Gestational Diabetes Mellitus and the Risks of Overall and Type-Specific Cardiovascular Diseases: A Population- and Sibling-Matched Cohort Study

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OBJECTIVE

To evaluate associations between gestational diabetes mellitus (GDM) and various incident cardiovascular disease (CVD) end points, considering the effects of the mediating role of type 2 diabetes and shared environmental/familial factors.

RESEARCH DESIGN AND METHODS

This population-based cohort study included 10,02,486 parous women in Denmark during 1978–2016. We used Cox regression to *1*) examine the associations of GDM with overall and type-specific CVDs using full-cohort and sibling-matched analysis, *2*) quantify the impact of type 2 diabetes after GDM using mediation analysis, and *3*) assess whether these associations were modified by prepregnancy obesity or maternal history of CVD.

RESULTS

Women with a history of GDM had a 40% increased overall CVD risk (hazard ratio [HR] 1.40, 95% CI 1.35–1.45). Sibling-matched analyses yielded similar results (HR 1.44, 95% CI 1.28–1.62). The proportion of association between GDM and overall CVD explained by subsequent type 2 diabetes was 23.3% (15.4–32.8%). We observed increased risks of specific CVDs, including 65% increased stroke risk and more than twofold risks for myocardial infarction, heart failure, and peripheral artery disease. The elevated overall risks were more pronounced among women with GDM and prepregnancy obesity or maternal history of CVD.

CONCLUSIONS

A history of GDM was associated with increased risks of overall and specific CVDs. Increased risks were partly explained by subsequent type 2 diabetes, and the need to identify other pathways remains important. Continuous monitoring of women with a history of GDM, especially those with prepregnancy obesity or maternal history of CVD, may provide better opportunities to reduce their cardiovascular risk.

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that first occurs during pregnancy (1). In the short-term, GDM is associated with pregnancy complications, such as preeclampsia, preterm birth, stillbirth, macrosomia, and

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cesarean birth (2,3). While GDM usually resolves after giving birth, the influence of GDM extends beyond pregnancy (1). Studies have shown that women with a history of GDM have a higher risk of developing type 2 diabetes, metabolic syndrome, chronic kidney disease, and cardiovascular disease (CVD) later in life (2,4,5).

Although a link between GDM and subsequent CVD has been reported, most of the research has stemmed from cross-sectional, case-control, or retrospective cohort studies (4,6–12), except for one prospective cohort in which only self-reported GDM was used as the exposure (13). In addition, evidence on the association of GDM with specific CVDs is also lacking. Furthermore, few studies have taken into consideration the interaction of various environmental factors and genetic susceptibility, which potentially influence the association between GDM and CVD (5,13,14). Finally, GDM is strongly associated with the development of type 2 diabetes, and both GDM and subsequent type 2 diabetes also predispose affected women to CVD (15). However, studies assessing the impact of type 2 diabetes on the association between GDM and CVD have often produced inconsistent findings (5,7,13,16). No studies have quantified the mediating role of type 2 diabetes in this association.

In this nationwide Danish cohort study with a follow-up of up to 39 years, we investigated the associations of a history of GDM with overall and specific types of CVD by using both population analysis and sibling-matched analysis, aiming to take into consideration shared stable unmeasured environmental factors within families and genetic susceptibility (17). We further quantified the mediating role of type 2 diabetes in the associations using mediation analysis and assessed whether the relationships differed by the presence of prepregnancy obesity or maternal history of CVD (18,19).

RESEARCH DESIGN AND METHODS

Study Population

All Danish residents are assigned a unique central personal register number (CPR), and high-quality data at the individual level from national registries can be linked using the CPR (Supplementary Text 1) (20,21). Based on data from several national registers, we conducted a population-based cohort study that included all adult women who had their first pregnancy during 1978–2016 (n = 1,098,962). After excluding *1*) 10,005 who were $<$18 years of age at the date of first delivery (i.e., adolescent mothers), *2*) 12,952 with preexisting type 1 diabetes or type 2 diabetes, 29,009 with CVD, and 39,045 with cancer before the first pregnancy, and *3*) 5,465 with congenital heart disease before a diagnosis of CVD, our final cohort comprised 1,002,486 parous women. Follow-up started at the date of first giving birth and ended at the date of the first CVD event, death, emigration, or 31 December 2016, whichever came first. Women who emigrated or died of non-CVD causes during follow-up were censored at the time of emigration or death.

GDM

History of GDM was identified at the date of the first delivery and updated at every pregnancy. GDM exposure was a time-varying variable; thus, a woman with a pregnancy without GDM and a later pregnancy with GDM would be considered as both unexposed and then exposed over the course of follow-up. Information on the diagnosis of GDM was obtained from the Danish National Patient Registry (DNPR) using the *International Classification of Disease* (ICD) codes (Supplementary Text 1 and 2) (20). The DNPR contains hospital discharge diagnoses from 1977 and outpatient and emergency diagnoses since 1995.

CVD Incidence

The outcome of interest was CVD incidence, defined as the first occurrence of CVD in the DNPR or the Danish Register of Causes of Death (20). The outcome was identified using the ICD codes for CVD or surgery codes for coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI). With the large study sample and a long follow-up, we were able to investigate the following specific types of CVD: ischemic heart disease, myocardial infarction, cerebrovascular disease, stroke, heart failure, atrial fibrillation, hypertensive disease, deep vein thrombosis, pulmonary embolism, CABG or PCI, and other types of CVD (specific codes are provided in Supplementary Table 1).

Mediator

A potential mediator was type 2 diabetes diagnosed before the CVD diagnosis. Information on type 2 diabetes diagnosis was obtained from the Danish National Diabetes Register, the DNPR, and the Danish National Prescription Registry (Supplementary Text 1 and 2) (20).

Covariates

Potential confounders were selected based on our directed acyclic graph (Supplementary Fig. 1). This included parity (one, two, or three or more) and the following covariates at the time of first delivery: age ($<$20, 20–24, 25–29, 30–34, or $\geq$35 years), cohabitation (single, cohabitating), education (0–9, 10–14, or $\geq$15 years), country of origin (Danish, non-Danish origin), residence (Copenhagen, cities with $\geq$100,000 inhabitants, or other), smoking during pregnancy (yes, no), prepregnancy obesity (yes, no), maternal and paternal CVD history (yes, no), and time period of first delivery ($\leq$1980, 5-year intervals during 1981–2010, or 2011–2016). Missing covariate values were treated as a separate category. The covariates were defined on the date of the first delivery. If a woman reported a non-GDM pregnancy and a subsequent GDM pregnancy, information on the covariates was updated accordingly. We also used complete case analysis and multiple imputations, with 10 imputations to handle missing values.

Statistical Analyses

Cox regression with follow-up time as the time scale was used to compute hazard ratios (HRs) with 95% CIs to assess the association of history of GDM with overall and specific CVDs. The evaluation of a log-minus-log plot suggested that the proportional hazard assumption was not violated. Considering non-CVD deaths as competing events, we estimated the cumulative incidence function among women with and without a history of GDM averaged over the distribution of covariates using inverse probability of treatment weighting (22). We evaluated whether the presence of prepregnancy obesity or maternal history of CVD further increased CVD risk by

examining their multiplicative and additive interactions (23). The relative excess risk due to interaction (RERI) was used to examine additive interactions (23). Additive and multiplicative interactions can both reveal whether the presence of effect modifiers changes the association between the exposure and outcome, but they differ in public health and clinical implications. The additive interaction measures the absolute change in risk and has more public health significance, while the multiplicative interaction measures the relative change in risk and has more etiological significance, which might be instructive in revealing the underlying mechanisms of disease.

We performed mediation analysis to examine how type 2 diabetes might mediate the effect of history of GDM on CVD risk (24). Under a counterfactual framework, the total effect of history of GDM on CVD risk can be decomposed into a controlled direct effect (CDE) and portion eliminated (PE) by eliminating the impact by type 2 diabetes (24). The CDE captures the influence of history of GDM on CVD if the link between a history of GDM and type 2 diabetes was hypothetically prevented or removed. To estimate CDE, we controlled for type 2 diabetes, time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, country of origin, maternal CVD history, paternal CVD history, and considered the interaction of history of GDM and type 2 diabetes. PE was obtained by dividing the CDE by the total effect. The PE measures the proportion of the total effect that would be eliminated by removing the mediation and interaction effects involving subsequent type 2 diabetes. The bootstrapped CIs for mediation analysis were obtained using 100 replicates. Sensitivity analysis was performed to evaluate the impact of violations of the assumption of no uncontrolled confounding for mediation analysis (Supplementary Text 3).

To evaluate the influence of uncontrolled confounding due to shared familial characteristics, we used a sibling-matched design. This entailed analyzing both half-sibling pairs from the same mothers and full-sibling pairs from the same mothers and fathers (17,25). We used stratified Cox regression with a separate stratum for each half-sibling pair identified by the mother's unique identification number and for each full-sibling pair identified by both the mother's and the father's unique identification numbers in which only sibling pairs discordant for both GDM and CVD are informative and contribute to the effect estimate. Stratified Cox regression allowed each sibling pair to have its own baseline rate function, which reflected shared familial characteristics. Thus a sibling-matched design using stratified Cox regression inherently controlled for unmeasured familial factors shared by sibling pairs (25). Moreover, we restricted analyses to women without preeclampsia/eclampsia, with only one pregnancy, at least 1 year of follow-up, without a stillbirth pregnancy, or who gave birth after 1980, 1985, 1991 (the year that smoking data became available), or 1994 (the year that the ICD-10 was adopted), 2001, or 2005. As the DNPR was established in 1977, the analysis was also restricted to women whose first pregnancy was after 1980 to allow for a 3-year window to sufficiently evaluate the exclusion criteria of no previous diabetes, CVD, or cancer. Restricted cubic splines were used to fit the potential nonlinear relation between continuous covariates (age at first pregnancy, calendar year) and CVD risk. We also performed analyses stratified by the time period of first delivery and used age as the time scale. We performed analyses with additional adjustment for gestational age, or prepregnancy hypercholesterolemia, or the prepregnancy Comorbidity Index score. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and Stata 15 (StataCorp, College Station, TX) software.

RESULTS

Of 1,002,486 parous women, 21,353 (2.1%) had a history of GDM. The median age at the time of the first delivery was 27 years (interquartile range 24–30 years). The proportion of women with a history of GDM increased over time, reaching 3.1% during 2011–2016. (Supplementary Fig. 2). A total of 37,339 women (3.7%) were censored at the end of follow-up due to noncardiovascular death (n = 9,989) or emigration (n = 27,350). Compared with women without a history of GDM, women with a history of GDM were more likely to have a higher parity, be older at first delivery, have a lower education level, cohabitate, be of non-Danish origin, have a higher prevalence of prepregnancy obesity, and develop type 2 diabetes (Supplementary Table 2).

During up to 39 years of follow-up (median follow-up 16.2 years, interquartile range 7.7–25.4 years), 3,015 women with a history of GDM and 182,805 women without a history of GDM were diagnosed with CVD. Women with a history of GDM had a higher overall risk of CVD than women without a history of GDM (HR 1.40, 95% CI 1.35–1.45; standardized cumulative incidence among unexposed women at the follow-up of 35 years: 39.1%, 95% CI 38.9–39.3%; standardized cumulative incidence difference: 18.0%, 95% CI 15.2–20.9%) (Table 1 and Supplementary Fig. 3). The increased risks were also observed for specific types of CVD for women with a history of GDM, in particular, a 65% increased risk for stroke and more than twofold risks for myocardial infarction, heart failure, hypertensive disease, peripheral artery disease, and CABG or PCI (Table 1).

CVD was diagnosed in 830 women (0.1%) with a history of GDM and subsequent type 2 diabetes, 1,976 women (0.2%) with a history of GDM but without type 2 diabetes, 5,587 women (0.6%) without a history of GDM but with type 2 diabetes, and 177,218 women (17.7%) without a history of GDM or type 2 diabetes. We found that history of GDM was strongly associated with the development of type 2 diabetes (crude risk ratio 7.26, 95% CI 6.99–7.54), and type 2 diabetes was related to a higher risk of developing CVD (crude risk ratio 1.71, 95% CI 1.67–1.74). Mediation analyses showed that the estimated proportion of total effect between history of GDM and overall CVD eliminated by hypothetically preventing type 2 diabetes was 23.3% (95% CI 15.4–32.8; HR_{PE} 1.07, 95% CI 1.05–1.10). The mediating role of type 2 diabetes was also observed for most specific types of CVD, particularly myocardial infarction, heart failure, hypertensive disease, atrial fibrillation, peripheral artery disease, and having CABG or PCI (Table 2).

A higher incidence of CVD was found in women with both a history of GDM

Table 1—HR for the associations between history of GDM and overall CVD and specific CVD types among 1,002,486 Danish women, 1978–2016

	History of GDM	No. of CVD cases	Rate per 1,000 person-years	HR (95% CI) model 1	HR (95% CI) model 2
Overall CVDs	No GDM	182,05	10.82	1.0 (Reference)	1.0 (Reference)
	GDM	3,015	16.84	1.73 (1.67–1.80)	1.40 (1.35–1.45)
Type-specific CVDs					
Ischemic heart disease	No GDM	23,537	1.27	1.0 (Reference)	1.0 (Reference)
	GDM	508	2.51	2.61 (2.39–2.85)	2.02 (1.85–2.21)
Myocardial infarction	No GDM	5,431	0.29	1.0 (Reference)	1.0 (Reference)
	GDM	121	0.59	2.74 (2.29–3.29)	2.35 (1.95–2.82)
Cerebrovascular disease	No GDM	17,091	0.92	1.0 (Reference)	1.0 (Reference)
	GDM	256	1.26	1.65 (1.46–1.86)	1.47 (1.30–1.67)
Stroke	No GDM	11,958	0.64	1.0 (Reference)	1.0 (Reference)
	GDM	190	0.93	1.77 (1.53–2.04)	1.65 (1.43–1.91)
Ischemic stroke	No GDM	9,328	0.50	1.0 (Reference)	1.0 (Reference)
	GDM	162	0.79	2.00 (1.71–2.34)	1.73 (1.48–2.02)
Heart failure	No GDM	3,804	0.20	1.0 (Reference)	1.0 (Reference)
	GDM	84	0.41	2.80 (2.25–3.48)	2.20 (1.76–2.74)
Atrial fibrillation	No GDM	7,083	0.38	1.0 (Reference)	1.0 (Reference)
	GDM	95	0.46	1.68 (1.37–2.06)	1.40 (1.14–1.72)
Hypertensive disease	No GDM	51,344	2.81	1.0 (Reference)	1.0 (Reference)
	GDM	1,358	6.93	3.31 (3.14–3.50)	2.63 (2.49–2.78)
Deep vein thrombosis	No GDM	8,621	0.46	1.0 (Reference)	1.0 (Reference)
	GDM	166	0.81	1.92 (1.65–2.24)	1.46 (1.25–1.70)
Pulmonary embolism	No GDM	4,349	0.23	1.0 (Reference)	1.0 (Reference)
	GDM	76	0.37	1.81 (1.44–2.27)	1.33 (1.06–1.68)
Peripheral artery disease	No GDM	2,763	0.15	1.0 (Reference)	1.0 (Reference)
	GDM	51	0.25	2.52 (1.91–3.33)	2.19 (1.65–2.90)
CABG or PCI	No GDM	3,569	0.19	1.0 (Reference)	1.0 (Reference)
	GDM	88	0.43	3.33 (2.69–4.11)	2.89 (2.33–3.59)
Other CVDs	No GDM	117,375	6.73	1.0 (Reference)	1.0 (Reference)
	GDM	15,78	8.27	1.27 (1.21–1.33)	1.06 (1.00–1.11)

Model 1: Follow-up time as time scale. Model 2: Follow-up time as time scale, controlled for time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, country of origin, maternal CVD history, and paternal CVD history.

and obesity (HR 1.76, 95% CI 1.59–1.95) compared with women with a history of GDM alone (HR 1.43, 95% CI 1.38–1.49), and only a multiplicative interaction was detected (P = 0.001 for multiplicative interaction) (Table 3). Women with a history of GDM and maternal history of CVD also had a higher risk of CVD (HR 1.75, 95% CI 1.66–1.84) compared with women with a history of GDM alone (HR 1.31, 95% CI 1.23–1.40) (Table 3). Our data suggested both multiplicative interaction (P = 0.042 for multiplicative interaction) and additive interaction (RERI 0.21, 95% CI 0.09–0.34) for these two factors.

The associations for overall CVD using a sibling-matched design in both half-sibling (HR 1.42, 95% CI 1.27–1.58) and full-sibling cohorts (HR 1.44, 95% CI 1.28–1.62) were similar to that of the full unmatched population. Similar patterns were also observed for type-specific CVDs (Fig. 1).

Results from analyses restricted to women without preeclampsia/eclampsia or stillbirth, with only one lifetime pregnancy, with at least 1 year of follow-up, with a first pregnancy since a specific calendar time (1980, 1985, 1991, 1994, 2000, or 2005), and with complete data were similar to those obtained in the primary analyses. Analyses using multiple imputations, restricted cubic splines for continuous covariates, or with additional adjustment for gestational age, or prepregnancy hypercholesterolemia, or prepregnancy Charlson Comorbidity Index score also were similar to those obtained in the primary analyses. Finally, analyses using stratified Cox regression by time period of the first delivery yielded results similar to those obtained in the primary analyses (Supplementary Table 3). Sensitivity analyses to assess the potential impact of unmeasured confounding in the mediation analysis found that even if the unmeasured confounder was strong enough to increase CVD risk by twofold, we would still observe the mediating effect of type 2 diabetes for most type-specific CVDs (Supplementary Text 3 and Supplementary Table 4).

CONCLUSIONS

We found that women with a history of GDM had increased risks of overall CVDs and varied increased risks for most common specific types of CVD, in particular, myocardial infarction, heart failure, hypertensive disease, peripheral artery disease, and CABG or PCI, even after accounting for prepregnancy sociodemographic, lifestyle, familial factors, and conventional CVD risk factors. Approximately 23% of the increased risks could be explained by the subsequent type 2 diabetes. The strongest associations were observed among women who had prepregnancy obesity or maternal history of CVD.

Table 2—The mediating role of type 2 diabetes in the association between history of GDM, overall CVD, and specific CVD types

Outcome	HR_{TE}*	HR_{CDE}†	HR_{PE}†	Proportion eliminated (%)†
Overall CVD	1.40 (1.35–1.45)	1.31 (1.25–1.36)	1.07 (1.05–1.10)	23.3 (15.4–32.8)
Type-specific CVDs				
Ischemic heart disease	2.02 (1.85–2.21)	1.77 (1.57–1.99)	1.14 (1.07–1.24)	25.0 (13.7–37.1)
Myocardial infarction	2.35 (1.95–2.82)	1.83 (1.42–2.36)	1.28 (1.05–1.53)	38.3 (8.9–65.0)
Cerebrovascular disease	1.47 (1.30–1.67)	1.46 (1.26–1.70)	1.01 (0.94–1.10)	2.1 (0.0–30.7)
Stroke	1.65 (1.43–1.91)	1.59 (1.33–1.89)	1.04 (0.97–1.14)	10.1 (0.0–34.1)
Ischemic stroke	1.73 (1.48–2.02)	1.58 (1.30–1.93)	1.09 (0.98–1.24)	19.7 (0.0–51.6)
Heart failure	2.20 (1.76–2.74)	1.43 (1.02–2.00)	1.54 (1.26–2.02)	64.2 (38.9–100.0)
Atrial fibrillation	1.40 (1.14–1.72)	1.24 (0.96–1.61)	1.13 (0.96–1.34)	39.5 (0.0–100.0)
Hypertensive disease	2.63 (2.49–2.78)	2.08 (1.93–2.24)	1.26 (1.21–1.33)	33.8 (27.7–39.2)
Deep vein thrombosis	1.46 (1.25–1.70)	1.47 (1.23–1.75)	0.99 (0.92–1.08)	—
Pulmonary embolism	1.33 (1.06–1.68)	1.37 (1.06–1.78)	0.97 (0.88–1.10)	—
Peripheral artery disease	2.19 (1.65–2.90)	1.28 (0.81–2.02)	1.71 (1.16–2.96)	76.3 (23.4–100.0)
CABG or PCI	2.89 (2.33–3.59)	1.76 (1.24–2.48)	1.65 (1.32–2.09)	60.0 (38.3–88.7)
Other CVDs	1.06 (1.00–1.11)	1.07 (1.02–1.14)	0.98 (0.96–1.00)	—

Data are presented with the 95% CI. *Follow-up time as time scale, controlled for time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, country of origin, maternal CVD history, and paternal CVD history. †Follow-up time as time scale, controlled for type 2 diabetes, time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, country of origin, maternal CVD history, and paternal CVD history. $HR_{PE} = (HR_{TE}/HR_{CDE})$. Proportion eliminated = $(HR_{TE} - HR_{CDE})/(HR_{TE} - 1)$, only present if the direction of CDE and PE was the same. The bootstrapped CIs for HR_{PE} and proportion eliminated were obtained using 100 replicates.

For the first time, we were able to investigate the association between GDM and a number of specific CVD outcomes, taking advantage of large study sample and long-term follow-up. Our findings of potential long-term effects of severe GDM on the risk of CVDs later in life are in line with the findings from studies examining a history of GDM and cardiovascular outcomes (6,8,9,11,13,16,26–28). A U.K. study (6) reported 85% and 178% increased risks for hypertension and ischemic heart disease related to GDM, respectively, but only for a relatively short-term effect over a median follow-up of 2.9 years. Self-reported GDM was associated with a 59% increased risk of myocardial infarction in the Nurses' Health Study II (n = 89,479) over a median of 25.7 years of follow-up (13). While we observed a 65% higher risk of stroke associated with a history of GDM, the corresponding risk in the Nurses' Health Study II (13) was 22%, but their estimate might not be informative due to the small number of cases (n = 33). Conversely, other studies in the U.K. and the Netherlands reported no association between history of GDM and stroke (6,27). These differences may be due to misclassification bias from self-reported GDM, the small number of events, or too short a follow-up time to evaluate stroke incidence. On the other hand, the development of CVD is a long process also influenced by both various environmental exposures and genetic factors (14), which may play a role in the pathway from GDM to CVD and has not been adequately examined. In addition to the inclusion of a wide range of potential confounders in our full population analysis, we further used a sibling-matched analysis to take into consideration factors, such as stable family environmental factors and genetic susceptibility, for which we do not have the information. Therefore, our study provided further evidence on the positive association of a history of GDM with subsequent CVDs and varied increased risks for type-specific CVD, in particular, myocardial infarction, heart failure, hypertensive disease, and peripheral artery disease.

The mechanisms linking a history of GDM and CVD risk remain to be studied (4). The mediating pathway of subsequently developed type 2 diabetes in the association of GDM with CVD has been widely discussed (5). However, whether elevated CVD risk following GDM depends on the development of type 2 diabetes (5,8,10,11) is still unclear. A Canadian study of >1 million women reported an increased risk of CVD for women with a history of GDM regardless of the presence of subsequent type 2 diabetes (7). However, the Nurses' Health Study II suggested an elevated CVD risk only for women with both a history of GDM and progression to type 2 diabetes (13). Another Canadian cohort of 8,191 women with a history of GDM and 81,262 women without a history of GDM concluded that much of the increased risk of CVD among women with a history of GDM was attributed to the subsequent development of type 2 diabetes (16). The findings from our mediation analysis suggest that type 2 diabetes development plays a mediating role in the association between a history of GDM and CVD risk, but this elevated CVD risk is only partly (one-fifth) attributable to type 2 diabetes, indicating the need to explore other pathways linking GDM and CVD. Previous studies have suggested that weight change from prepregnancy to postpregnancy, dyslipidemia, and high blood pressure may be associated with later adverse cardiovascular health (29). However, information on weight change, lipid level, lipoprotein level, and blood pressure was not available in our study. Further investigation is warranted to explore the roles of these factors in the association between GDM and subsequent CVD.

The differences in the association of GDM with risk of subsequent type-

Table 3—Effect modification by prepregnancy obesity and maternal history of CVD on the association between history of GDM and subsequent CVD in Danish women

Effect modifier	Exposure	No. of CVD cases	Rate per 1,000 person-years	HR (95% CI) model 1	HR (95% CI) model 2
Prepregnancy obesity*	No history of GDM and no prepregnancy obesity	179,385	10.78	1.0 (Reference)	1.0 (Reference)
	History of GDM only	2,651	16.85	1.69 (1.63–1.76)	1.43 (1.38–1.49)
	Prepregnancy obesity only	3,420	13.17	1.81 (1.75–1.87)	1.49 (1.44–1.54)
	History of GDM and prepregnancy obesity	364	16.76	2.29 (2.07–2.54)	1.76 (1.59–1.95)
	Multiplicative interaction (GDM × obesity)			0.75 (0.67–0.84)	0.82 (0.74–0.93)
	P for multiplicative interaction			<0.001	0.001
	RERI			−0.21 (−0.46 to 0.04)	−0.16 (−0.36 to 0.03)
	P for additive interaction			0.099	0.104
Maternal history of CVD†	No history of GDM and no maternal CVD	53,741	9.25	1.0 (Reference)	1.0 (Reference)
	History of GDM only	864	13.46	1.59 (1.49–1.70)	1.31 (1.23–1.40)
	Maternal CVD history only	98,837	11.67	1.17 (1.16–1.18)	1.22 (1.21–1.23)
	History of GDM and maternal CVD	1,572	18.77	2.04 (1.94–2.14)	1.75 (1.66–1.84)
	Multiplicative interaction (GDM × CVD)			1.10 (1.01–1.19)	1.09 (1.00–1.19)
	P for multiplicative interaction			0.032	0.042
	RERI			0.28 (0.13–0.43)	0.21 (0.09–0.34)
	P for additive interaction			<0.001	0.001

Model 1: Follow-up time as time scale. *Model 2: Follow-up time as time scale, controlled for time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, country of origin, maternal CVD history, and paternal CVD history. †Model 2: Follow-up time as time scale, controlled for time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, country of origin, and paternal CVD history.

specific CVDs and corresponding mediating effects of type 2 diabetes may be due to complex pathophysiology and the impacts of different risk factors on the development of type-specific CVDs (30). Further research is needed to elucidate underlying mechanisms and to explore the effects of other risk factors for specific CVDs.

GDM may also increase CVD risk via changes in cardiac structure (7,13,31,32). The Coronary Artery Risk Development in Young Adults (CARDIA) study found that a history of GDM was associated with impaired left ventricular relaxation, lower left ventricular systolic function, and increased left ventricular mass (32). Of note, women with a history of GDM had a higher prevalence or level of CVD risk factors, such as metabolic syndrome, prepregnancy HbA_{1c}, and hypoadiponectinemia, compared with women without a history of GDM (7,13,33). Various studies have reported that some CVD risk factors may present in the early postpartum period or even prior to pregnancy (4,7,33,34). These data suggest that the diagnosis of GDM may be considered as a precursor that signifies a high risk of CVD later in life. Additionally, some unrecognized CVD risk factors before or during pregnancy may contribute to the observed association of history of GDM with CVD. However, our analysis, which also examined women without prepregnancy obesity and without preeclampsia, still found an increased CVD risk among women with a history of GDM compared with their peers. These findings suggest that the observed associations are less likely due to complete confounding by unrecognized CVD risk factors before or during pregnancy and that a history of GDM may predispose women to CVD later in life.

Noticeably, we observed a 76% higher risk of developing CVD among women with a history of GDM and prepregnancy obesity compared with women without a history of GDM and prepregnancy obesity. Previous evidence has reported that being moderately overweight during pregnancy can lead to a higher likelihood of developing GDM (18). Our previous study also found that the offspring of mothers with a history of CVD had a 75% higher risk of developing CVD themselves (35). Maternal history of CVD was associated with an increased risk of dyslipidemia, other CVD risk factors, myocardial infarction, stroke, and cardiovascular mortality in offspring (19,36,37), and thus, familial aggregation may suggest genetic influences on the development of CVD (19,37). This finding is consistent with prior observations that the degree of insulin resistance among women may be affected by their obesity and genetic inheritance (31). The added influence of obesity and maternal history of CVD suggests that more attention should be paid to these women who already have a

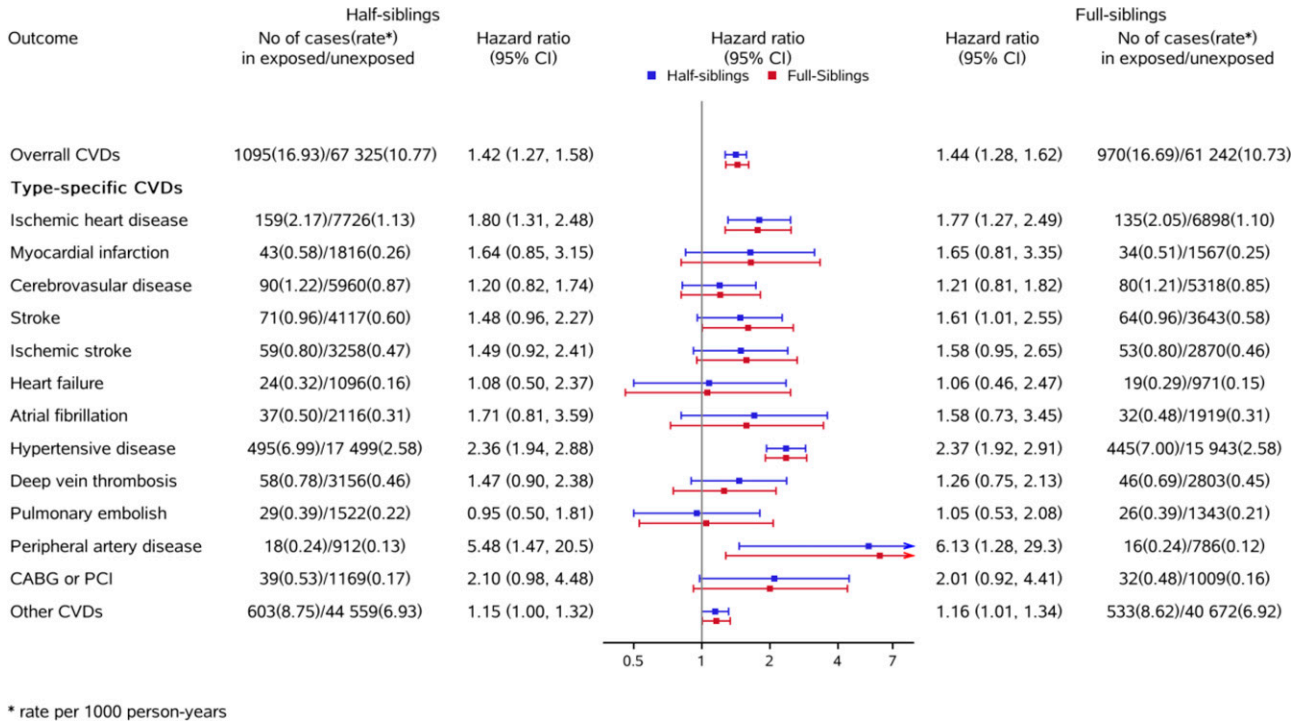

Figure 1—Sibship design for the association between history of gestational diabetes, overall CVD, and specific CVD types. Follow-up time as time scale controlled for time period of first delivery, parity, age at first delivery, education, smoking during pregnancy, cohabitation, residence, prepregnancy obesity, and country of origin.

high CVD risk when implementing intervention programs.

Strengths and Limitations of This Study

This study has several strengths. First, this prospective registry-based cohort study comprised almost all pregnant women in Denmark, thus minimizing the potential influence of selection bias, referral, and recall bias.

Second, a large sample size allowed for the examination of a wide range of specific CVDs and the use of a sibling design to reduce concerns of shared genetic or early life environmental confounding (17,25).

Third, substantial misclassification of CVD is unlikely because the validity of cardiovascular diagnoses and related procedures in the DNPR is high (38,39).

Finally, we used quantitative mediation analysis to explore the mechanism of the influence of a history of GDM on CVD risk. Elucidating the link between a history of GDM and CVD through type 2 diabetes might help inform the design and implementation of public health interventions aimed at reducing CVD risk.

Several limitations must also be noted. Although we adjusted for a wide range of potential confounders, we cannot entirely exclude uncontrolled confounding by unmeasured genetic or familial characteristics. Our sibship design from both full-sibling pairs and half-sibling pairs yielded results consistent with that of the unpaired study design of the whole cohort. These findings suggest that the observed associations are not entirely attributable to confounding by genetics and familial environment.

Although our study was able to adjust for several socioeconomic and lifestyle factors, such as education, smoking during pregnancy, and prepregnancy BMI, data on other factors (diet, sleep, alcohol consumption, etc.) were not available. The observed exposure-outcome associations could change if those factors were considered. Further research is warranted encompassing a broad range of socioeconomic and lifestyle factors.

Moreover, causal mediation analysis is subject to strict and untestable assumptions of no unmeasured confounding of exposure-mediator, exposure-outcome, and mediator-outcome links. As mentioned previously, not all potential confounders could be measured in our large-scale observational study. Sensitivity analyses exploring potential mediator-outcome confounding suggested that part of the estimated direct effects could be explained by high uncontrolled mediator-outcome confounding, using our assumed moderate to strong bias parameters and directionality of the mediator-confounder association. For instance, the mediation effect was reduced substantially for some specific CVD types when an unmeasured confounder was strong enough to increase CVD risk twofold (under the assumed scenario that we missed measuring and adjusting for such a strong confounder).

Also, the ascertainment of GDM solely based on hospital records is subject to potential misclassification bias, but we suspect that such misclassification in our prospective study design would be nondifferential.

Last, our findings suggest that the association is weaker in recent calendar periods than in the early beginning of our study period. This may be due to a mixture of increased use of

coding for GDM and type 2 diabetes in the ICD-10 system after 1994, a broadening of the GDM term after 1999, generally increased screening and thus detection of milder GDM and type 2 diabetes cases from the early 2000s, and a relatively young population with a lower number of CVD events in later periods. Further research is needed to explore the underlying mechanisms.

Conclusion and Implications

Our study showed that a history of GDM was associated with increased risks of CVD in general and several major types of CVD. The associations were stronger among those with prepregnancy obesity or maternal history of CVD. The increased risks of CVD due to GDM were only partially explained by subsequent type 2 diabetes. The history of GDM and subsequent type 2 diabetes should be taken into account when designing a low-cost screening test for future CVD in women (40). Continuous monitoring of women with a history of GDM, especially those with prepregnancy obesity or maternal history of CVD, might provide important opportunities to reduce their cardiovascular risk.

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