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Gestational diabetes mellitus in mothers and long term cardiovascular disease in both parents: Results of over a decade follow-up of the Iranian population

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HIGHLIGHTS

- Women with prior GDM showed 85% higher risk of CVD in the unadjusted model.
- The risk of prior GDM among women was not independent of CVD risk factors.
- Fathers with spousal history of GDM had 36% higher risk of CVD.
- This association among fathers was independent of CVD risk factors (including diabetes).

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ABSTRACT

Background and aims: We aimed at evaluating whether the presence of gestational diabetes mellitus (GDM) in mothers is associated with increased risk of incident cardiovascular disease (CVD) in both mothers and fathers.
Methods: In this population-based study, 4308 Iranian women, aged 18–64 years, with at least 1 live-birth delivery, and free of CVD at baseline, were followed. Corresponding spouses were identified in 2547 cases. The association between history of GDM and incident CVD was assessed using multivariate Cox's proportional hazard in 3 models: model 1, unadjusted; model 2, adjusted for age, body mass index, smoking (for men), maternal parity, miscarriage, physical activity, hypertension and hypercholesterolemia, and model 3, further adjusted for diabetes mellitus.
Results: After a median follow-up of 14.1 years, 314 mothers and 424 fathers experienced CVD. Women with history of GDM had an adjusted hazard ratio (HR), 95% CI of 1.85 (1.38–2.48) and 1.29 (0.96–1.75) for CVD in models 1 and 2, respectively. Furthermore, an independent association with CVD was observed in fathers with an adjusted HR of 1.35 (1.02–1.79) in the confounder adjusted model and even after further controlling for diabetes [1.36 (1.03–1.80)]. Moreover, all traditional risk factors, excluding BMI, showed an independent risk for CVD in both genders.
Conclusions: Women with prior GDM showed an increased risk of CVD that was not independent of important CVD risk factors. However, among men, spousal history of GDM was an independent risk factor for incident CVD, even after considering important traditional risk factors, including diabetes.

1. Introduction

Globally, gestational diabetes mellitus (GDM) complicates up to 14% of pregnancies with varying prevalence across countries [1]. In a systematic review and meta-analysis conducted in 24 studies in Iran, the prevalence of GDM was estimated to be 3.4%, with highest and lowest prevalence rates of 18.6% and 1.3%, respectively [2]. Focusing on Tehran, the metropolitan area of Iran, this prevalence ranged from

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2.9 to 6.9%, based on different criteria used for diagnosis of GDM [3].

Cardiovascular disease (CVD) is the first cause of death in females worldwide [4] and also among Iranian women. Importantly, a greater burden of CVD has been reported for the Middle East and North Africa (MENA) region [5]. Moreover, it was reported that more than 40% of mortality in Tehran has been attributed to CVD [6].

Women with GDM are at increased risk of type 2 diabetes mellitus, dyslipidemia, hypertension, obesity, metabolic syndrome, vascular dysfunction and, ultimately, CVD at younger ages [7,8]. Recently, two meta-analyses [8,9] that included studies conducted in North America and Europe showed that although GDM was associated with higher risk of CVD, there was significant heterogeneity between studies (I^2 [> 95%), indicating the need for further studies among different ethnicities in this regard. Despite the high incidence and burden of CVD in Iran [10] and the MENA region [5], to the best of our knowledge, no study has yet examined the association between GDM and incident CVD among mothers with history of GDM residing in this area.

Previous studies also show partners to be concordant for changes in weight, physical activity [11], diabetes [12] and hypertension [13]. Moreover, a possible correlation between GDM in mothers and higher risk of diabetes and CVD in fathers has previously been evaluated in a few studies [14,15], showing that higher risk of spousal concordance might be due to their shared lifestyle [16].

In the present study, we examined the associations between previous GDM and incident CVD in both mothers and fathers in the Middle Eastern region among participants of a population-based study, the Tehran Lipid and Glucose Study (TLGS).

2. Materials and methods

2.1. Study population

The TLGS is an ongoing longitudinal prospective population-based study initiated in 1999–2001 and conducted on a representative sample of Tehran. The TLGS, for which recruitment was conducted in two phases (first, 1999–2001 and the second, 2002–2005), is planned to continue for at least 20 years. Follow-ups have been conducted at approximately 3-year intervals; i.e. the third phase: 2005–2008, fourth phase: 2009–2011, fifth phase: 2012–2015 and the sixth phase: 2015–2018. Details of the design and enrollment of the TLGS cohort have been defined elsewhere [17].

Our study population consisted of 7043 women, aged 18–64 years (5816 participants from phase 1 and 1227 new participants from phase 2). Excluded were those who were single (n = 1174), had no live-birth delivery (n = 654) and those with previous CVD (n = 196). Moreover, we excluded participants with missing data on covariates including hypertension, diabetes, hypercholesterolemia, body mass index (BMI), physical activity, maternal parity and miscarriage (n = 268, considering overlap between numbers), and those without any follow up after the baseline recruitment (n = 443). The final sample comprised 4308 women with follow-up data up to 20 March 2014 (Response rate = 85.8%). We did not have any patients with history of type 1 diabetes. Corresponding fathers were identified for 2942 women, of whom, we excluded those with previous CVD (n = 167), missing data regarding hypertension, diabetes, hypercholesterolemia, BMI, physical activity and smoking (n = 209, considering overlap between numbers) as well as those without any follow up after the baseline recruitment (n = 19), leaving us with data of 2547 fathers for analysis. The study was conducted based on the guidelines of the Declaration of Helsinki. Furthermore, the medical ethics committee of the Research Institute for Endocrine Sciences approved the study proposal; written informed consents were obtained from all participants.

2.2. Clinical and laboratory measurements

A trained interviewer collected information regarding demographic data as well as medical and drug history using a standard questionnaire. The questionnaires included questions regarding parity and miscarriage. A standardized mercury sphygmomanometer (calibrated by Iranian Institute of Standards and Industrial Researches) was used to measure blood pressure on the right arm after participants had been seated for at least 15 min, and the mean of these two measurements of blood pressures, was considered as the participant's blood pressure. Details of anthropometric measures including height and waist circumference (WC) have been reported before [17]. In the first phase of the study, physical activity level was assessed using the Lipid Research Clinic (LRC) questionnaire [18]; due to some inaccuracies of the LRC, it was replaced from the second phase by the Modifiable Activity Questionnaire (MAQ); a questionnaire that measures all three forms of activities including leisure time, job, and household activities in the past year [19].

Blood was drawn after a 12–14 h overnight fasting for measurement of biochemical tests including glucose and lipid profiles. Details for measurement of fasting plasma glucose (FPG), 2-h post challenge plasma glucose (2 h-PCPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and triglycerides (TG), using standard techniques have been described elsewhere [17]. Analyses were carried out using related kits (Pars Azmon Inc. Tehran, Iran) and a Selectra 2 auto-analyzer (Vital Scientific, Spankeren, The Netherlands).

2.3. Outcome assessment

Details of the CVD outcomes have been published before [17]. In this study, CHD included cases of definite myocardial infarction (MI) diagnosed by electrocardiogram (ECG) and biomarkers, probable MI defined by positive ECG findings plus cardiac symptoms or signs and biomarkers showing negative or equivocal results, unstable angina pectoris, which referred to new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers, angiography proven CHD, and CHD death (any death in hospital due to CHD according to the above-mentioned criteria or sudden cardiac death caused by cardiac disease occurring ≤ 1 h after beginning of symptoms based on verbal autopsy documents outside of hospital). CVD was defined as a composite measure of any CHD events, stroke or cerebrovascular death.

2.4. Definition of terms

GDM was defined as the presence of macrosomia or a history of GDM self-reported by participants. Macrosomia was defined as a birth weight > 4 kg [20]. Parity was defined as the number of live childbirths as well as still birth (defined as birth of an infant that died in the mother's uterus, after 20 weeks of gestation). Miscarriage referred to the loss of an embryo or fetus before the 20th week of pregnancy. Type 2 diabetes was described as FPG ≥ 7 mmol/L, 2 h-PCPG ≥ 11.1 mmol/L or using anti-hyperglycemic agents. Hypercholesterolemia was defined as total cholesterol levels ≥ 5.1 mmol/L or using lipid lowering agents. Hypertension was defined as either systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg or anti-hypertensive drug treatment. Smoking status was stratified as current and past smokers versus nonsmoker (never smokers). In the first phase of study, we defined individuals participating in a vigorous physical activity at least three days per week as physically active. Moreover, for those who entered in the second phase, being physically active was defined as achieving a minimum of at least 600 MET (metabolic equivalent task)-minutes per week [19].

2.5. Statistical analysis

Continuous variables with normal distribution are shown as mean (SD) and those without normal distribution as median (interquartile range); moreover, frequency (%) for categorical variables was used to

Table 1
Baseline characteristics by history of GDM in mothers: Tehran Lipid and Glucose Study.

	Total N = 4308	Without GDM N = 3831	With GDM N = 477	*p* value
Continuous variables				
Age (y)	41.3 ± 11.2	40.8 ± 11.2	45.3 ± 9.4	< 0.001
Parity	3(2–4)	3(2–4)	4(3–5)	< 0.001
BMI (kg/m^2)	28.3 ± 4.8	28.0 ± 4.7	30.5 ± 4.9	< 0.001
WC (cm)	89.5 ± 12.0	88.8 ± 11.9	95.6 ± 11.8	< 0.001
SBP (mmHg)	117.7 ± 18.5	117.1 ± 18.2	122.5 ± 20.0	< 0.001
DBP (mmHg)	77.6 ± 10.7	77.3 ± 10.6	80.3 ± 11.2	< 0.001
FPG (mmol/L)	5.0(4.7–5.4)	4.9 (4.6–5.4)	5.3(4.8–6.2)	< 0.001
2 h-PCPG (mmol/L)	6.0(5.1–7.3)	6.0(5.1–7.2)	6.5(5.3–8.3)	< 0.001
Total cholesterol (mmol/L)	5.5 ± 1.2	5.4 ± 1.2	5.7 ± 1.1	< 0.001
HDL-C (mmol/L)	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.10
TG (mmol/L)	1.6(1.07–2.3)	1.54(1.03–2.2)	1.84(1.4–2.5)	< 0.001
Categorical variables				
Hypertension	891(20.7%)	755(19.7%)	136 (28.5%)	< 0.001
Hypercholesterolemia	2432(56.5%)	2124(55.4%)	308 (64.6%)	< 0.001
Education				< 0.001
Illiterate/primary school	1706(39.6%)	1478(38.6%)	228(47.8%)	
Below diploma/diploma	2270(52.7%)	2043(53.4%)	227(47.6%)	
Above diploma	439(17.3%)	396(17.3%)	43(16.7%)	
Smoking status				0.6
Never	4091(95.1%)	3643(95.2%)	448(94.5%)	
Former	60(1.4%)	51(1.3%)	9(1.9%)	
Current	150(3.5%)	133(3.5%)	17(3.6%)	
History of miscarriage	1400(32.5%)	1211(31.6%)	189(39.6%)	0.001
Physically active	1208(29.3%)	1055(28.8%)	153(34.2%)	0.02

Values are expressed as mean (SD) or median (interquartile range) for continuous variables with and without normal distribution, respectively; as well as n (%) for categorical variables.
GDM, gestational diabetes mellitus; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2 h-PCPG, 2-h post challenge plasma glucose; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

show baseline characteristics of participants. Comparison of baseline characteristics between mothers with and without history of GDM and fathers with and without spousal history of GDM was performed using Student's t-test, Mann-Whitney and Chi square tests as appropriate. The mean difference [95% confidence interval (CI)] of continuous variables and the mean difference in the prevalence [95% CI] of each category of categorical variables were estimated to compare respondents with non-respondents, including those with missing data of covariates at baseline or those without any follow up.

The incidence rate of CVD/CHD and respective 95% confidence interval (CI) were calculated for women and their spouses by dividing the total number of incident cases to the sum of person-times of follow-up. Time to event was defined as time of censoring or date of the incidence of CVD/CHD, whichever occurred first.

Cox proportional hazard regression was used to assess the association of GDM with CVD and CHD incidence in women (mothers) and men (fathers) separately for both outcomes. Survival time or time to event was defined as time of censoring or having event, whichever came first. We censored individuals at the time of other causes of non-CVD death, loss to follow up during the study period and those remaining in the study until 20 March 2014 (end of study), without any CVD/CHD events.

Univariable Cox analyses were performed for each potential risk factor including: Age (years), hypertension, hypercholesterolemia, BMI, smoking status (never smokers as reference), maternal parity, history of miscarriage, physical activity and diabetes. Then, covariates with p values < 0.20 in univariable analysis were selected to enter the multivariable model. Model 1, unadjusted; model 2 was adjusted for age, BMI, smoking status (adjusted only for fathers), maternal parity, history of miscarriage, physical activity, hypertension and hypercholesterolemia; model 3 was further adjusted for diabetes. The proportional hazards assumption in the Cox model was assessed with the Schoenfild residual test and generally, all proportionality assumptions were appropriate. Statistical analysis was performed using SPSS for windows version 20 and STATA version 12. p values < 0.05 were considered statistically significant.

3. Results

Among 4308 women, 477 participants (11.1%) had a history of GDM or macrosomia. Baseline characteristics of respondent and non-respondent groups are compared in Supplementary Table 1, indicating no clinically important differences between these two groups. Baseline characteristics of women with and without history of GDM are presented in Table 1. Mean age (SD) and BMI at baseline were 41.3 (11.2) years and 28.3 (4.8) kg/m^2, respectively. Moreover, women with history of GDM were more likely to be older, with higher BMI, WC, SBP and DBP. At baseline examination, there were statistically significant differences between the two groups in terms of parity, history of miscarriage and physical activity level. Women with history of GDM had higher levels of FPG, 2 h-PCPG, total cholesterol, TG, and higher prevalence of hypertension and hypercholesterolemia; they were also less educated, but the two groups did not differ in HDL level and smoking status.

A comparison of men's characteristics according to the presence of GDM in their spouses is presented in Table 2. Men with a spousal history of GDM were older (50.6 *vs*. 45.8), had higher BMI, WC, SBP and DBP, and were more frequently hypertensive, physically active and less educated; however, they did not differ in the levels of FPG, 2 h-PCPG, smoking status and lipid profiles.

Among women, incident diabetes occurred in 362 (9.4%) women without history of GDM and 119 (24.9%) of those with history of GDM; moreover, daily use of glucose lowering medications was reported in 121 (3.2%) of those without GDM and in 62 (13%) of those with a history of GDM. Among fathers, diabetes occurred in 245 (10.7%) and 38 (14.7%) men without and with spousal history of GDM, respectively; moreover, use of glucose lowering medications was reported in 31.5% and 26.5% of these diabetic patients, respectively.

During a median (IQR) of 14.11 (12.74–14.55) years of follow up, 314 incident CVD and 279 incident CHD events occurred among women; the corresponding incidence rates were 58.68 (95% CI) (52.54–65.54) for CVD and 52.03 (46.27–58.51) for CHD per 10,000 person-years.

Table 2
Baseline characteristics by spousal history of GDM in fathers: Tehran Lipid and Glucose Study.

	Total N = 2547	Without GDM N = 2289	With GDM N = 258	*p* value
Continuous variables				
Age (y)	46.3 ± 11.6	45.8 ± 11.5	50.6 ± 10.9	< 0.001
BMI (kg/m^2)	26.3 ± 3.9	26.3 ± 3.9	26.9 ± 3.8	0.005
WC (cm)	91.1 ± 10.8	90.8 ± 10.8	93.2 ± 10.5	0.001
SBP (mmHg)	120.2 ± 18.2	119.6 ± 17.6	124.9 ± 21.9	< 0.001
DBP (mmHg)	78.3 ± 11.2	78.2 ± 11.2	79.7 ± 10.9	0.034
FPG (mmol/L)	5.1(4.8–5.5)	5.1(4.8–5.5)	5.2(4.8–5.7)	0.054
2 h-PCPG (mmol/L)	5.7(4.6–7.0)	5.7(4.6–7.0)	5.9(4.7–7.3)	0.12
Total cholesterol (mmol/L)	5.35 ± 1.1	5.35 ± 1.1	5.4 ± 1.1	0.56
HDL-C (mmol/L)	0.97 ± 0.2	0.97 ± 0.2	0.99 ± 0.2	0.35
TG (mmol/L)	1.85(1.3–2.6)	1.85(1.3–2.6)	1.89(1.3–2.7)	0.82
Categorical variables				
Hypertension	533(20.9%)	466(20.4%)	67 (26.0%)	0.04
Hypercholesterolemia	1394(54.7%)	1249(54.6%)	145 (56.2%)	0.64
Education				< 0.001
Illiterate/primary school	736(28.9%)	629(27.5%)	107(41.5%)	
Below diploma/diploma	1369(53.8%)	1261(55.2%)	108(41.9%)	
Higher than diploma	439(17.3%)	396(17.3%)	43(16.7%)	
Smoking status				0.11
Never	1374(53.9)	1224(53.5)	150(58.1)	
Former	418(16.4)	372(16.3)	46(17.8)	
Current	755(29.6%)	693(30.3%)	62(24.0%)	
Physically active	716(28.3%)	627(27.6%)	89(34.6%)	0.019

Values are expressed as mean (SD) or median (interquartile range) for continuous variables with and without normal distribution, respectively; as well as n (%) for categorical variables.
GDM, gestational diabetes mellitus; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; 2 h-PCPG, 2-h post challenge plasma glucose; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides.

Furthermore, 424 incident CVD and 374 CHD events occurred among fathers during a median (IQR) of 13.80 (9.53–14.43) years follow up; corresponding incidence rates were 142.67 (129.72–156.92) and 125.14 (113.8–138.49) per 10,000 person-years, respectively.

As shown in Fig. 1 by Kaplan-Meier survival analysis for incident CVD and CHD, women with history of GDM and men with spousal history of GDM had significantly greater risk of CVD and CHD throughout the follow-up, compared with their non-GDM counterparts.

Table 3 shows the adjusted HRs and 95% CI for CVD among mothers and fathers. Accordingly, past history of gestational diabetes in mothers was associated with HR (95%CI) of 1.85 (1.38–2.48) in the unadjusted model. However, after considering covariates in model 2, the risk decreased to 29% [HR (95%CI) of 1.29 (0.96–1.75), $p = 0.09$] and was statistically non-significant. After further adjustment for subsequent development of diabetes, this risk was further attenuated [HR (95%CI) 1.12 (0.83–1.52)].

Focusing on fathers, spousal history of GDM was associated with higher risk of CVD, with HR (95% CI) of 1.61 (1.22–2.13) and 1.35 (1.02–1.79) in models 1 and 2 respectively, an association that remained statistically significant even after further adjustment for diabetes [1.36 (1.03–1.80)]. Importantly, in the multivariate model, traditional risk factors including age, hypertension, hypercholesterolemia and diabetes showed significant risk for CVD events among both mothers and fathers; whereas smoking showed a significant risk among fathers. Moreover, parity as well as history of miscarriage showed a significant hazard for CVD among mothers.

Similar associations were seen between history of prior GDM and incident CHD among mothers with adjusted HRs (95%CI) of 1.28 (0.93–1.76) after adjustment for covariates in model 2 and 1.09 (0.79–1.51), after further adjustment with subsequent development of diabetes (model 3). Furthermore, higher risks of 33% [1.33 (0.99–1.80) $p = 0.06$] and 32% [1.32 (0.98–1.79) $p = 0.07$] for CHD was also seen among fathers considering covariates in models 2 and 3, respectively (Supplementary Table 2).

4. Discussion

In this prospective population-based study, conducted over a decade long follow-up, we found that history of GDM among women was associated with about 30% higher risk of CVD/CHD in the presence of important confounders including age, BMI, physical activity, parity, history of miscarriage, hypercholesterolemia and hypertension, although the risk was statistically non-significant. Furthermore, among fathers, the presence of GDM in their spouses was associated with 36% higher risk of CVD, even after considering important traditional risk factors including diabetes mellitus.

In the recent meta-analysis [9], the relative risk (RR) for the association between GDM and CVD varied from 1.21, 95% CI (0.97–1.51) in the study conducted by Tobias et al. [21], to 5.76, 95% CI (4.96–6.68) among English women [22] with an overall RR of 1.98 (1.57–2.50), results that showed significant heterogeneity ($I^2 = 98.6\%$, $p = 0.000$). In line with this recent meta-analysis, in the current study, women with previous GDM showed an 85% higher risk of CVD in the unadjusted model as well as a 29% (0.96–1.75) higher risk of CVD after adjustment for important risk factors such as age, hypertension and hypercholesterolemia, parity and miscarriage, all of which showed strong risk for incident CVD events. Our findings were in line with studies that have reported the risk of CVD in women with history of prior GDM in the unadjusted model [15,23–25]; moreover, our effect size for GDM was in the range of relative risk reported in the recent meta-analysis [9]; although we did not find any prospective study which considered all of these confounders together in the multivariate analysis. In the same meta-analysis [9], among women who did not develop diabetes, the association between GDM and CVD was still significant, with an overall RR of 1.56 (1.04–2.32), with a significant heterogeneity ($I^2 = 98\%$, $p = 0.000$); in contrast, in the current study, the risk of CVD decreased from 29 to 12%, after adjustment for subsequent diabetes mellitus.

Varying estimates of the risk of GDM for CVD events in studies might be due to the different approaches used for diagnosis of GDM, different sample size, duration of follow-up, selection of participants (clinic vs. population based studies), and type and number of confounders. Some other sources of heterogeneity between the studies in

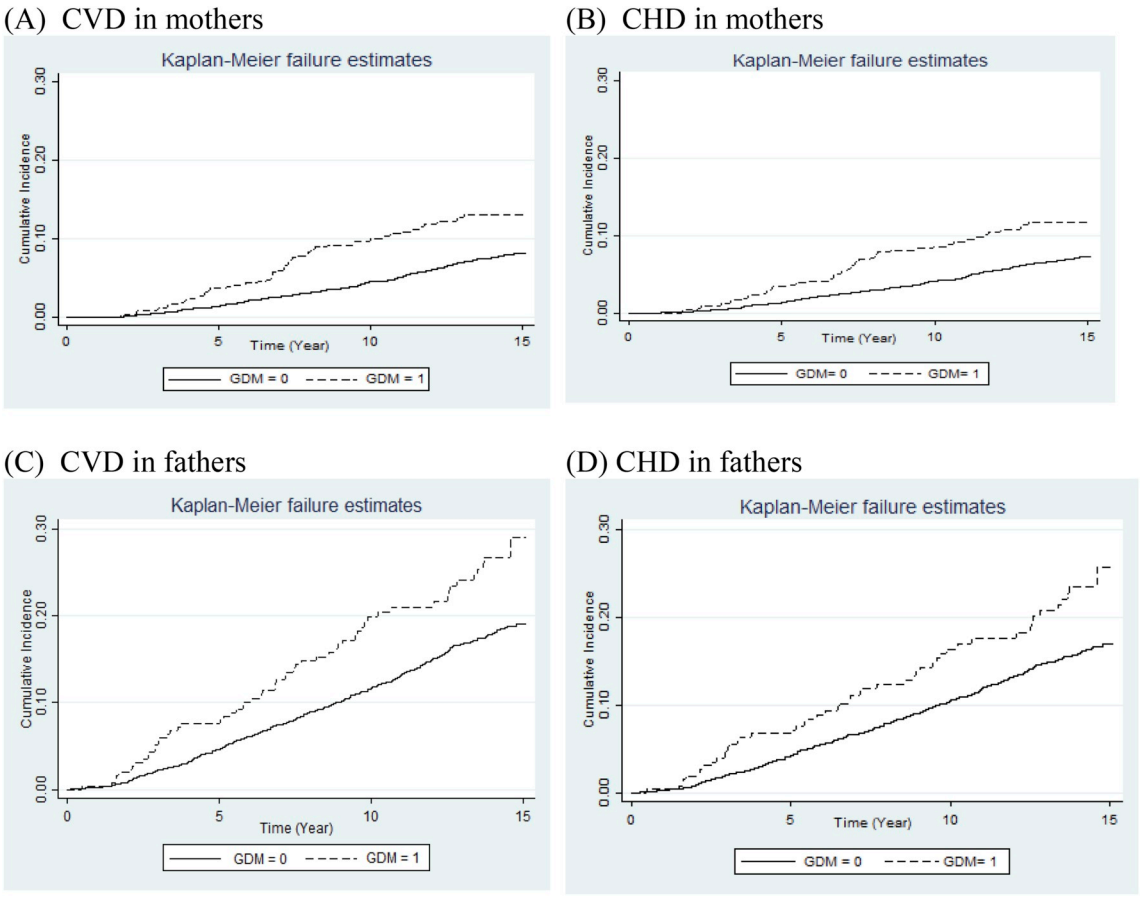

Fig. 1. Kaplan Meier curves for time to diagnosis of CVD in mothers (A), CHD in mothers (B), CVD in fathers (C) and CHD in fathers (D): Tehran Lipid and Glucose Study.

Table 3
Multivariate hazard ratios (HR) and 95% CI of CVD for a history of GDM in mothers or spousal history of GDM in fathers as well as other risk factors.

	Model 1			Model 2			Model 3		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Mothers									
History of GDM	1.85	1.38–2.48	< 0.001	1.29	0.96–1.75	0.09	1.12	0.83–1.52	0.466
Age (y)				1.06	1.05–1.08	< 0.001	1.06	1.05–1.08	< 0.001
BMI (kg/m^2)				1.01	0.98–1.03	0.43	1.01	0.98–1.03	0.507
Physical activity				1.24	0.95–1.61	0.11	1.10	0.92–1.56	0.174
Parity				1.12	1.05–1.19	< 0.001	1.10	1.03–1.17	0.002
Miscarriage				1.32	1.06–1.66	0.03	1.31	1.04–1.64	0.02
Hypertension				1.92	1.50–2.45	< 0.001	1.76	1.37–2.25	< 0.001
Hypercholesterolemia				1.90	1.37–2.65	< 0.001	1.84	1.32–2.57	< 0.001
Diabetes							2.43	1.91–3.01	< 0.001
Fathers									
Spousal history of GDM	1.61	1.22–2.13	0.001	1.35	1.02–1.79	0.03	1.36	1.03–1.80	0.03
Age (y)				1.06	1.05–1.07	< 0.001	1.06	1.05–1.07	< 0.001
BMI (kg/m^2)				1.02	1.00–1.05	0.05	1.01	0.99–1.04	0.288
Past smoker				1.34	1.04–1.72	0.02	1.32	1.03–1.70	0.029
Current smoker				1.74	1.38–2.21	< 0.001	1.75	1.38–2.22	< 0.001
Physical activity				1.09	0.87–1.38	0.45	1.06	0.85–1.32	0.605
Spousal parity				1.01	0.95–1.08	0.71	1.01	0.95–1.08	0.69
Spousal miscarriage				0.96	0.79–1.18	0.73	0.97	0.79–1.18	0.74
Hypertension				1.68	1.36–2.09	< 0.001	1.63	1.31–2.03	< 0.001
Hypercholesterolemia				1.62	1.31–2.00	< 0.001	1.58	1.29–1.95	< 0.001
Diabetes							1.81	1.43–2.30	< 0.001

CVD, cardiovascular disease; GDM, gestational diabetes mellitus; BMI, body mass index.
Model 1: unadjusted.
Model 2: for mothers: Age, body mass index, maternal parity, miscarriage, physical activity, hypertension and hypercholesterolemia; for fathers: Age, body mass index, spousal parity, miscarriage, physical activity hypertension, hypercholesterolemia, and smoking.
Model 3: model 2 + diabetes.

the meta-analysis might be attributable to the following factors: first, the higher association between GDM and CVD was mostly shown in studies with over 20 years of follow-up than in shorter studies, as development of CVD among young women need much more time; second, as in the current study, the definition of GDM was based on self-reported data and we need prospective cohorts of women with GDM defined by solid GDM diagnostic criteria to examine its association with incident CVD; third, another source of heterogeneity might be related to the age at index pregnancy, as it is apparently clear that the risk of GDM was greater in women with higher age at the time of pregnancy than in their younger counterparts. Unfortunately, in the current study, maternal age at index pregnancy was not available.

Within a household, spouses might share common living environments and behaviors leading to concordance for diseases. We found an elevated risk of CVD among spouses of mothers with history of GDM beyond the effect of men's own risk factors, including diabetes. Previously, significant positive spousal concordance for the main coronary risk factors, including diastolic blood pressure, triglycerides, total and low density lipoprotein cholesterol, weight and waist/hip ratio [26], diabetes mellitus [27] and hypertension [13] was reported in 3 meta-analyses. To our best knowledge, the link between GDM in mothers and future risk of CVD in fathers has been addressed only in one prospective study [15], showing an adjusted HR 95% (CI) of 1.2(1.1–1.3) for CVD. However, the authors considered combined GDM/gestational hypertension as a risk indicator in both mothers and fathers; also, they did not consider the traditional risk factors in their multivariate analysis. Our study extended the findings of the mentioned study by showing an independent association between the spousal history of GDM and incidence of CVD events among fathers in the presence of strong traditional risk factors, including diabetes; a finding which may be explained by spousal similarity. Several theories have been suggested to explain the couple similarity. Selection processes also referred to as assortative mating refers to the idea that peoples tend to choose partners who are similar to them based on certain characteristics including attitudes, demographics and health-related behaviors, such as diet, physical activity, BMI and smoking [28–30]. In our study, the risk of CVD in fathers did not decrease after adjustment for fathers' own BMI (as a surrogate for assortative mating); hence, assortative mating might not be the main cause for the observed association. Another hypothesis is referred to as the spousal convergence over time, which suggests that when people marry, they share a lifestyle as well as common stressors. Shared major and minor life events contribute to behavioral convergence [28,29]. Our finding that history of GDM in mothers is a risk factor for the development of CVD in fathers may be explained by the effect of behavioral convergence. Spouses typically have a common living environment and eat together [28,29]. As women in our country are responsible for preparing meals, it is conceivable that the dietary preferences of women with history of GDM may influence their spouse's dietary patterns. The association between diet and CVD is well recognized [31,32]. Some dietary patterns have been shown to modulate inflammation which is well known to be linked to the development and progression of CVD [32]. Finally, another theory that has been proposed to explain spousal similarity is referred to as mood convergence or affective contagion [29]. This theory suggests that one partner's distress can provoke similar emotional responses in their partner [28]. Although we related our findings to the two concordance theories, we could not test those theories due to the insufficient data, and this merits further studies.

Moreover, in line with our previous study [33], among the male population, traditional risk factors including hypertension, hypercholesterolemia, diabetes, current and former smoking were associated with a greater risk of CVD. In the present study, smoking was an important risk factor for incident CVD even in multivariate model, in the presence of other important traditional risk factors including diabetes mellitus. Actually, the impact of smoking on risk of CVD in the present study was equivalent to that of diabetes with a HR (95%CI) of 1.75 (1.38–2.22) for current smoking and 1.81 (1.43–2.30) for diabetes. Among the Iranian population, in a the meta-analysis of initial studies and risk factors of non-communicable disease surveillance system, smoking prevalence was estimated to be 21.7% and 19.8% in men and 3.6% and 0.94% in women, respectively [34]. In our dataset, about 95% of our women population was never smoker at baseline; thus, we did not have enough power to examine the effect of smoking among the female population.

Strengths of the present study include prospective, longitudinal and long term follow-up of a large cohort with careful adjustment for potential confounders, reliable measurements of different covariates and a study conducted on a cohort representative of the Iranian population. Moreover, this was the second study that examined the association between spousal history of GDM in fathers and future risk of CVD. Limitations include first, our reliance on self-reported GDM that might lead to exposure misclassification. Second, we did not evaluate some residual risk factors of CVD. Third, we had no data on nutritional habits as well as family income of the study participants at baseline examination. Finally, the generalizability of the findings to other ethnicities and rural parts requires additional investigations, given that this study was performed in an Iranian urban population.

In conclusion, according to the results of the present study, the increased risk of CVD for mothers with history of GDM was not independent of important CVD risk factors. However, spousal history of GDM was associated with > 30% risk of CVD in fathers. Thus, identifying families with a history of GDM in mothers, several years prior to CVD events may provide individuals and health care professionals the opportunity to intervene with preventive therapy and lifestyle modifications in the context of the family in order to improve their cardiovascular health, especially among fathers.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Author contributions

FH, MK, KG and FA conceived and planned the study. MH conducted the analyses. MK and FH developed the first draft of the manuscript. FH, MK, MH and AR developed the revised manuscript. All authors contributed to the writing of the paper, and have read and approved the final manuscript.

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Appendix A. Supplementary data

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