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Association of spontaneous abortion and lifestyle with diabetes mellitus in women: a cross-sectional study in UK Biobank

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Abstract

Background Spontaneous abortion has been associated with higher risk of type 2 diabetes mellitus (T2DM) and gestational diabetes mellitus (GDM), while the evidence remains equivocal. This study aimed to examine the association between spontaneous abortion and the risk of T2DM and GDM, and assesses whether lifestyle factors modified this association.

Methods This cross-sectional study used data from the UK Biobank, recruiting 170 599 ever-pregnant women from 22 assessment centers in England, Scotland, and Wales between 2006 and 2010. History of spontaneous abortion was self-reported and was confirmed by using medical records, categorized as none, 1, 2, or ≥3 spontaneous abortions. The primary outcomes, T2DM and GDM, were ascertained from medical records using ICD-10 codes. Multivariable logistic regression was performed to estimate the adjusted odds ratios (ORs) and 95% confidence intervals (CIs), adjusting for sociodemographic and health factors (e.g., age, ethnicity, cancer, chronic hypertension), reproductive factors (e.g., use of oral contraceptives, use of hormone treatment, hypertensive disorders of pregnancy), and lifestyle score. The lifestyle score was constructed based on smoking status, alcohol intake, physical activity, television viewing time, sleep duration, and diet quality. Effect modification by lifestyle score was assessed using multiplicative interaction terms in the regression models.

Results Among 170 599 ever-pregnant women (mean [SD] age, 56.4 [8.0] years), a history of spontaneous abortion was associated with higher odds of T2DM (OR 1.17, 95% CI 1.10–1.24) and GDM (OR 1.38, 95% CI 1.20–1.60). The odds were higher for recurrent spontaneous abortions (for T2DM: ORs were 1.33 [95% CI 1.14–1.56] for three or more spontaneous abortions, 1.07 [95% CI 0.93–1.23] for two, and 1.09 [95% CI 1.01–1.17] for one compared with none; for GDM: the corresponding ORs were 2.01 [95% CI 1.48–2.71], 1.21 [95% CI 0.90–1.64], and 1.20 [95% CI 1.01–1.42], respectively). The odds of T2DM and GDM higher with less healthy lifestyle behaviors in both categories of spontaneous abortion, although no significant interactions between spontaneous abortion and lifestyle score were observed ($P_{\text{-interaction}}$>0.05).

Conclusions Spontaneous abortion was associated with higher odds of T2DM and GDM, with a stronger association observed in women who experienced recurrent spontaneous abortions. It is imperative to integrate reproductive history into routine diabetes risk assessment, particularly for women with a history of multiple spontaneous abortions.

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Keywords Spontaneous abortion, Type 2 diabetes mellitus, Gestational diabetes mellitus, Lifestyle, Cross-sectional study

Introduction

Spontaneous abortion or miscarriage, the loss of a pregnancy before viability, is a significant global health issue with profound implications for women's health. Globally, it is estimated that 10–20% of all clinically recognized pregnancies end in miscarriage [1, 2], with prevalence reported in the United Kingdom (UK) being substantially higher. According to the National Health Service, approximately 1 in 4 pregnancies ends in miscarriage, equivalent to around 250 000 miscarriages annually in the UK [3]. Despite its frequency, the long-term health consequences of miscarriage, particularly its potential role in predisposing women to type 2 diabetes mellitus (T2DM, non-gestational DM) and gestational diabetes mellitus (GDM), remain somewhat equivocal [4–6].

The increasing prevalence of diabetes, which now affects over 537 million adults worldwide, has become one of the most pressing public health challenges [7]. Emerging evidence suggests that women who experience spontaneous abortion may be at an increased risk of T2DM and GDM later in life [4, 5]. For example, a retrospective cohort study of 102 259 pregnant women in China found that those with a history of spontaneous abortion was associated with a higher risk of GDM in subsequent pregnancies [8]. However, a recent meta-analysis showed that there was no significant association between a history of abortion and the risk of GDM [6]. These differences may be due to the variations in study design, population characteristics, or unmeasured confounding factors, highlighting the need for further study to clarify the association between spontaneous abortion and the risk of diabetes, particularly given the intersection of these two global health burdens.

Lifestyle factors, including diet, physical activity, smoking, and COVID-19 are well-established contributors to the development and progression of T2DM and GDM [9–12]. The World Health Organization has identified unhealthy lifestyle as one of the primary drivers of the global diabetes epidemic [13]. A large-scale meta-analysis involving 1 693 753 participants demonstrated that healthy lifestyle behaviors—such as regular physical activity, a balanced diet, and avoidance of tobacco use—can reduce the risk of developing T2DM by up to 80% [14]. However, the effect of lifestyle interventions on women with a history of spontaneous abortion, particularly in relation to their risks of T2DM or GDM, remains poorly understood.

Using data from the UK Biobank, we aimed to investigate the association between spontaneous abortion and the risk of both T2DM and GDM. Additionally, we aimed to explore the modifying effect of lifestyle factors on this association. By addressing these gaps, our study provides insights that could inform the development of targeted preventive strategies for women with a spontaneous abortion, and highlights opportunities for targeted preventive strategies to reduce the global burden of diabetes.

Material and methods

Study design and participants

This cross-sectional study was conducted using data from the UK Biobank (UKB), a large, population-based cohort study that recruited over 500 000 participants aged 39–71 years across the UK between 2006 and 2010. Participants were drawn from 22 assessment centers located in England, Scotland, and Wales, ensuring a broad geographic representation of the UK population. Participants were invited to join the study through mailed invitations sent to individuals registered with the National Health Service, and those who consented to participate attended one of the assessment centers where they completed a series of baseline assessments. These assessments included detailed questionnaires on medical history, lifestyle behaviors (such as diet, physical activity, smoking, and alcohol consumption), and socioeconomic factors. Additionally, physical measurements (e.g., height, weight, blood pressure) were taken, and biological samples (including blood, urine, and saliva) were collected. This study was approved by the UK North West Multicentre Research Ethics Committee (11/NW/0382), and all participants provided informed consent in line with the principles of the Declaration of Helsinki.

For this study, we initially included a total of 231 772 ever-pregnant women from UKB cohort. We then excluded women with missing (n=4029) or inconsistent data (n=239, 0.1%) on the number of spontaneous abortions, those missing data on lifestyle factors (n=56 432), and those without a diagnosis of type 2 diabetes mellitus (T2DM) or gestational diabetes mellitus (GDM) (n=473). Finally, 170 559 pregnant women were included in these analyses (Figure 1).

Exposure assessment

The exposure of interest in this study was spontaneous abortion, identified through a combination of self-reported data and medical records. At enrollment,

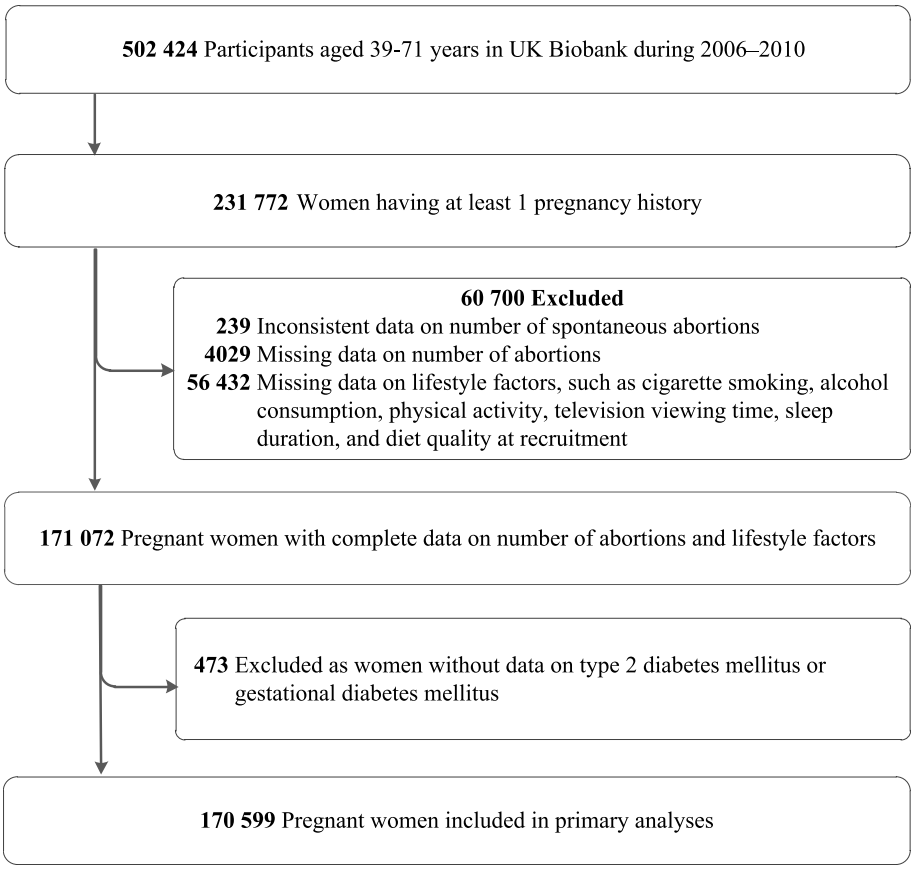

Fig 1. Flow chart of participants selection.

participants provided information through self-report via a touchscreen questionnaire or a verbal interview, answering two key questions: "Have you ever had any stillbirths, spontaneous miscarriages or terminations?", and "How many spontaneous miscarriages?" To enhance the accuracy of classification, self-reported spontaneous abortions were validated using International Classification of Diseases, tenth version (ICD-10) code O03 (date of spontaneous abortion) from medical records. Only participants who reported a date of spontaneous abortion in their medical records were classified as having a history of spontaneous abortion.

Outcome ascertainment

The primary outcomes of interest in this study were T2DM, also known as non-insulin-dependent DM, and GDM. T2DM was primarily identified using the ICD-10 code E11, which refers to the first recorded instance of non-insulin-dependent DM. GDM was identified using the ICD-10 code O24, which refers to DM first reported during pregnancy. In addition, participants were asked two questions: "Has a doctor ever told you that you have diabetes?" and "Did you only have diabetes during pregnancy?" to identify any additional cases.

Covariates assessment

Participants' age was calculated from their date of birth to the date of the baseline assessment. Educational attainment was determined from self-reported qualifications, categorized into levels such as college or university degree, vocational qualifications like NVQ or HND, and secondary education levels including A levels, GCSEs, and equivalents, which was further categorized into college or University degree, or others. Ethnicity was also self-reported and initially categorized into groups like white, mixed, Asian or Asian British, black or black British, Chinese, or others. Due to the small numbers in non-white subgroups, participants were further classified as either white or non-white. Household income was self-reported and categorized into five income brackets ranging from less than £18 000 to more than £100 000. Body mass index (BMI) was calculated from measured weight and height during the initial assessment and categorized according to WHO criteria into underweight, normal weight, overweight, and obesity [15]. Non-communicable

diseases such as cardiovascular disease, chronic hypertension, and cancer, were self-reported in the baseline questionnaire. The Townsend Deprivation Index (TDI), a composite measure of socioeconomic status derived from national census data, reflects levels of material deprivation based on factors such as unemployment, non-home-ownership, overcrowding, and lack of car ownership; for this study, TDI values were categorized into quintiles.

Lifestyle factors included smoking status, alcohol intake, physical activity, television viewing time, sleep duration, and diet quality. Smoking status was categorized as never, former, or current smoker. Alcohol intake was quantified by calculating the average number of drinks per week across various types of alcohol. Physical activity was measured using the validated short International Physical Activity Questionnaire [16] and expressed as metabolic equivalent tasks (MET-hours/week). Dietary quality was assessed through a validated questionnaire that inquired about the frequency of consumption of various foods, such as fruits, vegetables, oily fish, red meat, and processed meat, over the past year. To evaluate overall lifestyle, a composite lifestyle score was created based on a previously published scoring system [17]. This system assigned 0 points for each lifestyle factor considered "not at risk" and 1 point for those "at risk", summing these to create an unweighted score ranging from 0 to 9, with higher scores indicating an unhealthier lifestyle (Supplemental Table 2) [18]. Participants were then categorized into three groups based on their lifestyle score: most healthy (scores of 0–2), moderately healthy (scores of 3–5), and least healthy (scores of 6–9).

Statistical analysis

Baseline characteristics were presented as frequencies (percentages) for categorical data and means (standard deviation, SD) or median (25^{th}–75^{th} percentile) for continuous data, as appropriate.

A sequence of multivariable logistic regression models were used to estimate the adjusted odds ratio (OR) and 95% confidence interval (CI) for T2DM and GDM across dichotomous (none or yes) and multi-class (none, 1, 2, and ≥3) spontaneous abortion: (1) only adjusted for sociodemographic variables (e.g., age, educational attainment, ethnicity, household income, TDI quintile, BMI) and health status (e.g., chronic hypertension, cardiovascular disease [(e.g., stroke, angina, vascular heart problems,] cancer at baseline); (2) additionally adjusted for reproductive factors (e.g., hemorrhage during early pregnancy, endometriosis, ectopic pregnancy, use of oral contraceptives, and use of hormone treatment); (3) further adjusted for lifestyle score. Stratified analyses by lifestyle score were conducted to examine possible modifying effect on the associations of spontaneous abortion with T2DM and GDM. The Directed Acyclic Graph was plotted to identify potential confounders, mediators, and colliders, informing the selection of variables for adjustment in multivariable models (Supplemental Figure 1). Interactions between the spontaneous abortion and lifestyle score on T2DM and GDM were tested using both multiplicative and additive interaction analyses. The multiplicative interaction was assessed by including a cross-product interaction term between spontaneous abortion and lifestyle score in the logistic regression models [19]. A significant interaction term would indicate that the combined effect of spontaneous abortion and lifestyle score on the odds of T2DM or GDM is different from the product of their individual effects on a multiplicative scale. The relative excess risk due to interaction (RERI) was calculated as an index of additive interaction to evaluate whether the combined effect of spontaneous abortion and lifestyle score on the odds of T2DM and GDM exceeded the sum of their individual effects [20]. Numerical variables with missing data were categorized, with values encoded as integers starting from 0, and missing data designated as "9" in a separate category.

Several sensitivity analyses were performed to test the robustness of the findings. First, multiple imputation approach with five imputations were used for missing values on covariates in the multivariable models. Second, individuals with T2DM or GDM were mutually excluded from the analysis. Third, individual lifestyle factors were included in multivariable models to assess the potential differences between the effect of individual versus composite lifestyle factors. Fourth, the analyses were repeated among women with at least one livebirth.

Results

Among 170 599 women with a history of pregnancy, the mean (SD) age was 56.4 (8.0) years, with the majority being White ethnicity and having an education level below a college degree (Table 1). Most women had no history of spontaneous abortion (75.1%), and 17.8% experienced one, 4.5% had two, and 2.5% had three or more spontaneous abortions. Women with a higher number of spontaneous abortions tended to be younger, had a higher Townsend deprivation index, and had a higher prevalence of comorbidities (P for trend <0.05) (Table 1). More details were presented in Table 1.

The overall prevalence of T2DM and GDM was 3.41% and 0.64%, respectively. In multivariable analyses adjusting for age, BMI, ethnicity, education, Townsend deprivation index, cancer at baseline, chronic hypertension, and cardiovascular disease at baseline, women with a history of spontaneous abortion had higher odds of T2DM (odds ratios [OR] 1.17, 95% confidence interval [CI] 1.10–1.24) and GDM (OR 1.38, 95%CI 1.20–1.60) compared to those

Table 1 Baseline characteristics of pregnant women according to the number of spontaneous abortions

Characteristic	Number of spontaneous abortions (*N*=170 599)				*P*
	None	1	2	≥3	
Pregnant women	128197	30396	7715	4291	
Sociodemographic					
Age at recruitment (years)	56.6±7.9	55.9±8.1	55.5±8.1	55.1±8.2	<0.001
≤54	48585 (37.9)	12841 (42.2)	3431 (44.5)	1997 (46.5)	
55-59	24264 (18.9)	5476 (18)	1359 (17.6)	764 (17.8)	
60-64	32481 (25.3)	7135 (23.5)	1737 (22.5)	871 (20.3)	
≥65	22867 (17.8)	4944 (16.3)	1188 (15.4)	659 (15.4)	
Ethnicity					<0.001
White	121856 (95.1)	28859 (94.9)	7204 (93.4)	3972 (92.6)	
Non-white	5090 (4.0)	1215 (4.0)	398 (5.2)	251 (5.8)	
Missing	1251 (1)	322 (1.1)	113 (1.5)	68 (1.6)	
Educational attainment					<0.001
College or University degree	13741 (10.7)	3493 (11.5)	942 (12.2)	529 (12.3)	
Others	93226 (72.7)	22782 (75)	5746 (74.5)	3212 (74.9)	
Missing	21230 (16.6)	4121 (13.6)	1027 (13.3)	550 (12.8)	
Average total household income					<0.001
Less than £18 000	25706 (20.1)	5677 (18.7)	1475 (19.1)	866 (20.2)	
£18 000–51999	57321 (44.7)	13407 (44.1)	3339 (43.3)	1772 (41.3)	
£52000–100000	21476 (16.8)	5650 (18.6)	1442 (18.7)	786 (18.3)	
More than £100 000	5544 (4.3)	1713 (5.6)	497 (6.4)	296 (6.9)	
Missing	18150 (14.2)	3949 (13)	962 (12.5)	571 (13.3)	
Townsend deprivation index quintile					<0.001
1 (least deprived)	25957 (20.2)	6017 (19.8)	1512 (19.6)	775 (18.1)	
2	25594 (20.0)	5985 (19.7)	1509 (19.6)	791 (18.4)	
3	25764 (20.1)	6119 (20.1)	1480 (19.2)	765 (17.8)	
4	25668 (20.0)	6115 (20.1)	1545 (20.0)	895 (20.9)	
5 (most deprived)	25214 (19.7)	6160 (20.3)	1669 (21.6)	1065 (24.8)	
BMI at recruitment (kg/m^2)					<0.001
<18.5	839 (0.7)	204 (0.7)	57 (0.7)	36 (0.8)	
18.5-24.9	51087 (39.9)	12058 (39.7)	3101 (40.2)	1577 (36.8)	
25-29.9	47964 (37.4)	11246 (37)	2802 (36.3)	1525 (35.5)	
≥30	27806 (21.7)	6768 (22.3)	1717 (22.3)	1133 (26.4)	
Missing	501 (0.4)	120 (0.4)	38 (0.5)	20 (0.5)	
Lifestyle					
Smoking status					<0.001
Never	75648 (59.0)	17664 (58.1)	4392 (56.9)	2404 (56.0)	
Previous	41678 (32.5)	10137 (33.3)	2571 (33.3)	1392 (32.4)	
Current	10871 (8.5)	2595 (8.5)	752 (9.7)	495 (11.5)	
Alcohol intake, times/week	1.5 (0.5-3.5)	1.5 (0.5-3.5)	1.5 (0.5-3.5)	1.5 (0-3.5)	0.002
Television viewing time, h/day	3 (2-4)	2 (2-4)	2 (1-3)	2 (1-4)	<0.001
Sleep duration, h/day	7 (7-8)	7 (7-8)	7 (7-8)	7 (6-8)	<0.001
Fruit and vegetables intake, g/day	480 (320-720)	480 (320-720)	480 (320-720)	480 (320-720)	0.075
Oily fish intake, portions/week	1 (0.5-1)	1 (0.5-1)	1 (0.5-1)	1 (0.5-1)	0.036
Red meat intake, portions/week	1.5 (1.5-2.5)	1.5 (1.5-2.5)	1.5 (1.5-2.5)	1.5 (1.5-2.5)	0.230
Processed meat intake, portions/week	0.5 (0.5-1)	0.5 (0.5-1)	0.5 (0.5-1)	0.5 (0.5-1)	0.365
Physical activity at moderate intensity					<0.001
No	68830 (53.7)	16166 (53.2)	4095 (53.1)	2298 (53.6)	
Yes	59367 (46.3)	14230 (46.8)	3620 (46.9)	1993 (46.4)	

Table 1 (continued)

Characteristic	Number of spontaneous abortions (*N*=170 599)				*P*
	None	1	2	≥3	
Health status					
Cardiovascular disease at recruitment					0.003
No	96274 (75.1)	22983 (75.6)	5809 (75.3)	3132 (73.0)	
Yes	31778 (24.8)	7381 (24.3)	1898 (24.6)	1159 (27.0)	
Missing	145 (0.1)	32 (0.1)	8 (0.1)	0 (0)	
Cancer at recruitment					0.112
No	116360 (90.8)	27620 (90.9)	6973 (90.4)	3869 (90.2)	
Yes	11478 (9.0)	2689 (8.8)	707 (9.2)	408 (9.5)	
Missing	359 (0.3)	87 (0.3)	35 (0.5)	14 (0.3)	
Chronic hypertension					0.016
No	101505 (79.2)	24193 (79.6)	6131 (79.5)	3327 (77.5)	
Yes	26692 (20.8)	6203 (20.4)	1584 (20.5)	964 (22.5)	
Reproductive condition					
Hemorrhage during early pregnancy					<0.001
No	127752 (99.7)	29925 (98.5)	7531 (97.6)	4147 (96.6)	
Yes	445 (0.3)	471 (1.5)	184 (2.4)	144 (3.4)	
Endometriosis					<0.001
No	124064 (96.8)	29195 (96)	7404 (96)	4083 (95.2)	
Yes	4133 (3.2)	1201 (4)	311 (4)	208 (4.8)	
Ectopic pregnancy					<0.001
No	127809 (99.7)	30161 (99.2)	7606 (98.6)	4206 (98)	
Yes	388 (0.3)	235 (0.8)	109 (1.4)	85 (2.0)	
Use of oral contraceptives					<0.001
No	20695 (16.1)	4616 (15.2)	1262 (16.4)	701 (16.3)	
Yes	107374 (83.8)	25744 (84.7)	6437 (83.4)	3585 (83.5)	
Missing	128 (0.1)	36 (0.1)	16 (0.2)	5 (0.1)	
Use of hormone treatment					<0.001
No	78327 (61.1)	18992 (62.5)	4914 (63.7)	2646 (61.7)	
Yes	49598 (38.7)	11341 (37.3)	2784 (36.1)	1634 (38.1)	
Missing	272 (0.2)	63 (0.2)	17 (0.2)	11 (0.3)	

Data are presented as number (percentage), mean (SD), or median (P25, P75).

without a history of spontaneous abortion (Table 2). These associations did not substantially change after additional adjustment for reproductive factors (hemorrhage during early pregnancy, endometriosis, ectopic pregnancy, use of oral contraceptives, and use of hormone treatment), or lifestyle score. Even when all these covariates were included in the model, the association remained significant, with women who had a history of spontaneous abortion showing 11% (4%–19%) higher odds of T2DM and 30% (12%–51%) higher odds of GDM, compared to those without.

The joint association between spontaneous abortion (with or without) and lifestyle scores (most healthy, moderately healthy, least healthy) with the odds of T2DM and GDM was presented in Figure 2. For T2DM, compared to women without a history of spontaneous abortion, the odds of T2DM increased with a less healthy lifestyle within each category of spontaneous abortion, with the highest odds observed among those with a history of spontaneous abortion and a moderately healthy lifestyle (OR 1.31, 95% CI 1.19–1.45; *P* for trend<0.001, Figure 2A). However, there was no significant multiplicative interactions between spontaneous abortion and lifestyle score in relation to the odds of T2DM (*P* for interaction=0.662). A similar pattern was observed for GDM, with the highest odds among women with a history of spontaneous abortion and a least healthy lifestyle (OR 1.70, 95% CI 0.79–3.66; *P* for trend=0.001), although the interaction between spontaneous abortion and lifestyle score was not

Table 2 Odds ratios (ORs) for spontaneous abortion with the risk of type 2 diabetes mellitus and gestational diabetes mellitus

	Type 2 diabetes mellitus			Gestational diabetes mellitus		
	Spontaneous abortion			Spontaneous abortion		
Model	None	Yes	*P* value	None	Yes	*P* value
No. of cases/total	4207/128197	1614/42402		719/128197	367/42402	
Multivariable adjusted sociodemographic and health factors[a]	1 [Reference]	1.17 (1.10-1.24)	<0.001	1 [Reference]	1.38 (1.20-1.60)	<0.001
Multivariable adjusted reproductive factors[b]	1 [Reference]	1.11 (1.04-1.19)	0.002	1 [Reference]	1.30 (1.12-1.51)	0.001
Multivariable adjusted lifestyle factors[c]	1 [Reference]	1.17 (1.10-1.24)	<0.001	1 [Reference]	1.38 (1.20-1.60)	<0.001
Model include all covariates	1 [Reference]	1.11 (1.04-1.19)	0.002	1 [Reference]	1.30 (1.12-1.51)	0.001

[a] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, and CVD.

[b] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, CVD, use of oral contraceptives, use of hormone treatment, menopausal status, gestational diabetes mellitus/type 2 diabetes mellitus, hypertensive disorders of pregnancy, hemorrhage during early pregnancy, endometriosis, ectopic pregnancy.

[c] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, CVD, lifestyle score.

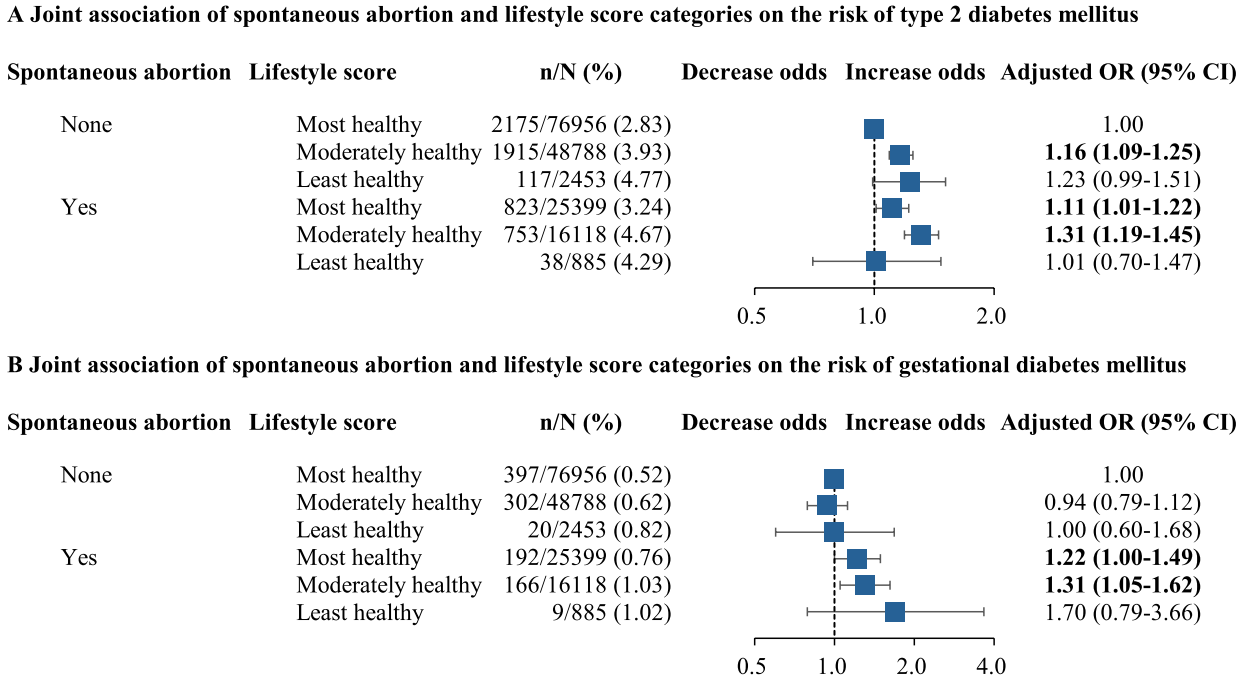

Fig 2. Spontaneous abortion, lifestyle score and risk of **A**, type 2 diabetes mellitus and **B**, gestational diabetes mellitus. Adjusted ORs with 95% CIs were calculated by using multivariable logistic regression models, with adjustment for maternal factors including age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, CVD, lifestyle score

statistically significant (*P* for interaction=0.314, Figure 2B). Additionally, no significant additive interaction was observed between spontaneous abortion and an unhealthy lifestyle in relation to the odds of T2DM (RERI 0.01, 95% CI -0.06–0.09) and GDM (RERI 0.04, 95% CI -0.12–0.21; Supplemental Table 3).

The number of spontaneous abortions was significantly associated with higher odds of T2DM and GDM, showing a clear dose-response relationship (Table 3). In the fully adjusted model, compared with women who had no history of spontaneous abortion, the odds of T2DM increased with the number of spontaneous abortions,

Table 3 Odds ratios (ORs) for risk of type 2 diabetes mellitus and gestational diabetes mellitus, according to the number of spontaneous abortions

Model	Number of spontaneous abortions				*P* trend
	None	1	2	3	
Type 2 diabetes mellitus					
No. of cases/total	4207/128197	1087/30396	285/7715	242/4291	
Multivariable adjusted sociodemographic and health factors[a]	1 [Reference]	1.12 (1.04-1.20)	1.11 (0.98-1.26)	1.55 (1.35-1.78)	<0.001
Multivariable adjusted reproductive factors[b]	1 [Reference]	1.09 (1.01-1.17)	1.07 (0.94-1.23)	1.33 (1.14-1.56)	<0.001
Multivariable adjusted lifestyle factors[c]	1 [Reference]	1.12 (1.04-1.20)	1.11 (0.98-1.26)	1.55 (1.35-1.78)	<0.001
Model include all covariates	1 [Reference]	1.09 (1.01-1.17)	1.07 (0.93-1.23)	1.33 (1.14-1.56)	<0.001
Gestational diabetes mellitus					
No. of cases/total	719/128197	230/30396	637715	74/4291	
Multivariable adjusted sociodemographic and health factors[a]	1 [Reference]	1.25 (1.06-1.48)	1.31 (0.97-1.76)	2.22 (1.65-2.97)	<0.001
Multivariable adjusted reproductive factors[b]	1 [Reference]	1.20 (1.01-1.42)	1.21 (0.90-1.64)	2.00 (1.48-2.71)	<0.001
Multivariable adjusted lifestyle factors[c]	1 [Reference]	1.25 (1.06-1.48)	1.31 (0.97-1.76)	2.22 (1.65-2.97)	<0.001
Model include all covariates	1 [Reference]	1.20 (1.01-1.42)	1.21 (0.90-1.64)	2.01 (1.48-2.71)	<0.001

[a] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, and CVD.

[b] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, CVD, use of oral contraceptives, use of hormone treatment, menopausal status, gestational diabetes, hypertensive disorders of pregnancy, hemorrhage during early pregnancy, endometriosis, ectopic pregnancy.

[c] Multivariable models were adjusted for age at baseline, BMI at baseline, race/ethnicity, education, average total household income, Townsend deprivation index, cancer at baseline, chronic hypertension, CVD, lifestyle score.

with ORs of 1.09 (95% CI 1.01–1.17) for one spontaneous abortion, 1.07 (0.93–1.23) for two, and 1.33 (1.14–1.56) for three or more (*P* trend <0.001). A similar pattern was observed for GDM, with corresponding ORs of 1.20 (1.01–1.42), 1.21 (0.90–1.64), and 2.01 (1.48–2.71) for one, two, and three or more spontaneous abortions, respectively (*P* trend <0.001).

A series of sensitivity analyses was performed to assess the robustness of the findings and to ensure the observed associations were not driven by confounding factor. First, the associations remained consistent when missing values on covariates were addressed using the multiple imputation method (Supplemental Table 4). Second, excluding women with T2DM or GDM in a mutual sensitivity analysis did not materially change the results (Supplemental Table 5). Third, adjusting for individual lifestyle factors also yielded similar findings (Supplemental Table 6). Fourth, the associations remained consistent in a multivariable model after excluding women with cancer at baseline, chronic hypertension, and CVD (Supplemental Table 7). Finally, among women with at least one live birth, the associations between the number of spontaneous abortions and the odds of T2DM and GDM were evident. The fully adjusted ORs for T2DM were 1.08 (95% CI 1.01–1.17) for one spontaneous abortion, 1.07 (0.92–1.25) for two, and 1.34 (1.11–1.61) for three or more; for GDM, the corresponding ORs were 1.16 (1.00–1.41), 1.22 (0.87–1.72), and 2.16 (1.54–3.04) (Supplemental Table 8).

Discussion

In this large cross-sectional study using data from the UKB, a history of spontaneous abortion was associated with higher odds of T2DM and GDM. These associations persisted after adjusting for a wide range of sociodemographic, medical, reproductive, and lifestyle factors. Women with a history of spontaneous abortion showed 11% higher odds of T2DM and 30% higher odds of GDM compared to those without. The odds increased with the number of spontaneous abortions, with a more pronounced association observed in women who had experienced three or more spontaneous abortions. Additionally, the odds of T2DM and GDM increased with less healthy lifestyle behaviors in all categories of spontaneous abortion, although no significant interactions between spontaneous abortion and lifestyle score were observed.

Comparison with previous studies

Previous studies have identified an association between spontaneous abortion and higher odds of T2DM [5]. However, conflicting evidence was found in the studies regarding the association between spontaneous abortion and GDM [6, 21]. A large meta-analysis of 21 studies demonstrated that women with a history of spontaneous abortion had a 15% higher risk of developing T2DM compared to those without a history (OR 1.15, 95% CI 1.02–1.28), and the odds of T2DM increased by 14 %

for each additional increase in the number of miscarriages (OR 1.14, 95 % CI 1.00–1.31) [5]. In a retrospective nationwide register-based cohort study, which followed more than 161 206 women, found that women a history of miscarriages had 14% higher odds of T2DM (OR 1.14, 95% CI 1.10–1.18) compared with women with no history of miscarriage [22]. Similarly, a case-control study from Danish nationwide cohort of 272 514 women showed that those with 1, 2 and ≥ 3 pregnancy losses had ORs for T2DM of 1.18 (95% CI 1.13–1.23), 1.38 (95% CI 1.27–1.49) and 1.71 (95% CI 1.53–1.92) respectively, compared with ever-pregnant women who had never experienced a pregnancy loss [23]. Findings from our study were consistent with these results, as we observed ORs for T2DM of 1.09 (95% CI 1.01–1.17) for women with one spontaneous abortion, 1.07 (0.93–1.23) for those with two, and 1.33 (1.14–1.56) for those with three or more, compared with women who with no history of spontaneous abortion.

The association between spontaneous abortion and GDM from meta-analysis of 9 studies, demonstrated that women with a previous spontaneous abortion had 44% increased odds of GDM in a subsequent pregnancy (pooled OR 1.44, 95% CI 1.23–1.68) [21]. Similarly, a retrospective cohort study conducted at a tertiary hospital in China, involving 102 259 pregnant women, found that only spontaneous abortion (relative risk [RR], 1.25, 95% CI, 1.18–1.31) was associated with increased risk of GDM, and the association was dose-dependent, with the risk of GDM increasing by 18% (RR 1.18, 95% CI 1.11–1.26) for women with 1 spontaneous abortion, 41% (RR 1.41, 95% CI 1.27–1.57) for those with 2, and 43% (RR 1.43, 95% CI 1.22–1.67) for those with more than 2 spontaneous abortions [8]. However, a meta-analysis of 1 826 454 pregnant women from diverse international cohorts found no significant association between a history of abortion and GDM (OR 1.55, 95% CI 0.91–2.64) [6]. Our study found that spontaneous abortion was associated with increased odds of GDM (OR 1.30, 95% CI 1.12–1.51) in a number-dependent manner. Compared with pregnant women with no history of abortion, the OR for GDM increased by 18% (OR 1.20, 95% CI 1.10–1.42) for women with one spontaneous abortion, by 21% (OR 1.21, 95% CI 0.90–1.64) for those with two, and by 101% (OR 2.01, 95% CI 1.48–2.71) for those with more than two spontaneous abortions.

In addition to prior studies linking spontaneous abortion to diabetes risk, studies have explored the role of lifestyle factors. A meta-analysis of 14 studies with approximately 1 million participants showed that compared with participants with the healthiest healthy lifestyle had a significantly lower risk of T2DM (HR 0.25, 95% CI 0.18–0.35) compared to those with the least healthy lifestyle [24], although the pregnancy history was not considered. Our study did not find significant multiplicative or additive interactions between spontaneous abortion and lifestyle score in relation to the risk of T2DM and GDM. This suggests that the contribution of spontaneous abortion to diabetes risk may be independent of lifestyle factors. While lifestyle behaviors like diet and physical activity are known to influence diabetes development, the biological pathways linking spontaneous abortion to diabetes may function through distinct mechanism.

Possible mechanism

Several potential mechanisms may explain the observed association between spontaneous abortion and increased risks of T2DM and GDM. One possible explanation is the involvement of shared risk factors between spontaneous abortion and diabetes. For example, chronic inflammation, endothelial dysfunction, and immune dysregulation are common pathways implicated in both recurrent miscarriages and the development of metabolic disorders [25–28]. For example, elevated levels of inflammatory markers, such as interferon-γ and tumour necrosis factor alpha, was associated with increased risk of recurrent pregnancy loss and are also strongly associated with insulin resistance and the progression to diabetes [29] that predisposes them to the development of insulin resistance [30, 31], which suggested that women with a history of spontaneous abortion may have an underlying pro-inflammatory or pro-thrombotic state that predisposes them to metabolic disturbances. Additionally, spontaneous abortion has been associated with alterations in hormonal regulation [32], particularly involving the hypothalamic-pituitary-ovarian axis [33]. Dysregulation of hormonal pathways may impair glucose metabolism and reduce insulin sensitivity, further contributing to the increased risk of T2DM and GDM [34]. For example, hyperandrogenism and disrupted progesterone levels, frequently seen in conditions polycystic ovary syndrome, are associated with both pregnancy loss and an increased risk of diabetes [35]. Moreover, it is also possible that the relationship between spontaneous abortion and diabetes is bidirectional. Underlying metabolic disorders, such as insulin resistance and polycystic ovary syndrome, may predispose women to both recurrent miscarriages and an increased risk of diabetes. This suggests that rather than spontaneous abortion directly increasing diabetes risk, women with metabolic dysfunction may be more susceptible to both adverse reproductive outcomes and metabolic disorders. Furthermore, genetic predisposition might play a role in the observed association. Genetic variants related to glucose metabolism, insulin signaling, and inflammatory pathways may increase susceptibility

to both spontaneous abortion and diabetes. For example, polymorphisms in genes such as *TCF7L2* was implicated in diabetes [36].

The insignificant interaction between spontaneous abortion and lifestyle factors in relation to T2DM and GDM may reflect the independent and multifactorial nature of diabetes pathogenesis, where their independent effects may overshadow any combined effect. Additionally, this finding might be partially attributed to the limited statistical power due to the small proportion of participants with both spontaneous abortion and unhealthy lifestyles. Moreover, different pathophysiological pathways, such as immune dysfunction and endothelial dysfunction, may underlie the associations, reducing the likelihood that lifestyle factors would significantly modify these associations. Measurement limitations in lifestyle assessment—such as the reliance on self-reported physical activity and dietary habits—may also contribute, as they may not accurately capture long-term behavioral patterns. Furthermore, while lifestyle interventions are well-established strategies for diabetes prevention, they may not fully counteract the metabolic risks associated with reproductive health history, which may involve complex hormonal, genetic, and inflammatory mechanisms. Future studies should explore potential underlying mechanisms, and assess whether specific lifestyle interventions could mitigate diabetes risk among women with a history of spontaneous abortion.

Strengths and limitations

This study has several strengths. The large sample size enabled us to explore the associations between spontaneous abortion and diabetes with robust statistical power. Additionally, the detailed sociodemographic, clinical, and reproductive data available in the UKB cohort allowed for comprehensive adjustment for potential confounders, thereby strengthening the validity of our findings. However, several limitations should be acknowledged. First, the diagnosis of spontaneous abortion mainly relied on self-reported data, which may introduce recall bias and misclassification. While previous studies have suggested that self-reported reproductive outcomes tend to be reliable [37, 38], there is still the possibility of underreporting or misclassification. Second, the UKB cohort is not entirely representative of the general population, particularly in terms of ethnic and socioeconomic diversity, which may limit the generalizability of our findings. Future studies in more diverse populations are needed to confirm our findings and to explore potential variations in the associations across different population subgroups. Third, although we adjusted for a wide range of confounders, residual confounding by unmeasured factors, such as the severity of diabetes, insulin resistance, hormonal profiles, or access to healthcare, cannot be entirely ruled out. Fourth, the observational nature of this study limits its causal inference and makes it challenging to determine the temporal ordering of certain covariates and outcomes, relative to spontaneous abortion. These factors may act as confounders or mediators, and adjustments could potentially introduce collider bias [39]. Fifth, our study may have been underpowered to detect interactions, particularly for GDM, due to smaller case numbers in subgroup analyses. Moreover, the changes in diagnostic criteria for diabetes over time may have led to an underestimation of the incidence rates in our study, potentially attenuating the observed associations. Additionally, although the observed associations were statistically significant, the absolute risk increase remains modest. For example, the absolute risk difference for T2DM and GDM between individuals with and without a history of spontaneous abortion was 0.52% and 0.30%. This suggests that while the association is relevant at the population level, the individual-level impact should be interpreted with caution. Future large-scale prospective study is needed to confirm the associations and unravel the underlying causal pathways.

Conclusions

Our study showed that a history of spontaneous abortion was associated with higher odds of both T2DM and GDM, independent of sociodemographic, lifestyle, and reproductive factors. These findings suggest that clinicians should consider integrating reproductive history into routine diabetes risk assessments, especially for women who have experienced multiple spontaneous abortions. Further prospective studies are warranted to validate our findings, explore the underlying mechanisms linking spontaneous abortion to diabetes, and evaluate potential strategies for mitigating these risks.

Abbreviations

T2DM	Type 2 diabetes mellitus
GDM	Gestational diabetes mellitus
ICD-10	The International Classification of Diseases, tenth version
SD	Standard deviation
ORs	Odds ratios
95% CIs	95% confidence intervals
TDI	Townsend Deprivation Index
RERI	Relative excess risk due to interaction
UKB	UK Biobank
BMI	Body mass index
IQR	Interquartile range

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
LY had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: SWL, LY, and BBS. Acquisition, analysis, or interpretation of data: SWL, YPC, AMZ, XXC, LY, and BBS. Statistical analysis: SWL. Drafting of the manuscript: SWL, BBS. Critical revision of the manuscript for important intellectual content: SWL, YPC, AMZ, XXC, LY, and BBS. Administrative, technical, or material support: LY, and BBS. Supervision: SWL, LY, and BBS.

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Data availability
Access to data from UK Biobank (https://www.ukbiobank.ac.uk/) is available upon application.

Declarations

Ethics approval and consent to participate
This study was approved by the UK North West Multi-centre Research Ethics Committee (11/NW/0382). All participants provided informed consents.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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