

# Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case–control study

H Fadl,<sup>a</sup> A Magnuson,<sup>b</sup> I Östlund,<sup>a</sup> S Montgomery,<sup>b,c</sup> U Hanson,<sup>a,d</sup> E Schwarcz<sup>e</sup>

<sup>a</sup> Department of Obstetrics and Gynaecology, School of Health and Medical Sciences, Örebro University, Örebro, Sweden <sup>b</sup> Clinical Epidemiology and Biostatistics, Örebro University Hospital, School of Medical Health and Sciences, Örebro University, Örebro, Sweden <sup>c</sup> Clinical Epidemiology Unit, Karolinska Institutet, Stockholm, Sweden <sup>d</sup> Department of Women's and Children's Health, Uppsala University, Uppsala, Sweden <sup>e</sup> Department of Internal Medicine, School of Health and Medical Sciences, Örebro University, Örebro, Sweden  
*Correspondence:* H Fadl, Department of Obstetrics and Gynaecology, Örebro University Hospital, SE 70185 Örebro, Sweden.  
Email [helena.fadl@orebroll.se](mailto:helena.fadl@orebroll.se)

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**Objective** To identify if gestational diabetes mellitus (GDM) is a clinically useful marker of future cardiovascular disease (CVD) risk and if GDM combined with other risks (smoking, hypertension or body mass) identifies high-risk groups.

**Design** Population-based matched case–control study.

**Setting** National Swedish register data from 1991 to 2008.

**Population** A total of 2639 women with a cardiovascular event and matched controls.

**Methods** Conditional logistic regression examined associations with CVD before and after adjustment for conventional risk factors and confounders. Effect modification for the association of GDM with CVD by body mass index (BMI), smoking and chronic hypertension was assessed by stratification and interaction testing. Adjustment for diabetes post-pregnancy evaluated its mediating role.

**Main outcome measures** Inpatient diagnoses or causes of death identifying ischemic heart disease, ischemic stroke, atherosclerosis or peripheral vascular disease.

**Results** The adjusted odds ratios (and 95% confidence intervals) for the association of CVD with GDM are 1.51 (1.07–2.14), 2.23 (2.01–2.48) for smoking, 1.98 (1.71–2.29) for obesity and 5.10 (3.18–8.18) for chronic hypertension. In stratified analysis the association of CVD with GDM was only seen among women with BMI  $\geq 25$ , with an odds ratio of 2.39 (1.39–4.10), but only women with a BMI  $< 30$  accounted for this increased risk. Adjustment for post-pregnancy diabetes attenuated it somewhat to 1.99 (1.13–3.52).

**Conclusions** In the absence of other recognised cardiovascular risk factors, such as smoking, obesity or chronic hypertension, GDM is a useful marker of raised CVD risk among women with BMI between 25 and 29.

**Keywords** Body mass index, cardiovascular disease, gestational diabetes mellitus.

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## Introduction

The immediate adverse maternal and neonatal outcomes of hyperglycaemia during pregnancy are well known,<sup>1,2</sup> as well as the long-term complications in the form of raised diabetes risk and the metabolic syndrome later in life.<sup>3,4</sup> Future maternal morbidity in terms of cardiovascular disease (CVD) after gestational diabetes mellitus (GDM) has been shown in two studies.<sup>5,6</sup> A Finnish population-based cohort study has demonstrated an association with later hypertension, especially among the group of women with GDM who were over-

weight.<sup>7</sup> It is uncertain if this association can be explained by contemporaneous characteristics that are recognised risks for CVD or whether such characteristics may be used to identify a subset of women with GDM who are at particularly raised risk for future CVD. However, not all women with GDM develop subsequent CVD. It would be clinically valuable to have a risk marker at the time of pregnancy so that long-term follow up and possible interventions can be focused on the women at greatest risk in a timely manner.

The aim was therefore to evaluate whether the association of GDM with subsequent severe CVD is independent

of conventional CVD risks that are readily identifiable during pregnancy and to identify if a subset of women with GDM is at a particularly raised risk of CVD. The pregnancy characteristics investigated were smoking, overweight and chronic hypertension.

The possible mediating role of diabetes after pregnancy was also evaluated.

## Methods

Data were from the Swedish National Board of Health and Welfare and Statistics Sweden, from 1991 to 2008. Linkage between registries was performed using the unique personal identification number issued to Swedish residents.<sup>8</sup> The Swedish Medical Birth Register (SMBR) contains data on more than 98% of all births in Sweden from 1973 onwards. Starting with the first visit at the end of the first trimester, information on all hospital births is gathered prospectively and includes demographic data, reproductive history and complications during pregnancy, delivery and the neonatal period. The SMBR was validated in 2002 and the quality is generally high.<sup>9</sup> The Patient Register contains data on inpatient discharge diagnosis since 1964 but did not reach full coverage until 1987 and outpatient diagnoses have been registered since 2001. Since 2001 both private and public caregivers have been obliged to report to the register. The Inpatient Register has been validated recently and the validity of the different diagnosis of cardiovascular disease is high.<sup>10</sup> The Cause of Death Register was used to identify deaths due to cardiovascular disease. The Prescription Register was used to identify individuals who were prescribed pharmaceutical treatment for diabetes according to ATC codes (A10). This register provides data on prescriptions beginning from 1 July 2005. Statistics Sweden is responsible for the national Register of Population and Population Changes, which was used to select controls and provided data on education.

### Cases and controls

Cases were defined as women diagnosed with a first cardiovascular event or death in a cardiovascular event (ischaemic heart disease, stroke, atherosclerosis or peripheral vascular disease) using the ninth or tenth revision of the International Classification of Diseases (ICD-9, ICD-10). For each case, five controls were selected. All of the women had to have had a pregnancy before the date that they were defined as cases or controls. Cases and controls were the same age when they gave birth to a child during the same year. The controls had to be alive at the time of matching and resident in Sweden. Neither cases nor controls should have had cardiovascular events before the matched pregnancy. We identified nine individuals with a diagnosis of diabetes mellitus before the index pregnancy, indicating a

misdiagnosis of GDM among 4.3%: these women were excluded. After exclusion because of incomplete or inaccurate data, there were 4590 cases and 22 398 controls for analysis. Of these, 2639 cases and 13 310 controls with complete data for all relevant measures were included in the main analysis. Sensitivity analysis was performed for those with missing data to evaluate potential bias. The analysis used information from the pregnancy used for matching cases and controls.

Diabetes after pregnancy was considered as a potential mediating factor. To tackle possible surveillance bias it was necessary for diagnoses of diabetes to have been recorded before the diagnosis of CVD. Cases and controls were assessed for diabetes diagnosed after pregnancy but before the diagnosis of CVD and the equivalent time point among controls. The first diagnosis of diabetes was identified through the Patient Register or through prescribed diabetes treatments recorded in the Prescription Register.

In Sweden, screening strategies for GDM during the study period have been described previously.<sup>2,11–13</sup> Diagnosis of GDM is based on the 75-g oral glucose tolerance test (OGTT) and the main diagnostic criteria for GDM were fasting capillary whole blood glucose  $\geq 6.1$  mmol/l (fasting plasma glucose  $\geq 7.0$  mmol/l) and/or 2-hour blood glucose  $\geq 9.0$  mmol/l (plasma glucose  $\geq 10.0$  mmol/l).<sup>14</sup> Complications during pregnancy are classified according to the Swedish version of the ICD, using the ninth revision (ICD-9) from 1987 until 1996 and the tenth revision (ICD-10) since 1997. Data on smoking are collected in early pregnancy at the first visit in maternal care. In this study, smoking was categorised as smoking/non-smoking in early pregnancy. Parity is categorised as 0, 1 or  $\geq 2$  previous births. Ethnicity is defined as Nordic (Sweden, Finland, Denmark, Norway, Iceland) or non-Nordic, according to country of birth.

Body mass index (BMI) was measured in early pregnancy and height and weight are routinely measured in Sweden by midwives, not self-reported. BMI was categorised into following groups  $<18.5$ , 18.5–24, 25–29 and  $>30$  kg/m<sup>2</sup>. Chronic hypertension was defined as hypertension diagnosed before pregnancy, or blood pressure  $\geq 140/90$  mmHg before 20 weeks of gestation.

Education level was measured once at the time nearest to the studied pregnancy. Education level was categorised into five classes: I, no education; II, compulsory school (9–10 years of education); III, post compulsory school (2–3 years); IV, further education (3–4 years of education after post compulsory school); and V, higher education (academic studies).

### Statistical methods

Conditional logistic regression was used to evaluate the association of GDM with CVD, both before and after

adjustment for potential confounding factors; chronic hypertension, smoking, ethnicity, parity, BMI and education level, all modelled as categorical variables. The measure of association is the odds ratio (OR), with 95% confidence intervals (95% CI). Stratification and interaction testing were used to assess effect modification of the association of GDM with CVD by BMI (normal weight, BMI 18.5–24 kg/m<sup>2</sup> and overweight, BMI  $\geq$ 25 kg/m<sup>2</sup>), smoking and chronic hypertension. To assess the role of post-pregnancy diabetes as a mediating factor for later development of CVD, ORs were calculated with additional adjustment for diabetes mellitus. A  $P < 0.05$  or confidence intervals not including 1.00 were regarded as statistically significant. The chi-squared test was used to compare background characteristics between cases and controls.

The statistical analysis used SPSS, version 18 (SPSS Inc., Chicago, IL, USA) and STATA (StataCorp 2007; Stata Statistical Software: Release 10. (College Station, TX, USA).

## Results

Of the 2639 cases with complete data on all variables, 1488 (56.4%) had a diagnosis of ischaemic heart disease, 917 (34.7%) had a diagnosis of ischaemic stroke, 119 (4.5%) had a diagnosis of atherosclerosis and 192 (7.3%) had a diagnosis of peripheral ischaemic disease.

A total of 13 310 matched controls were included. Among cases there were 88 (3.3%) CVD-related deaths. Some 80.8% of the pregnancies occurred between 1991 and 1997. The women's mean age at time of diagnosis was 40.7 years (SD 7.3). The mean time period from index pregnancy to cardiovascular event was 9.1 years (SD 4.3). There were significant differences between cases and controls regarding the prevalence of GDM (2.4% versus 1.1%), chronic hypertension during pregnancy (2.1% versus 0.3%), smoking in early pregnancy (35.3% versus 18.1%), overweight (BMI  $>$ 25, 42.0% versus 30.3%), parity (mean 2.44, SD 1.2 versus 2.62, SD 1.2), lower education level (I/II, 23.4% versus 15.1%) and non-Nordic origin (14.2% versus 11.4%) (Table 1).

Associations with cardiovascular disease for GDM and other characteristics are presented in Table 1. Chronic hypertension, smoking, GDM, parity, BMI and lower education were notably associated with CVD events. After adjustment for chronic hypertension, GDM, smoking, BMI, education level, parity and ethnicity, respectively, all factors were statistically significantly associated with an increased risk of CVD events.

The unadjusted odds ratio (and 95% confidence interval) for the association of GDM with cardiovascular disease was 2.19 (95% CI 1.59–3.01) and 1.51 (95% CI 1.07–2.14) after adjustment. Table 1 demonstrates that hypertensive diseases

and smoking during pregnancy have higher magnitude associations with cardiovascular disease than GDM.

Stratification by BMI indicated that GDM was statistically significantly associated with CVD among overweight women, but not among normal weight women (Table 2). For women with BMI  $\geq$  25 the odds ratio for the association of GDM with CVD was 2.23 (95% CI 1.38–3.62) before adjustment and 2.39 (95% CI 1.39–4.10) after adjustment, but only women with a BMI  $<$ 30 accounted for this increased risk. For women with a BMI  $\geq$ 30 GDM did not represent an additional risk for CVD, with an odds ratio of 0.76 (95% CI 0.16–3.58). The interaction test in the adjusted model between overweight/normal weight and GDM was statistically significant ( $P = 0.006$ ). GDM was not associated with CVD in smokers (GDM did not add any risk to the baseline risk for smoking) but a risk with crude odds ratio of 2.78 (95% CI 1.98–3.91) was found in non-smokers (as shown in the Table S1). Analyses were stratified by chronic hypertension, but there were an insufficient number of participants in some cells to produce interpretable estimates.

A diagnosis of diabetes after pregnancy represents a high risk for CVD with an adjusted odds ratio of 4.80 (95% CI 3.23–7.13), and after additional adjustment for diabetes the modest statistical significance of the association of GDM with CVD among all women was eliminated. However, among overweight and obese women, where the association of GDM with CVD is most profound, additional adjustment for post-pregnancy diabetes in analysis stratified by BMI attenuated the association of GDM with CVD only slightly to 1.99 (95% CI 1.13–3.52). Pre-eclampsia was handled as a mediating factor and therefore data are not shown in the analysis. Calculations did, however, show a similar association with CVD as in previous studies and adding pre-eclampsia in the adjusted model did not change the main results.

From the original selected group of cases (4590) and controls (22 398), exclusion because of missing data was mainly due to the BMI variable, which was missing in 40.7% of the cases and 38.8% of controls; and this difference was statistically significant ( $P = 0.018$ ). In 1991 and 1992 the recording of BMI in SMBR was incomplete, but coverage improved after 1992. In this material, 46.6% of the pregnancies were between 1991 (25.1%) and 1992 (21.5%). Smoking data were missing in 6.3% of the cases and 5.3% of the controls ( $P = 0.005$ ). Information on education level was lacking for 0.2% in controls and in 0.1% in cases ( $P = 0.009$ ).

Women among the cases and controls with missing data for any of the variables used in the analysis did not differ by age, prevalence of GDM or ethnicity, compared with women with complete data. Lower education level (classes I and II) was more common in the group with complete

**Table 1.** Demographic and clinical characteristics for cases and controls

Characteristics and clinical data	Cases (n = 2639)	Controls (n = 13 310)	Crude		Adjusted*	
			OR (95% CI)	P value	OR (95% CI)	P value
<b>Non-GDM</b>	2577 (97.6)	13162 (98.9)	Reference		Reference	0.019
<b>GDM</b>	62 (2.4)	148 (1.1)	2.19 (1.59–3.01)	<0.001	1.51 (1.07–2.14)	
<b>No chronic HT</b>	2584 (97.9)	13265 (99.7)	Reference		Reference	<0.001
<b>Chronic HT</b>	55 (2.1)	45 (0.3)	6.24 (3.99–9.78)	<0.001	5.10 (3.18–8.18)	
<b>No smoking</b>	1708 (64.7)	10898 (81.9)	Reference		Reference	<0.001
<b>Smoking</b>	931 (35.3)	2412 (18.1)	2.48 (2.25–2.74)	<0.001	2.23 (2.01–2.48)	
<b>Nordic</b>	2264 (85.8)	11792 (88.6)	Reference		Reference	0.125
<b>Non-Nordic</b>	375 (14.2)	1518 (11.4)	1.28 (1.13–1.46)	<0.001	1.12 (0.97–1.29)	
<b>Parity</b>						
0	565 (21.4)	1505 (11.3)	Reference		Reference	<0.001
1	1012 (38.4)	5680 (42.7)	0.47 (0.41–0.53)	<0.001	0.54 (0.47–0.61)	
≥2	1062 (40.2)	6125 (46.0)	0.45 (0.40–0.52)	<0.001	0.45 (0.39–0.51)	<0.001
<b>BMI</b>						
<18.5	62 (2.3)	336 (2.5)	1.11 (0.83–1.48)	0.474	0.98 (0.73–1.32)	0.910
18.5–24	1470 (55.7)	8942 (67.2)	Reference		Reference	
25–29	686 (26.0)	2981 (22.4)	1.43 (1.29–1.59)	0.003	1.34 (1.21–1.50)	<0.001
>30	421 (16.0)	1051 (7.9)	2.37 (2.07–2.71)	<0.001	2.01 (1.74–2.33)	<0.001
<b>Education level**</b>						
I no education	47 (1.8)	136 (1.0)	1.72 (1.20–2.46)	0.003	1.45 (0.98–2.13)	0.062
II compulsory school	569 (21.6)	1882 (14.1)	1.46 (1.30–1.65)	<0.001	1.23 (1.09–1.40)	0.001
III post compulsory school	1389 (52.6)	6603 (49.6)	Reference		Reference	
IV further education	334 (12.6)	2447 (18.4)	0.63 (0.55–0.72)	<0.001	0.76 (0.66–0.87)	<0.001
V higher education ≥3 years	300 (11.4)	2242 (16.8)	0.61 (0.53–0.70)	<0.001	0.76 (0.66–0.88)	<0.001

HT, hypertension.

Crude and adjusted ORs (95% CI) for the association of different variables with CVD. Values are numbers (%) unless stated otherwise.

\*Adjustment for GDM, chronic hypertension, smoking, BMI, ethnicity, education level, parity, respectively.

\*\*Education level: I, <9 years of education or no education; II, 9–10 years of education; III, 2–3 years of education after compulsory school; IV, 3–4 years of education after compulsory school; V, academic studies.

data; 20.7% lower education in the group with complete data compared with 16.5% in the group with missing data ( $P < 0.001$ ). To assess potential selection bias, the unadjusted odds ratio for the association of GDM with CVD was calculated in the entire population ( $n = 26\,988$ ) with an odds ratio of 2.2 (95% CI 1.7–2.8), and this was similar to the odds ratio for the subset with complete data. Excluding the pregnancies from 1991 and 1992 did not change the results. The crude odds ratio for GDM in overweight women was 2.43 (95% CI 1.62–3.63) and in the adjusted model was 2.0 (95% CI 1.3–3.1), indicating that selection bias is unlikely or had minimal impact on the results.

## Discussion

### Main findings

This general population based case–control study shows that pregnancies complicated by GDM are associated with increased risk of later CVD. In stratified analysis the

association was only seen among women with a BMI  $\geq 25$  kg/m<sup>2</sup>, but only women with a BMI  $< 30$  kg/m<sup>2</sup> accounted for this increased risk. The association between GDM and CVD in this group was comparable in magnitude to the effects of smoking or obesity and appears to be mediated, at least in part, though diabetes that develops after the pregnancy.

### Strengths and weaknesses of the study

Strengths of this study include that it is general population based and that the national health registers used have been validated and have good coverage, the data were collected prospectively and the recording of exposures was not influenced by the outcome. Importantly, it was possible to adjust for maternal characteristics to confirm that the association of GDM with CVD is independent of other CVD risk factors. The matching criteria were used to take into account potential variation for local strategies for screening and diagnosis of GDM or variation in recording of maternal characteristics or disease risk. During the period 1991

**Table 2.** Odds ratios (95% CI) for GDM as a risk factor for cardiovascular disease in normal weight versus overweight women

		Cases (n = 2639)		Controls (n = 13 310)		Crude		Adjusted*		
		n (%)		n (%)		OR (95% CI)	P value	OR (95% CI)	P value	
<b>Stratified by BMI</b>										
<18.5 (n = 398)	No GDM	62 (100.0)	335 (99.7)	NE		NE				
	GDM	0 (0.0)	1 (0.3)							
18.5–24 (n = 10 412)	No GDM	1462 (99.5)	8885 (99.4)	Reference		Reference		0.280		
	GDM	8 (0.5)	57 (0.6)	0.80 (0.36–1.80)	0.601	0.63 (0.27–1.46)				
25–29 (n = 3667)	No GDM	664 (96.8)	2944 (98.8)	Reference		Reference		0.053		
	GDM	22 (3.2)	37 (1.2)	2.39 (1.00–5.72)	0.050	2.56 (0.99–6.63)				
≥ 30 (n = 1472)	No GDM	389 (92.4)	998 (95.0)	Reference		Reference		0.725		
	GDM	32 (7.6)	53 (5.0)	1.00 (0.24–4.08)	1.000	0.76 (0.16–3.58)				
≥ 25 (n = 5139)	No GDM	1053 (95.1)	3942 (97.8)	Reference		Reference		0.002		
	GDM	54 (4.9)	90 (2.2)	2.23 (1.38–3.62)	0.001	2.39 (1.39–4.10)				
<b>Interaction</b>							0.013	0.006		
<b>P-value</b>										

\*Adjusted for chronic hypertension, parity, smoking, education level, ethnicity.

to 1997, when most of the pregnancies in this study occurred, the screening and diagnosis of GDM in Sweden was quite uniform (personal communication). Regional variation in screening methods and diagnostic criteria took place during the late 1990s, but this will be addressed by the matched structure of the sample and analysis. The screening strategies used in Sweden do not identify all women with GDM, which means there is undiagnosed GDM among both cases and controls. This could diminish the precision of an association, but probably not overestimate it.

Weaknesses of the study include that a proportion of the women could not be included in the analysis due to missing data, particularly for BMI. Registration of BMI in the SMBR started in the early 1990s and during the first years, when many of our pregnancies were identified, registration was poorer. As the associations of GDM with CVD were not notably different to the main results in the group with missing values, the exclusion of those with missing data should not introduce important selection bias. Weight and height are routinely recorded by a midwife, reducing the inaccuracies associated with self-reported height and weight. There were also few diagnoses of chronic hypertension, which made stratification by hypertension not possible.

The interval between diagnosis of GDM and first CVD event was relatively short and a longer interval would have increased the rate of women with CVD and strengthened the associations.

Identification of post-pregnancy diagnoses of diabetes is likely to be incomplete, as the registers available to us did not include diagnoses from primary care. As well as inpatient and outpatient diagnoses, the registers covered

prescriptions for diabetes during the later calendar period of the study. Hence, while more severe disease is more likely to have been identified, type 2 diabetes diagnosed in primary care and managed without prescribed pharmaceutical treatment is less likely to have been identified. It is therefore possible that the mediating role of post-pregnancy onset diabetes has been somewhat underestimated in the association of GDM with CVD.

### Interpretation

The main evidence before this research that GDM is a risk for subsequent CVD comes from two studies. Shah et al.<sup>6</sup> conducted a retrospective cohort study based on administrative data from Ontario Canada, and reported an unadjusted hazard ratio for GDM of 1.71 (95% CI 1.08–2.69). Further clinical information on the women during pregnancy was not reported. Compared with their study, our research has the strength that it was possible to adjust for multiple potential confounding factors during pregnancy, so demonstrating that GDM is a useful independent marker of subsequent CVD risk. We have also shown in this study that the combination of GDM with overweight or obesity represents a particularly raised risk for later CVD and this association remains significant even after adjustment for DM that developed after pregnancy. We could also identify characteristics that potentially modify the risk of GDM for CVD. Carr et al.<sup>5</sup> showed that in women with a family history of type 2 diabetes, previous GDM was associated with an increased prevalence of CVD. Their study, unlike ours, was limited by self-reported measures of GDM and CVD, potentially introducing recall and selection bias. In addition, the earlier study may have been rendered less precise as screen-

ing during pregnancy was not uniform. Which specific levels of hyperglycaemia are predictive of future CVD is not known. In this study we show an association for the specific diagnostic criteria used in Sweden. Whether similar associations exist for women with lower levels of hyperglycaemia, remains to be studied. The two earlier studies evaluating GDM as a risk for CVD<sup>5,6</sup> have provided valuable information, but we believe that this study adds further clinically relevant information. Our finding that women with GDM who are overweight are at particular risk for later severe CVD has not been shown previously, as earlier work identified an association with the less severe outcome of hypertension. GDM was rarer among the normal weight women reflecting the fact that the aetiology of GDM differs. The aetiology of GDM in overweight women may be more closely related to components of the metabolic syndrome,<sup>15</sup> while among normal weight women autoimmune and monogenic diseases are more frequently the causes.<sup>16,17</sup> Women with GDM have characteristics of hyperinsulinaemia and hyperlipidaemia with the metabolic syndrome, which is also a risk for future CVD. Hence the association between GDM and later CVD, especially among overweight women, is reasonable. GDM is predictive of CVD in the overweight group but not the obese group. One explanation for the apparently counterintuitive result among obese women is that the risk for CVD is already so much increased in obese women that GDM does not add to this baseline risk. A similar explanation may be applicable to the association of GDM with CVD among women who were smokers. This study and the study by Pirkola et al.<sup>7</sup> basically identified similar associations with BMI: the combination of GDM with overweight identifies a subgroup of women with underlying pathology or a greater predisposition to cardiovascular disease.

Smoking and hypertension are known risk factors for CVD<sup>18–20</sup> and the first recommendation for prevention of CVD is smoking cessation. The present study also confirms that smoking is a strong risk factor for CVD and that GDM and smoking do not have a multiplicative effect on total risk of CVD. The incidence of hypertension in pregnancy is increasing, probably due to increasing overweight among women,<sup>21</sup> and evaluation of the risk for CVD associated with the combination GDM and overweight might have given clinically valuable results. Unfortunately, there were too few women with chronic hypertension in our material for this analysis to produce meaningful results.

## Conclusion

If recognised risks for CVD such as smoking and obesity are not present, then GDM is a potentially useful marker of future cardiovascular disease risk among women with a BMI between 25 and 29 kg/m<sup>2</sup>. The risk increase in this

group is comparable in magnitude to the effects of smoking and obesity but lower than for chronic hypertension. Further studies are needed regarding the association of later CVD and degree of hyperglycaemia during pregnancy.

## Disclosure of interests

None to declare.

## Contribution to authorship

All authors (HF, AM, IÖ, SM, UH, ES) contributed to the design and conduct of the paper, critically reviewed manuscript details, and approved the final version.

## Details of ethics approval

The study was approved by the regional Ethics Committee in Uppsala, Sweden, Number 2009/027, date of approval 2009-03-11.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Odds ratios (95% confidence interval) for GDM as a risk factor for cardiovascular disease in smoking versus non-smoking women ■

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