	
Heart failure	427.0,427.1,782.4	I110, I130, I132, I50	
Atrial fibrillation	427.93, 427.94	I48	
Hypertensive disease	400-404	I10-I15	
Deep vein thrombosis	451.00	I80.1-I80.3	
Pulmonary embolism	450.99	I26	
Peripheral artery disease	44389-44399	I739	
Coronary artery bypass graft (CABG)			30009, 30019, 30029, 30039, 30049, 30059, 30069, 30079, 30089, 30099, 30109, 30119, 30120, 30129, 30139, 30149, 30159, 30169, 30179, 30189, 30199, 30200, KFNA-KFNE, KFNH20
Percutaneous coronary intervention (PCI)			30350, 30354, 30240, KFNG, KFNF
Other CVDs	Remainder of codes (390-444.1, 444.3-458, 782.4)	Remainder of codes (I00-I99)	Without the surgery codes above for PCI and CABG

* The information on cardiovascular disease is from the Danish National Patient Registry or the Danish Register of Cause of Death.

Table S2. Baseline characteristics by history of GDM among 1 002 486 Danish women during 1978-2016

	No. (%)	
Variable	**History of GDM* (n=21,353)**	**No history of GDM* (n=981,133)**
Parity		
1	5,075 (24)	273,897 (28)
2	9,585 (45)	485,976 (50)
≥3	6,693 (31)	221,260 (23)
Age at first delivery, years		
<20	803 (4)	40,173 (4)
20-24	4,896 (23)	277,333 (28)
25-29	7,985 (37)	402,170 (41)
30-34	5,247 (25)	197,548 (20)
35+	2,422 (11)	63,909 (7)
Smoking during pregnancy†		
No	15,256 (79)	512,942 (77)
Yes	3,278 (17)	123,130 (18)
Unknown	876 (5)	31,240 (5)
Education, years		
0-9	5,347 (25)	241,854 (25)
10-14	9,401 (44)	438,652 (45)
15+	5,429 (25)	268,854 (27)
Unknown	1,176 (6)	31,773 (3)
Cohabitation		
No	11,534 (54)	578,557 (59)
Yes	9,786 (46)	399,343 (41)
Unknown	33 (0)	3,233 (0)
Residence		
Copenhagen	2,562 (12)	143,631 (15)
Big cities≥100,000 inhabitants	3,115 (15)	137,027 (14)
Others	15,676 (73)	700,475 (71)
Country of origin		
Non-Danish origin	5,431 (25)	122,941 (13)
Danish origin	15,911 (75)	854,315 (87)
Unknown	11 (0)	3,877 (0)
Pre-pregnancy Obesity		
No	17,435 (82)	943,866 (96)
Yes	3,918 (18)	37,267 (4)
Subsequent type 2 diabetes		
No	18,547 (87)	963,373 (98)
Yes	2,806 (13)	17,760 (2)

Maternal history of CVD		
No	8,389 (39)	386,326 (39)
Yes	8,790 (41)	445,890 (45)
Unknown	4,174 (20)	148,917 (15)
Paternal history of CVD		
No	7,132 (33)	327,319 (33)
Yes	9,794 (46)	488,434 (50)
Unknown	4,427 (21)	165,380 (17)

* Expressed as frequency (percentage). Percentages have been rounded and may not total to 100%.

† Smoking during pregnancy was available from 1991 to 2016.

Abbreviation: GDM=gestational diabetes mellitus, CVD=cardiovascular disease.

Table S3. Sensitivity analyses for the associations between history of GDM and overall CVD

	History of GDM	No. of CVD cases	Rate per 1000 person-years	HR (95%CI) Model 1	HR (95%CI) Model 2
Age as time scale	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.62(1.56-1.67)	1.38(1.33-1.43)
Women without preeclampsia/eclampsia	No GDM	167813	10.48	1.0 (ref)	1.0 (ref)
	GDM	2461	15.43	1.65(1.59-1.72)	1.36(1.30-1.41)
Women with at least 1 year of follow-up	No GDM	177680	10.52	1.0 (ref)	1.0 (ref)
	GDM	2892	16.20	1.71(1.65-1.77)	1.42(1.37-1.48)
Women with only 1 pregnancy	No GDM	39134	11.33	1.0 (ref)	1.0 (ref)
	GDM	438	16.09	2.03(1.85-2.23)	1.43(1.30-1.57)
Complete case analysis	No GDM	69266	10.11	1.0 (ref)	1.0 (ref)
	GDM	1671	14.99	1.48(1.41-1.55)	1.35(1.29-1.42)
Women without stillbirth	No GDM	181819	10.81	1.0 (ref)	1.0 (ref)
	GDM	2968	16.78	1.73(1.67-1.79)	1.42(1.37-1.47)
Stratified by year of delivery	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.41(1.36-1.47)
Multiple imputation	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.40(1.35-1.45)
Spline function for age and calendar year*	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.39(1.34-1.44)
Women with 1st pregnancy after 1980	No GDM	163395	10.71	1.0 (ref)	1.0 (ref)
	GDM	2962	16.74	1.69(1.63-1.75)	1.40(1.35-1.45)
Women with 1st pregnancy after 1985	No GDM	125342	10.49	1.0 (ref)	1.0 (ref)
	GDM	2767	16.33	1.59(1.53-1.65)	1.39(1.34-1.45)
Women with 1st pregnancy after 1991	No GDM	81007	10.09	1.0 (ref)	1.0 (ref)
	GDM	2141	15.07	1.48(1.42-1.55)	1.35(1.29-1.41)
Women with 1st pregnancy after 1994	No GDM	61363	9.84	1.0 (ref)	1.0 (ref)
	GDM	1781	14.28	1.43(1.36-1.50)	1.32(1.25-1.38)
Women with 1st pregnancy after 2000	No GDM	31735	9.33	1.0 (ref)	1.0 (ref)
	GDM	1125	12.96	1.36(1.29-1.45)	1.24(1.17-1.32)
Women with 1st pregnancy after 2005	No GDM	14281	8.53	1.0 (ref)	1.0 (ref)
	GDM	596	11.71	1.36(1.25-1.47)	1.20(1.11-1.31)
Additional adjustment for gestational age	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.39(1.34-1.44)
Additional adjustment for pre-pregnancy hypercholesterolemia	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.40(1.35-1.45)

Additional adjustment for pre-pregnancy Charlson Comorbidity Index score (0, 1, 2+)	No GDM	182805	10.82	1.0 (ref)	1.0 (ref)
	GDM	3015	16.84	1.73(1.67-1.80)	1.39(1.34-1.44)

* Spline function for age at first pregnancy and calendar year (restricted cubic spline with five knots at five evenly spaced)

Abbreviations: GDM=gestational diabetes mellitus; CVD=cardiovascular disease; HR=hazard ratio; CI=confidence interval; ref=reference.

Table S4. Sensitivity analyses of the influence of uncontrolled mediator-outcome confounding [*, †, ‡, §]

CVD	Original results				Moderate unmeasured confounding (HR_U=1.4)			Strong unmeasured confounding (HR_U=2)		
	HR_{TE}	HR_{CDE}	HR_{PE}	Proportion eliminated	HR_{CDE}	HR_{PE}	Proportion eliminated	HR_{CDE}	HR_{PE}	Proportion eliminated
Overall CVD	1.40	1.31	1.07	23%	1.35	1.03	11%	1.41	0.99	-
Type-specific CVDs										
Ischemic heart disease	2.02	1.77	1.14	25%	1.83	1.10	19%	1.92	1.06	11%
Myocardial infarction	2.35	1.83	1.28	38%	1.90	1.24	33%	1.98	1.18	27%
Cerebrovascular disease	1.47	1.46	1.01	2%	1.52	0.97	-	1.59	0.93	-
Stroke	1.65	1.59	1.04	10%	1.65	1.00	1%	1.72	0.96	-
Ischaemic stroke	1.73	1.58	1.09	20%	1.64	1.05	12%	1.72	1.01	2%
Heart failure	2.20	1.43	1.54	64%	1.48	1.48	60%	1.55	1.42	54%
Atrial fibrillation	1.40	1.24	1.13	39%	1.29	1.09	28%	1.35	1.04	14%
Hypertensive disease	2.63	2.08	1.26	34%	2.16	1.22	29%	2.25	1.17	23%
Deep vein thrombosis	1.46	1.47	0.99	-	1.52	0.96	-	1.59	0.92	-
Pulmonary embolism	1.33	1.37	0.97	-	1.42	0.93	-	1.49	0.89	-
Peripheral artery disease	2.19	1.28	1.71	76%	1.33	1.65	72%	1.39	1.58	-
CABG or PCI	2.89	1.76	1.65	60%	1.82	1.59	57%	1.90	1.52	52%
Other CVDs	1.06	1.07	0.98	-	1.11	0.95	-	1.16	0.91	-

[*] Proportion eliminated: = $(HR_{TE} – HR_{CDE})/(HR_{TE}-1)$, only present if the direction of CDE and PE was the same.

[†] Original results: the primary result of this study (Table 2).

[†] HR_U: denotes the effect if unmeasured confounding U increased the likelihood of the CVD risk by a factor of 1.4 or 2.

[§] The prevalence of *U* was 20% and 30% for women with and without GDM conditional on type 2 diabetes, respectively.

Abbreviations: CVD=cardiovascular disease; CABG=coronary artery bypass graft; PCI=percutaneous coronary intervention; HR=hazard ratio; TE=total effect; CDE= controlled direct effect; PE=portion eliminated.

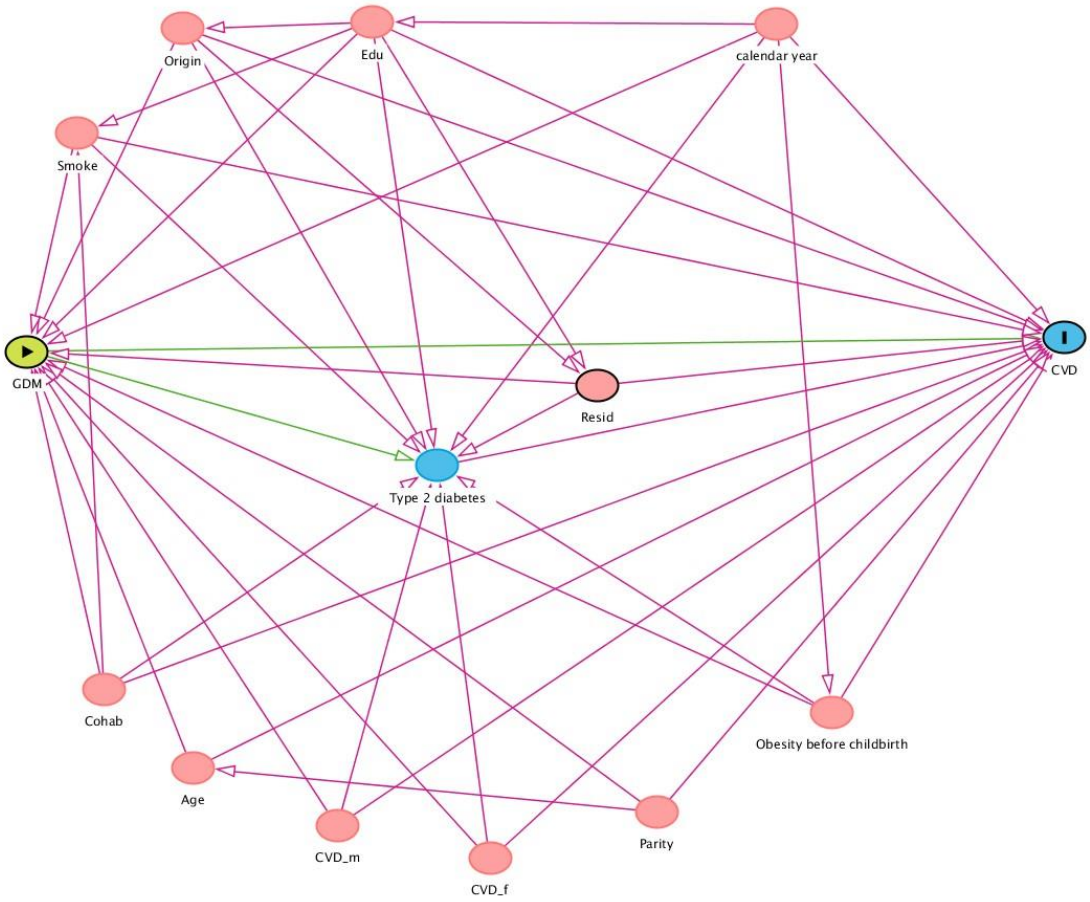


Figure S1. Causal diagram used to select covariates for confounding control *

* GDM: gestational diabetes mellitus, age: age at first delivery, cohab: cohabitation, edu: education, origin: country of origin, resid: residence, smoke: smoking during pregnancy, CVD_m and CVD_f: maternal and paternal CVD history.

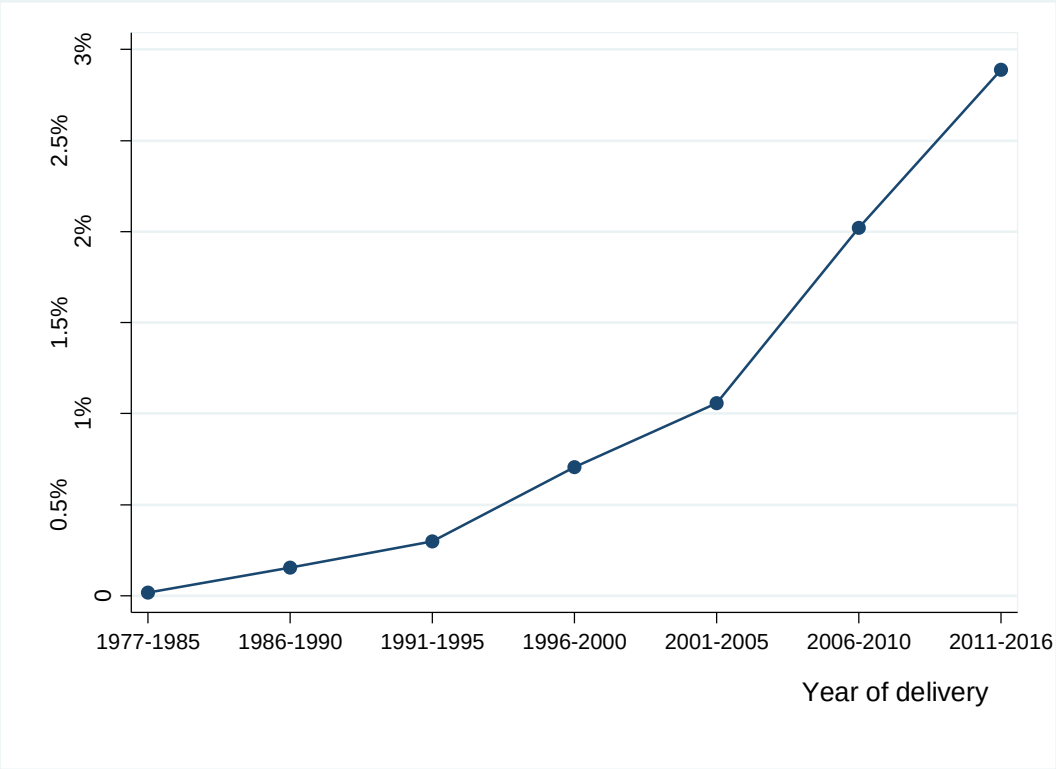
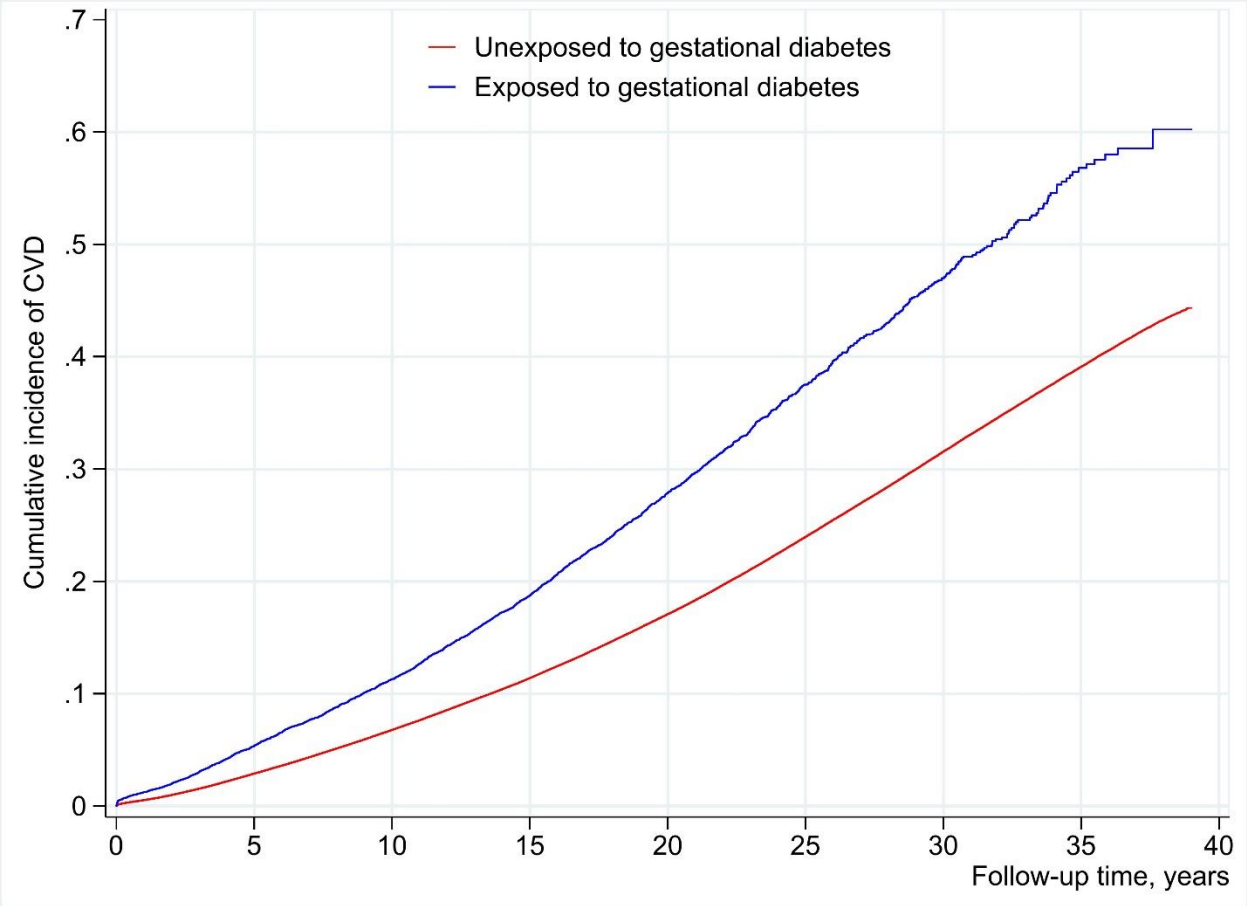


Figure S2. The proportion of pregnant women with gestational diabetes, by time period of delivery



Number at risk									
Unexposed	992 606	829 461	678 161	534 446	394 189	259 466	144 753	59 515	0
Exposed	9880	10 778	8746	6045	3509	1580	540	126	0

Figure S3. Cumulative incidence of CVD among women with and without a history of GDM

Abbreviation: CVD=cardiovascular disease; GDM=gestational diabetes mellitus.