Received: 29 January 2024 | Revised: 4 April 2024 | Accepted: 6 April 2024

DOI: 10.1111/dom.15612

WILEY

ORIGINAL ARTICLE

Association of gestational diabetes with long-term risk of premature mortality, and cardiovascular outcomes and risk factors: A retrospective cohort analysis in the UK Biobank

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Funding information
National Institute for Health and Care Research Applied Research Collaboration Oxford and Thames Valley; Oxford-MRC Doctoral Training Partnership; British Nutrition Foundation; NIHR Oxford Health Biomedical Research Centre; NIHR Oxford Biomedical Research Centre; Ministerio de Ciencia e Innovación, Grant/Award Numbers: RYC2020-028818-I, MCIN/AEI/10.13039/501100011033

Abstract

Aim: To investigate the association of gestational diabetes mellitus (GDM) with premature mortality and cardiovascular (CVD) outcomes and risk factors.

Materials and Methods: Parous women recruited to the UK Biobank cohort during 2006-2010 were followed up from their first delivery until 31 October 2021. The data were linked to Hospital Episode Statistics and mortality registries. Multivariate Cox proportional hazard models investigated associations of GDM with all-cause mortality, CVD, diabetes, hypertension and dyslipidaemia.

Results: The maximum total analysis time at risk and under observation was 9 694 090 person-years. Among 220 726 women, 1225 self-reported or had a recorded diagnosis of GDM. After adjusting for confounders and behavioural factors, GDM was associated with increased risk for premature mortality [hazard ratio (HR): 1.44, 95% confidence interval (CI): 1.12-1.86], particularly CVD-related death (HR: 2.38, 95% CI: 1.63-3.48), as well as incident total CVD (HR: 1.50, 95% CI: 1.30-1.74), non-fatal CVD (HR: 1.41, 95% CI: 1.20-1.65), diabetes (HR: 14.37, 95% CI: 13.51-15.27), hypertension (HR: 1.49, 95% CI: 1.38-1.60), and dyslipidaemia (HR: 1.30, 95% CI: 1.22-1.39). The total CVD risk was greater in women with GDM who did not later develop diabetes than in those with GDM and diabetes.

Conclusions: Women with GDM are at increased risk of premature death and have increased CV risk, emphasizing the importance of interventions to prevent GDM. If GDM develops, the diagnosis represents an opportunity for future surveillance and intervention to reduce CVD risk factors, prevent CVD and improve long-term health.

KEYWORDS
cardiovascular disease, cohort study, diabetes complications, observational study

1 | INTRODUCTION

The incidence of gestational diabetes mellitus (GDM), a form of diabetes that develops or is first recognized during pregnancy, is increasing globally, with >17 million live births in women of reproductive age being affected annually.[1] Although GDM usually resolves after giving birth, it increases the lifetime risk for future type 2 diabetes in the mother by up to 70%.[2–5] In recent years, large population-based cohort studies have also shown that GDM is a risk factor for overall and type-specific cardiovascular disease (CVD),[6,7] and there is limited evidence of association with hypertension[8] and dyslipidaemia.[9] However, most observational studies on the relationship between GDM and future maternal outcomes have been limited by relatively short periods of follow-up (10-25 years postpartum) and by insufficient adjustment of analyses for covariates.[8–12] There is also limited evidence regarding associations between GDM and long-term premature mortality,[13–15] with only a couple of studies focusing on death from any cause.[13,15] In this study, we aimed to use data from the UK Biobank cohort, an older population with ongoing follow-up, to explore the long-term health outcomes for women with a history of GDM by investigating its association with premature all-cause mortality, CVD outcomes and traditional CVD risk factors, including future diabetes, hypertension and dyslipidaemia.

2 | MATERIALS AND METHODS

2.1 | Study design

The UK Biobank is a large-scale prospective cohort study that recruited 502 536 UK participants aged 40-69 years, between 2006 and 2010. Participants self-reported most information about themselves through self-completed touchscreen questionnaires and nurse-led verbal interviews, including information on sociodemographic factors, medical history and health behaviours. Participants also had physical assessments where blood pressure, height and weight were measured, and blood, saliva and urine samples were collected for analysis. These assessments were repeated after a year or two in a representative sample of individuals to correct for random measurement error and for short-term variability in risk factors. To account for the potential dilution effects of risk factors on health outcomes over the course of decades and to allow for the effects of longer-term within-person variability, the UK Biobank has been inviting a sample of the cohort to repeat the assessments every 2-3 years. Participants' research data collected as part of the UK Biobank cohort are linked to Hospital Episodic Statistics (HES)[16] and death records from the Office for National Statistics. Full details about the UK Biobank study and protocols are openly available (http://www.ukbiobank.ac.uk/wpcontent/uploads/2011/11/UK-Biobank-Protocol.pdf).

The UK Biobank study was conducted according to the Declaration of Helsinki, and ethical approval was granted by the Northwest Multi-centre Research Ethics Committee (reference number 06/MRE08/65). At recruitment, all participants gave informed consent to participate and be followed up through data linkage.

2.2 | Procedures

We obtained data for analysis from all self-reported and measured data during the UK Biobank assessment centres, the linked HES (main inpatient information, diagnoses, operations) and the Office for National Statistics death records to maximize the information we could analyse.

2.3 | Population

Eligible participants were women with at least one birth (live or not), determined by a self-reported touchscreen questionnaire (live births only) or the presence of at least one delivery episode recorded in the linked HES data (both live and non-live births). From these women, we excluded those with pre-pregnancy diabetes, determined from self-reported and/or HES data. We determined the entry point for all women (i.e. time point of becoming 'at risk'), regardless of whether and when they had GDM, as the age when they had their first delivery, using the youngest age available from self-reports in the touchscreen questionnaire and HES data. All eligible women were followed up until the earliest occurrence of an outcome of interest, death from any cause, or the latest collection of data. For analysis of total and non-fatal CVD, diabetes, hypertension and dyslipidaemia, we also excluded participants for whom these occurred at an age younger or equal to maternal age at first delivery to ensure that the remaining were incident postpartum cases.

2.4 | Exposure

Women who had GDM in any pregnancy comprised the exposed group. The occurrence of GDM was defined as any of the following:

- Reporting diabetes that occurred only during pregnancy in the UK Biobank touchscreen questionnaire.
- Reporting GDM in the verbal interviews.
- Presence of ICD-10 (International Classification of Diseases, 10th version) code O24.4 (diabetes mellitus arising in pregnancy) or O24.9 (unspecified diabetes in pregnancy) in the linked HES.

2.4.1 | Comparator

Women who did not have a diagnosis of GDM as defined above comprised the comparator group.

2.4.2 | Outcomes

The primary outcome of interest was premature all-cause mortality. Secondary outcomes were the incidence of total CVD, non-fatal CVD, CVD death, diabetes, hypertension and dyslipidaemia. All outcomes

were defined as primary or secondary events by combining data from self-reports, HES and the death registry, where applicable, linked to the UK Biobank (Appendix Table S1).

2.4.3 | Covariates

We created directed acyclic graphs for the associations between GDM and each outcome to determine which covariates to include in the analysis. Covariates were selected from ethnicity (White, Black, Asian and all others), Townsend index of deprivation (a composite measure of deprivation based on unemployment, non-car ownership, non-home ownership and household overcrowding, categorized in quintiles 1-5, with higher scores indicating more deprivation),[17] education group (higher degree, any school degree or vocational qualification, unknown), family history of CVD, diabetes, hypertension (yes, no and unknown), body mass index (BMI) group (<18.5, 18.5-24.9, 25-29.9, 30-34.9 and ≥35 kg/m^2), health behaviours including smoking status (never, current, previous and unknown), physical activity [meeting recommendations (≥150 min of moderate-intensity activity and/or ≥75 min of vigorous activity per week), not meeting recommendations and unknown], fruit and vegetable consumption (meeting five portions a day, not meeting five portions a day, and unknown), saturated fat intake (none, low, moderate, high and unknown) and alcohol consumption (none, occasional, moderate, heavy and unknown), and pregnancy-related factors including gestational hypertension/pre-eclampsia (yes, no), menopause (yes, no and unknown) and self-reported number of live births as a proxy for parity (touchscreen questionnaire only, because HES data were very limited). Although enrolment into the UK Biobank happened several years after the date of entry into the analysis (first delivery), covariates collected or referring to a time point after enrolment, such as BMI or behavioural factors, were included in the analysis because there is evidence that they may influence the outcomes of interest and may explain some of the residual confounding.[18–22] Details on the identification and derivation of covariates are in Appendix Table S2. Pharmacotherapy, including blood glucose-, blood pressure-, and cholesterol-lowering medication, could also affect the outcomes of all-cause mortality and CVD. However, medication use was recorded at the time of enrolment to the UK Biobank for all participants, and only for a subsample in the years after enrolment. As medications could have changed throughout the years, we did not include medication use in the main analysis of these two outcomes, but we conducted sensitivity analyses taking into account reported medication use from all time points combined (see Section 2.5.2).

2.5 | Statistical analysis

2.5.1 | Participant characteristics

Participant characteristics were analysed using descriptive statistics. We report the mean and SD for normally distributed continuous variables, and for non-normally distributed variables, we also provide the median and interquartile range. We used proportions to report categorical variables. As the collection of data for the UK Biobank happened after enrolment in the study, typically several years after most women had first given birth, most of these characteristics do not correspond to the exposure time point (which we defined as the time point of first delivery), but to the time at which they enrolled in the UK Biobank (2006-2010). Missing data in categorical variables were coded as 'unknown' and entered as a separate category, with the exception for gestational hypertension/pre-eclampsia, where missing data were assumed to mean no occurrence of the condition.

2.5.2 | Associations between gestational diabetes mellitus and outcomes

Multivariate Cox proportional hazard models with age (years) as the underlying time covariate were used to estimate hazard ratios (HR) for having had a history of GDM compared with no history of GDM. We created nested models by sequentially adjusting for sociodemographics, family history of CVD, diabetes, hypertension (each where relevant), BMI, behavioural factors and pregnancy-related factors (each where relevant). The proportional hazards assumption using Schoenfeld residuals' plots for the exposure was not violated. Person-time follow-up was calculated from the age at first delivery for all participants (considered as the age of becoming 'at risk'), until the age at which the outcome occurred, or death from any cause for other than mortality outcomes, whichever happened first (latest available data on 30 September 2021 for England and Wales, and 31 October 2021 for Scotland), or the end of data collection (censoring) (30 September 2021 for England, 31 July 2021 for Scotland, and 28 February 2018 for Wales). For women who developed CVD, diabetes, hypertension or dyslipidaemia, we used the age of interview or questionnaire completion as the age of occurrence, if there was no age specified at which it occurred and no hospital record.

As data collection happened when participants were older, outcomes may have occurred before enrolment in the study, and data on covariates may refer to a time point after outcome occurrence, which can bias the results. We therefore conducted sensitivity analyses, excluding participants who developed CVD, diabetes, hypertension and dyslipidaemia after pregnancy but before enrolment in the UK Biobank, to explore whether it affected the effect estimates. We also conducted sensitivity analyses for the outcomes of all-cause mortality and CVD, where we added into the main model the use of either blood glucose-, blood pressure-, or cholesterol-lowering medication, as reported from all available time points combined.

We fitted multiplicative interaction terms in the fully adjusted model to examine heterogeneity in the association of GDM with mortality and total CVD by the development of incident CVD (relevant to all-cause mortality outcome only), diabetes, hypertension, dyslipidaemia, and by age group, self-reported ethnicity and BMI group. We calculated likelihood ratios to determine p values for heterogeneity without correction for multiple testing.

All analyses were conducted using Stata (version 16; StataCorp LP). A two-sided p value of <.05 was defined as statistically significant.

3 | RESULTS

3.1 | Participant characteristics

From the UK Biobank sample of 502 536 participants, 220 726 women comprised the eligible cohort (Figure 1). Women gave their first birth on average in their mid-to-late twenties; the majority were of White ethnic background (94.4%) and had a median (interquartile range) BMI of 26.2 (6.2) kg/m^2. A greater proportion of women with GDM tended to be from areas of greater socio-economic deprivation than women without GDM. More women with GDM tended to report a family history of diabetes than women without GDM, but a lower proportion reported a family history of CVD. Women with GDM also had greater prevalence rates of obesity and gestational hypertension/pre-eclampsia, but fewer had reached menopause than women without GDM. More women with GDM reported never having smoked, but fewer of them reported meeting physical activity recommendations than non-GDM women. Although heavy alcohol intake was less common in women with GDM than women without GDM, most women with GDM had not reported alcohol consumption (Table 1).

3.1.1 | Follow-up time

The earliest entry time point of becoming 'at risk' (earliest pregnancy/delivery) was 12 years of age, and the latest observed exit was 85 years of age. A total analysis time at risk and under observation of 9 694 090 person-years for the mortality outcome, 9 383 184 person-years for total CVD, 9 274 950 person-years for diabetes, 7 835 099 person-years for hypertension and 7 175 289 person-years for dyslipidaemia. In total, 12 439 participants died during follow-up. Of these, 3292 were deaths from CVD (Table 1). There were more new cases of CVD, diabetes, hypertension and dyslipidaemia per 1000 person-years in women with GDM compared with those without GDM (Table 1).

3.1.2 | Associations between gestational diabetes mellitus and outcomes

GDM was associated with an increased risk for all-cause mortality [HR: 1.44, 95% confidence interval (CI): 1.12-1.86] and more than twice the risk of a CVD-related death (HR: 2.38, 95% CI: 1.63-3.48), as well as increased risk for incident total CVD (HR: 1.50, 95% CI: 1.30-1.74) and non-fatal CVD (HR: 1.41, 95% CI: 1.20-1.65) in the fully adjusted models (Figure 2). Stepwise models are presented in Appendix Table S3. Sensitivity analysis excluding participants who developed CVD after pregnancy but before recruitment in the UK Biobank (n = 8895) did not change the effect of GDM on total CVD

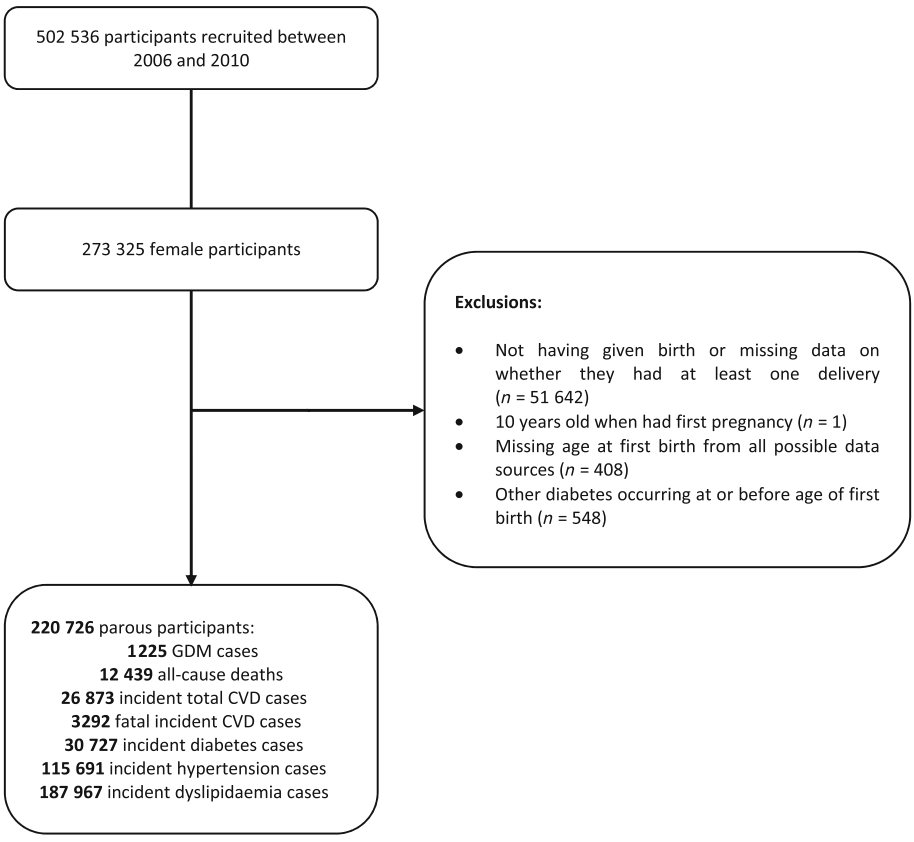

FIGURE 1 Participant flowchart. CVD, cardiovascular disease; GDM, gestational diabetes.

TABLE 1 Characteristics of participants with and without history of gestational diabetes in the UK Biobank.

Characteristics	Total (N = 220 726)	GDM (n = 1225)	No GDM (n = 219 501)	GDM vs. no GDM *p*-value
Demographics				
Age at first birth, years				
Mean ± SD	25.9 ± 5.2	27.7 ± 6.2	25.9 ± 5.1	<.001[a]
Median (IQR)	25.0 (7.0)	27.0 (9.0)	25.0 (7.0)	
Ethnicity, %				<.001[b]
White	94.4	82.1	94.5	
Black	1.7	4.0	1.7	
Asian	2.1	9.0	2.0	
Other (mixed, other and unknown)	1.8	4.9	1.8	
Socio-economic status				
Townsend index (quintiles), %				<.001[b]
Q1	19.9	17.7	20.0	
Q3	20.0	18.3	20.0	
Q5	20.0	28.3	19.9	
Unknown	0.1	0.3	0.1	
Education group, %				.01[b]
Any school or vocational qualification (A level, AS level, O level, GCSE, CSE, NVQ, HND and HNC)	36.0	35.8	35.9	
Higher degree (college, university, or professional degree/qualification)	44.0	47.3	44.0	
Unknown	20.0	16.9	20.1	
Family history, %				
CVD	62.5	57.9	62.5	.003[b]
Diabetes	20.2	42.5	20.0	<.001[b]
Hypertension	41.4	40.3	41.4	.943[b]
Physical factors and medical conditions				
BMI, kg/m^2				
Mean ± SD	27.1 ± 5.1	29.2 ± 6.0	27.1 ± 5.1	<.001[a]
Median (IQR)	26.2 (6.2)	28.1 (7.7)	26.2 (6.2)	
BMI group, %				
Underweight, <18.5	0.7	0.3	0.7	
Healthy weight, 18.5 to <25	37.7	24.8	37.7	
Overweight, 25 to <30	37.6	36.7	37.6	<.001[b]
Obese I, 30 to <35	15.9	21.7	16.0	
Obese II and III, >35	7.7	15.8	7.7	
Unknown	0.4	0.7	0.4	
Gestational hypertension/pre-eclampsia, %	1.1	4.1	1.1	<.001[b]
Menopausal status, %				
Yes	65.1	44.7	65.3	<.001[b]
Unknown	0.1	0.4	0.1	
Live births				<.001[a]
Mean ± SD	2 ± 1	3 ± 1	2 ± 1	
Median (IQR)	2 (1)	2 (1)	2 (1)	
Incident diabetes				
%	13.9	90.8	13.5	<.001[b]
Mean (range) years after first birth	33 (1-64)	23 (1-57)	33 (1-64)	<.001[a]

(Continues)

TABLE 1 (Continued)

Characteristics	Total (N = 220 726)	GDM (n = 1225)	No GDM (n = 219 501)	GDM vs. no GDM *p*-value
Incidence rate per 1000 person-years	3.3	38.4	3.2	<.001
% Blood glucose medication	0.7	23.0	2.4	<.001[b]
Incident hypertension				
%	52.4	55.4	52.4	.001[b]
Mean (range) years after first birth	32 (1-67)	26 (1-58)	33 (1-67)	<.001[a]
Incidence rate per 1000 person-years	14.8	20.6	14.7	<.001
% Blood pressure medication	40.9	30.4	22.0	.001[b]
Incident dyslipidaemia				
%	85.1	81.4	85.2	.001[b]
Mean (range) years after first birth	31 (1-67)	25 (1-59)	31 (1-67)	<.001[a]
Incidence rate per 1000 person-years	26.2	31.1	26.2	<.001
% Cholesterol medication	14.4	29.8	14.8	.001[b]
Incident CVD				
% Total CVD	12.2	14.8	12.2	.005[b]
Mean (range) years after first birth	39 (1-65)	33 (1-63)	39 (1-65)	<.001[a]
Incidence rate per 1000 person-years	2.9	4.2	2.9	<.001
% Fatal CVD	1.5	2.2	1.5	.039[b]
Mean (range) years after first birth	48 (14-65)	47 (29-59)	48 (14-65)	<.813[a]
Incidence rate per 1000 person-years	0.3	0.6	0.3	.007
% Blood glucose, blood pressure, or cholesterol medication	55.9	73.1	55.8	.001[b]
All-cause mortality				
%	5.6	5	5.6	.318[b]
Mean (range) years after first birth	46 (4-65)	44 (9-61)	46 (4-65)	<.07[a]
Incidence rate per 1000 person-years	1.2	1.3	1.2	.734
Health behaviours				
Smoking, %				.006[b]
Never	59.2	63.7	59.2	
Previous	31.9	27.4	32.0	
Current	8.5	8.4	8.5	
Unknown	0.4	0.5	0.4	
Physical activity, %				<.001[b]
Not meeting recommendations	48.2	54.6	48.1	
Meeting recommendations	47.8	41.5	47.9	
Unknown	4.0	3.9	4.0	
Dietary intake, %				.068[b]
Fruit and vegetables	64.7	65.9	64.7	
Not meeting recommendations	35.1	33.8	35.2	
Meeting recommendations unknown	0.1	0.3	0.1	
Saturated fat intake group				
None				
Low, <1 day/week	0.2	0.1	0.2	
Moderate, 1-4 days/week	47.2	48.5	47.2	
High, ≥5 days/week	22.0	20.9	22.0	.336[b]
Unknown	30.6	30.4	30.6	

TABLE 1 (Continued)

Characteristics	Total (N = 220 726)	GDM (n = 1225)	No GDM (n = 219 501)	GDM vs. no GDM *p*-value
Alcohol group	0.0	0.1	0.0	
Occasional, <1 unit/week	7.0	10.8	7.0	<.001[b]
Moderate, 1-14 units/week	37.4	30.9	37.4	
Heavy, >14 units/week	29.5	22.3	29.6	
Unknown	26.1	36.0	26.0	

Note: Time point at which each of these data refer to, are detailed in Appendix Table S1, because some data were collected only at enrolment, while other data were collected with repeated assessments at different time points, which we combined (e.g. taking the average among time points of assessment), or sometimes we needed to only use the data from the most recent assessment time point. The use of blood glucose, blood pressure and cholesterol-lowering medication was considered present if reported in at least one time point.

Abbreviations: A level, advanced level; AS level, advanced subsidiary level; BMI, body mass index; CSE, certificate of secondary education; CVD, cardiovascular disease; GCSE, general certificate of secondary education; GDM, gestational diabetes mellitus; HNC, higher national certificate; HND, higher national diploma; IQR, interquartile range; NVQ, national vocational qualification; O level, ordinary level; Q1/Q2/Q3, quintiles; SD, standard deviation.

[a]Two-sample t-test.

[b]Pearson's chi-squared test.

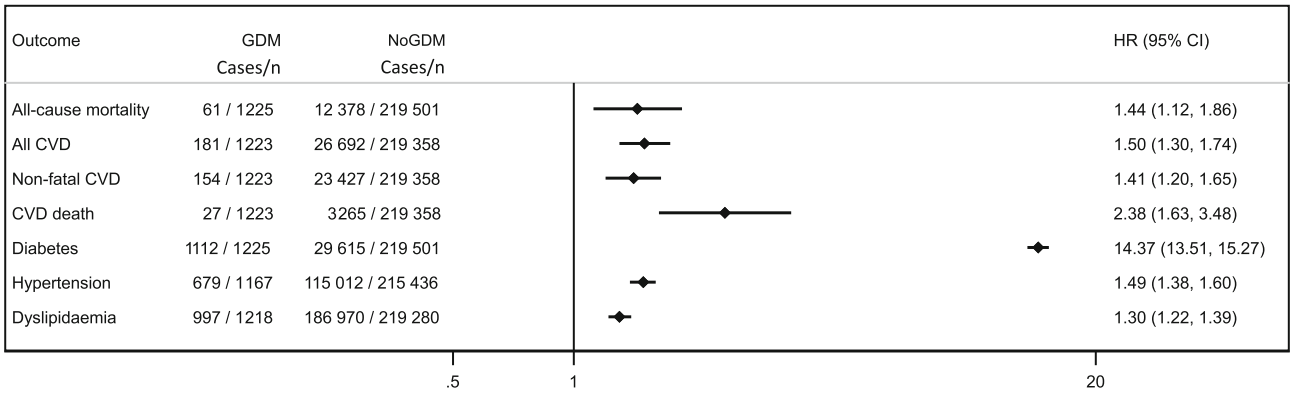

FIGURE 2 HRs (95% CIs) for the associations between gestational diabetes and premature all-cause mortality, incident cardiovascular disease (CVD), diabetes, hypertension and dyslipidaemia, in the fully adjusted models. n, number of participants with and without GDM. Model for all-cause mortality and incident CVD, adjusted for age, sociodemographics, family history of CVD, diabetes and hypertension, body mass index (BMI), health behaviours and all pregnancy-related factors. Model for incident diabetes, adjusted for age, sociodemographics, family history of diabetes, BMI, health behaviours and number of live births. Model for incident hypertension, adjusted for age, sociodemographics, family history of diabetes and hypertension, BMI, health behaviours and all-pregnancy-related factors. Model for incident dyslipidaemia, adjusted for age, sociodemographics, family history of diabetes, BMI, health behaviours, number of live births and menopause. CI, confidence interval; HR, hazard ratio.

(HR: 1.50, 95% CI: 1.24-1.82). GDM was also associated with the future development of diabetes (HR: 14.37, 95% CI: 13.51-15.27), hypertension (HR: 1.49, 95% CI: 1.38-1.60) and dyslipidaemia (HR: 1.30, 95% CI: 1.22-1.39) (Figure 2). After excluding participants who developed each of these risk factors after pregnancy but before enrolment in the UK Biobank in the sensitivity analyses, the risk of developing diabetes increased (HR: 19.91, 95% CI: 18.52-21.40), and the absolute risk decreased for hypertension and dyslipidaemia but remained significant (HR: 1.39, 95% CI: 1.24-1.55; and HR: 1.20, 95% CI: 1.1.2-1.29, respectively). After adding the use of either blood glucose-, blood pressure-, or cholesterol-lowering medication to the fully adjusted model for the outcomes of all-cause mortality and CVD, effect estimates were attenuated but remained significant (Appendix Table S4).

There were no significant interactions in the association of GDM with all-cause mortality (Appendix Figure S1). A significantly higher risk of total CVD was observed among women with GDM who did not develop diabetes later in life (HR: 5.74, 95% CI: 4.39-7.50), compared with women with GDM who also developed diabetes (HR: 1.41, 95% CI: 1.17-1.69) ($p < .0001$, Appendix Figure S2).

4 | DISCUSSION

Among parous women in the UK Biobank study, during a long-term follow-up, those who developed GDM had a significantly greater risk of premature all-cause mortality, including CVD-related death, compared with their peers with no history of GDM. The risk of incident

total and non-fatal CVD and common CVD risk factors (diabetes, hypertension and dyslipidaemia), was also significantly increased in women with a history of GDM compared with those without GDM.

The strengths of this study include the long-term follow-up time, which, apart from the risk of incident CVD, also quantified the less well-documented risk of premature mortality following GDM. The UK Biobank dataset also enabled us to adjust for a variety of demographic, socio-economic, anthropometric and behavioural factors, and to ascertain outcomes from a variety of sources (both self-reported and HES data). The study also has several limitations. First, the prevalence of GDM in this cohort was less than 1%, while the current expected prevalence in the UK is about 16%.[23] This is probably because the majority of women in this cohort were pregnant before the late 1990s, when women would be tested for GDM only if there was clinical indication from their medical history and assessment, and arbitrary diagnostic criteria were used by different clinics.[24] This may have resulted in exposure misclassification, underestimation of the prevalence of GDM, and possibly underestimation of the impact of GDM on outcomes. The results of interaction analyses should also be interpreted with caution. The number of women with GDM analysed in interaction analyses, and the number of cases in each condition, age, or BMI category, was small, which led to lower statistical power and may have compromised the accuracy of the HRs. Secondly, monitoring and pharmacotherapy for conditions such as diabetes, hypertension, or dyslipidaemia, could affect the risk of CVD. However, medication use for these conditions was collected mainly at enrolment into the UK Biobank and only from a subsample of participants in the years after enrolment. As such, it is probable that medication changed throughout the decades, which meant that we could not adjust our primary analyses for it. Sensitivity analyses for all-cause mortality and CVD, where we adjusted for reported blood glucose-, blood pressure-, or cholesterol-lowering medication use, combining information from all time points available, led to attenuated effect estimates but showed that GDM still significantly affected these outcomes. Thirdly, not having licensed access to primary care records and our inability to infer from the available data sources the pregnancies affected by GDM may have biased the time to event analyses. Fourthly, we did not have available data on pre-pregnancy BMI, which is a major confounder, and instead adjusted for BMI later in life. However, there is evidence that a history of GDM might be a CVD risk marker independent of pre-pregnancy obesity.[25] Fifthly, we cannot exclude the possibility of reverse causation affecting the results; however, the average length of time between first delivery and each outcome was many years, and we excluded cases with the outcome of interest happening before the first birth. Finally, the results of this study may not be necessarily generalizable because participants in the UK Biobank have lower rates of obesity, would not probably smoke and drink alcohol, and would not probably live in deprivation.[26]

To our knowledge, two other studies have investigated the longitudinal association of GDM with premature all-cause mortality.[13,15] In a diverse prospective cohort of 48 197 participants from 12 US clinical centres, GDM or impaired glucose tolerance during pregnancy, was associated with a 14% greater risk of all-cause mortality.[13] A recent analysis of 91 426 women from the Nurses' Health Study (NHS) II, with 2 609 753 person-years of follow-up (>30 years of follow-up data), also showed that participants with a history of GDM were at significantly higher risk of subsequent all-cause mortality (HR: 1.28, 95% CI: 1.13-1.44), compared with those who did not develop GDM, even in the absence of developing type 2 diabetes postpartum. Furthermore, the authors reported that the risk was higher in participants who had GDM in two or more pregnancies and in those who reported concurrent chronic diseases and other adverse pregnancy or birth outcomes.[15] In the current cohort, we found that GDM was associated with a 44% increased risk for premature mortality, after adjustment for potential confounders and behavioural factors.

Likewise, a recent analysis of the UK Biobank study showed a smaller increase in the risk of total CVD (HR: 1.36, 95% CI: 1.18-1.55), partly mediated by the subsequent development of diabetes, hypertension and dyslipidaemia.[12] However, their analysis included women who developed GDM before enrolment into the UK Biobank, while we included women if they ever had GDM, thus also including women who developed GDM at an older age after enrolment. In the main analysis, they used as the index date the time point of enrolment, whereas we went back in time when participants became at risk (first pregnancy/delivery), which resulted in a longer follow-up period. Only in a secondary analysis, the authors reported the longer-term risk for CVD for a subsample of participants for whom age at pregnancy affected by GDM for cases was known and reported a two-fold increased risk of developing total CVD, but it is unclear how the age of the GDM-affected pregnancy was determined, given the very limited information of this in the UK Biobank verbal interviews or HES.

Women who develop GDM would also probably display a cluster of common CVD risk factors, although it remains unclear if these actually develop postpartum or if they pre-exist and are opportunistically identified after GDM diagnosis.[27,28] Our findings are consistent with previous cohort studies showing an association between GDM and diabetes, hypertension and dyslipidaemia postpartum.[8,10,29] We found that the impact of GDM on CVD risk was much higher in women with GDM who did not later develop diabetes, compared with women with GDM with a later diabetes diagnosis. It is plausible that the impact of GDM on CVD risk is particularly increased in women with a more favourable metabolic phenotype,[6,7] because once women have developed diabetes later in life, the risk conferred by the diabetes may supersede that conferred by GDM. Alternatively, the difference in CVD risk between women with GDM who later developed diabetes and women with GDM who did not progress to diabetes may be because the former may have had better monitoring and may have used blood glucose-lowering medications, which would partly lower their chances of developing CVD. The lack of significance in other interactions may be explained by the small prevalence of GDM in this cohort, but in their totality, interaction analyses suggested that all women with GDM are at increased risk for premature death and CVD, regardless of whether or not they develop chronic diseases postpartum and regardless of their demographics and BMI.

From the above, we gather that the considerable association of GDM with mortality emphasizes the importance of interventions for the primary prevention of GDM to improve women's long-term health

outcomes. Such interventions would offer potential opportunities to also help control risk factors for later CVD. In addition, once GDM has developed, there is limited clinical recognition of it as a pre-CVD state. Although current guidelines recommend postpartum screening for type 2 diabetes,[30–34] screening and monitoring for CVD are not part of clinical guidelines for the postpartum management of women with GDM.[30–34] A diagnosis of GDM should be considered an opportunity in routine care to inform women about their increased CVD risk, as well as to offer monitoring and treatment of CVD risk factors at an early point in women's lives, when risk modification may have more chances of helping to prevent CVD and improve long-term outcomes. There are some postpartum recommendations for offering advice on weight, diet and exercise either to all women diagnosed with GDM[30,33] or only to those found to have hyperglycaemia during postpartum screening,[31] but recommendations for postpartum monitoring and treatment of other established CVD risk factors such as hypertension and dyslipidaemia in these women should also be considered to reduce the risk of future CVD.

In conclusion, in this UK cohort study, GDM was shown to be associated with an increased risk of premature mortality, CVD, diabetes, hypertension and dyslipidaemia, emphasizing the importance of primary prevention of GDM to improve women's long-term health, as well as offering risk factor monitoring and interventions after a pregnancy affected by GDM to help prevent CVD.

ACKNOWLEDGMENTS

This research was conducted using the UK Biobank resource under application number 14990. CP received a British Nutrition Foundation pump-priming award that paid for the access to the data. CP is currently funded by a grant RYC2020-028818-I, MCIN/AEI/10.13039/501100011033 and 'ESF Investing in your future' (Ministry of Science and Innovation, Spain). During the analysis of this study, MM was funded by the National Institute for Health and Care Research (NIHR) Oxford Biomedical Research Centre and Oxford-Medical Research Centre (MRC) Doctoral Training Partnership, and is currently funded by the NIHR Applied Research Collaboration Oxford and Thames Valley. NMA and SAJ are funded by the NIHR Oxford Biomedical Research Centre. MG is funded by the NIHR Oxford Health Biomedical Research Centre. The funders had no role in designing the study, the analysis, or the decision to submit the paper. The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15612.

DATA AVAILABILITY STATEMENT

Researchers can apply to use the UK Biobank resource at http://www.ukbiobank.ac.uk/register-apply and access the data used. The code for this analysis can be available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Michalopoulou M, Piernas C, Jebb SA, Gao M, Astbury NM. Association of gestational diabetes with long-term risk of premature mortality, and cardiovascular outcomes and risk factors: A retrospective cohort analysis in the UK Biobank. *Diabetes Obes Metab*. 2024;26(7):2915-2924. doi:10.1111/dom.15612