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DOI:
10.1136/bmjopen-2023-078167

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Song, A, Okoth, K & Adderley, N 2023, 'Association between preterm delivery and subsequent maternal risk of hypertension and type 2 diabetes mellitus in a UK population-based retrospective cohort study', *BMJ open*, vol. 13, no. 11, e078167. https://doi.org/10.1136/bmjopen-2023-078167

BMJ Open

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To cite: Song A, Okoth K, Adderley NJ. Association between preterm delivery and subsequent maternal risk of hypertension and type 2 diabetes mellitus in a UK population-based retrospective cohort study. *BMJ Open* 2023;**13**:e078167. doi:10.1136/bmjopen-2023-078167

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-078167).

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Received 25 July 2023
Accepted 09 November 2023

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ABSTRACT

Objectives Women with a history of preterm delivery (PTD) are at higher risk of developing cardiovascular diseases (CVD) later in life. However, it is not well established whether PTD is associated with CVD risk factors, hypertension and type 2 diabetes mellitus (T2DM). Therefore, in this study, we examined the associations between PTD compared with term delivery and subsequent risk of hypertension and T2DM.

Design Retrospective matched population-based open cohort study.

Setting Clinical Practice Research Datalink GOLD data in the UK.

Participants A total of 3335 18–49-year-old women with preterm delivery were matched by age and region to 12 634 without a record of preterm delivery.

Primary outcome measures Outcomes of interest were newly diagnosed hypertension or T2DM at least 6 months after delivery. During the study period (January 2000–December 2019), hypertension or T2DM events in the medical records of women with (exposed) and without (unexposed) preterm delivery were compared. HR and 95% CI were estimated using Cox proportional hazards models adjusted for potential confounders.

Results Over a median follow-up period of 5.11 (IQR 2.15–9.56) years, the HRs for hypertension in women who delivered preterm compared with women who delivered at term were 1.42 (95%CI 1.09 to 1.80) and 1.18 (95%CI 0.90 to 1.56) in the unadjusted and adjusted models, respectively. For T2DM, over a median follow-up period of 5.17 (IQR 2.18–9.67) years, the HRs in women who delivered preterm compared with those who delivered at term were 1.67 (95%CI 1.12 to 2.48) and 1.10 (95%CI 0.72 to 1.68) in the unadjusted and adjusted models, respectively.

Conclusion We found no independent effect of preterm delivery on risk of hypertension or type 2 diabetes in this study. While significant associations were observed in unadjusted analyses, associations were lost after adjustment and may be attributable to other reproductive complications. Additional studies are needed to confirm these findings.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study used a large primary care database that is generalisable to the UK and included more than 16 000 women with a record of pregnancy.
⇒ Female-specific diseases or reproductive complications were included as potential confounders in analyses exploring the association between preterm delivery and maternal risk of hypertension and type 2 diabetes.
⇒ The outcomes of the present study are well recorded in UK primary care, as hypertension and diabetes are part of the Quality and Outcomes Framework, a payment incentive scheme for achieving performance targets for the management of patients on chronic disease registers.
⇒ However, patients with undiagnosed or unreported hypertension and type 2 diabetes, or who developed outcomes after the follow-up period, would not have been captured.
⇒ The present study could not investigate gestational age, multiple pregnancy and recurrent pregnancy events. The exposure variable, preterm delivery, was treated as only a dichotomous variable.

INTRODUCTION

The WHO estimates that 15 million preterm deliveries (PTD) occur every year, and the incidence has been rising globally.[1] The estimated PTD rate ranges between 5% and 18% by country.[1] In the UK, the PTD rate has remained stable since 2010, ranging between 7% and 8% of live deliveries.[2 3] Maternal and fetal morbidity and mortality are significantly associated with pregnancy complications.[4 5] Previous studies have proven that women with a history of PTD are at increased risk of maternal mortality and subsequent chronic health conditions, such as cardiovascular diseases (CVD) and kidney diseases, compared with women without a history of PTD.[5–7]

CVD is the major cause of death in women, accounting for 35% of all deaths globally in 2019.[8] Hypertension and diabetes are chronic

health conditions which are well-established risk factors for CVD.[8–10] An increased risk of fatal CVD is related to each complex and heterogeneous phenotype of hypertension and diabetes.[11] Hypertension and diabetes have sex-specific characteristics. Socioeconomical status, lifestyle and pathophysiological mechanisms are all linked to differences in the prevalence of CVD between men and women.[12] Women tend to have a lower prevalence of CVD than men in general as endogenous oestrogens influence vasodilation and help premenopausal women maintain a lower blood pressure.[12 13] However, after menopause, women's blood pressure is higher than that of men of the same age.[12] Health condition awareness may also be related to this gap.[14 15] It would be beneficial to identify the risk factors specific to women and educate individuals about the value of routine health check-ups for those in high-risk groups. Initial management and prevention of related health conditions for high-risk groups enable patients to reduce their risk of CVD.[16 17]

While multiple studies have suggested evidence of the association between PTD and an increased risk of CVD,[6] the association of PTD with hypertension and type 2 diabetes mellitus (T2DM) is not well established. Previous studies have demonstrated a positive association between PTD and hypertension or diabetes.[18–21] However, the size of effect and significance level of the association varies between the studies, potentially as a result of variation in cardiometabolic risk factors between study populations. There is a lack of studies in the UK population. A single prospective cohort study[22] within a UK population suggested only a weak association between preterm delivery and systolic blood pressure and no association with glucose level. Therefore, the objective of this study was to conduct a retrospective matched cohort study using routinely collected UK primary care data to explore the association between PTD and subsequent development of hypertension or T2DM in a UK primary care setting.

MATERIAL AND METHODS

Data source

We conducted a retrospective cohort study utilising patient data from Clinical Practice Research Datalink (CPRD) GOLD. CPRD has patient electronic health records from primary care; CPRD GOLD is dataset from contributing practices which use Vision electronic medical records software. It includes anonymised longitudinal medical records for more than 20 million patients from almost 1000 primary care practices spread throughout the UK, with median follow-up time for patients of 5.6 years.[23 24] CPRD contains data on diagnoses, consultations, symptoms, tests/investigations, referrals and prescriptions. Validation of CPRD has demonstrated a high positive predictive value for diagnoses or incidence of many chronic conditions compared with other sources.[24] Data extraction was conducted using the Data Extraction for Epidemiological Research tool.[25]

Practice eligibility criteria

The study period was 1 January 2000 to 31 December 2019. General practices were eligible from the later of 1 year after the date they started using electronic medical records or 1 year after the 'up-to-standard' date, which indicates a practice is considered to have a continuous and complete recording of patient data later than 1995.[26]

Study population

Women of reproductive age from 18 to 49 years at baseline with available pregnancy history data between the registration date and the study entry date in the CPRD GOLD database from January 2000 to December 2019 were eligible for inclusion. Women under 18 and over 49 years were excluded as they may have different risk factors and outcomes due to their unusually younger or older maternal age.[27] The participants were eligible for inclusion 1 year after registering with an eligible practice to ensure all baseline information was recorded in their medical records. Participants' age was defined at study entry, and they were not censored when they reached age over 49 during follow-up.

Exposure

Exposure was defined using the CPRD GOLD code list for preterm delivery (online supplemental table S1). The unexposed group was composed of women with a record of pregnancy who delivered at term and without any medical code of preterm delivery at any time point. The unexposed group were matched by delivery date within 365 days of their corresponding exposed woman's delivery date to avoid immortal time bias.[28] Each individual exposed participant was matched with up to four unexposed participants by age (±1 year) and region.[24] Additional pregnancy events after the index delivery were not accounted for in the study.

Follow-up period

The index date (start of follow-up) was defined as 6 months after the delivery date; a 6-month lag period was introduced to allow sufficient time to develop these outcomes following the exposure and to ensure any pre-existing, but unrecorded diagnoses of hypertension or T2DM were not captured in the outcomes. The participants were followed-up from the index date to the earliest date of the following dates: outcome date (hypertension or T2DM), transfer date (when the patient left the practice), death date, collection date (latest date when the practice contributed to the dataset) or the study end date.

Outcomes

The incident diagnosis of either hypertension or T2DM was identified using previously published CPRD GOLD code lists of relevant read codes.[29] We excluded codes for type 1 diabetes from the outcome code list. Hypertension and diabetes are part of UK Quality and Outcomes Framework (QOF) and are therefore well recorded in UK primary care.[30] Women with a record of the outcome of interest at baseline were excluded from the

corresponding analysis: that is, patients with a record of hypertension at baseline were excluded from the hypertension analyses, and patients with a record of type 1 or 2 diabetes at baseline were excluded from the T2DM analysis. Also, participants who developed outcomes during the 6-month lag phase were excluded, as outcomes that developed in this period were unlikely to be associated with preterm delivery.

Covariates

Study covariates were selected based on biological plausibility, previous research and data availability from routinely collected primary care data.[31–34] The covariates included age (years), ethnicity, Body Mass Index (BMI; body weight divided by square of height, kg/m^2), smoking status, lipid-lowering medication prescription, CVD (ischaemic heart disease, heart failure, myocardial infarction, peripheral vein disease, stroke, transient ischaemic attack), migraine, polycystic ovary syndrome (PCOS), hypertension, diabetes, sexually transmitted diseases (STD; syphilis, hepatitis C, HIV infection), chronic inflammatory diseases (CID; adenomyosis, endometriosis, interstitial cystitis), and reproductive tumours (uterine fibroids, gynaecological cancer). Comorbidities recorded ever up to the delivery date were defined using relevant medical codes. The latest record up to the delivery date was used for each of the study covariates. Pre-pregnancy BMI was not available for all participants at baseline; 4929 participants' BMI (31%) was recorded during their pregnancy.

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the two groups. Continuous variable (age, normal distribution) was presented using mean SD, and categorical variables (all other variables) were reported by number (%).

Crude incidence rates of hypertension and T2DM were calculated by dividing the number of newly diagnosed outcomes by the total number of person-years at risk contributed by the exposed and unexposed groups. Cox proportional hazards regression models were used to examine crude HRs, adjusted HRs (aHRs) and their corresponding 95% CI for the association of PTD with the risk of hypertension or T2DM. HRs were calculated separately for hypertension and T2DM outcome events. The reference group was women with term delivery. The Nelson-Aalen cumulative hazard function was performed to plot the cumulative hazard of outcomes.

The proportional hazards assumption was checked by comparing log-log plots of survival and performing the Schoenfeld residuals test; the latter showed some violation of the proportional hazards assumption for both outcomes.[35] This may have been caused by outcome susceptibility variation between the exposed and unexposed groups, as participants in the exposed group were more likely to develop hypertension or T2DM in the early study stage. For this reason, we also conducted a sensitivity analysis using a Poisson regression model, accounting for person-time, to explore the impact of the proportional hazards assumption violation on the findings; results were reported as incidence rate ratios (IRR).

The outcomes of this study were evaluated using two nested adjusted Cox models (separately for hypertension and T2DM). Model 1 was adjusted for demographical characteristics (age, ethnicity, BMI, smoking status). Model 2 was adjusted for variables in model 1 plus clinical characteristics (lipid-lowering medication prescription, CVD, migraine, PCOS, STD, CID, reproductive tumours, hypertension for T2DM outcome and T2DM for hypertension outcome).

Missing data were 4.3% for ethnicity, 13.8% for BMI and 5.4% for smoking status. Missing data were included in missing data categories in the primary analysis. However, in order to explore the impact of missing data on the results, a sensitivity analysis was carried out in which missing values for BMI and smoking status were handled using multiple imputation. Multiple imputation was performed using chained equations with predictive mean matching.[36] Twenty multiply imputed datasets were created. Imputation was conducted using the following covariates: PTD, age, lipid-lowering medication prescription, CVD, migraine, PCOS, STD, CID, reproductive tumours, baseline hypertension and baseline diabetes. As a high proportion of missing values was observed for ethnicity, a missing data category was used for this variable in all models to maintain data validity.

Women with hypertensive disorders of pregnancy (HDP) or gestational diabetes mellitus (GDM) were not excluded in the primary analysis. To explore any differences in the associations between women with and without HDP and GDM, two subgroup analyses were conducted exploring hypertension outcomes in women with and without a record of HDP and exploring T2DM outcomes in women with and without GDM.

StataSE, version 17.0 (StataCorp LLC) was used for all analyses. P<0.05 was considered statistically significant, and estimates were calculated with 95% CIs.

RESULTS

A study flow diagram illustrating participant selection and inclusion is shown in figure 1. After applying inclusion and exclusion criteria, 3335 patients with history of preterm delivery (exposed) and 12 634 corresponding matched controls with term delivery (unexposed) were included in the analysis. After excluding participants with a pre-existing outcome at baseline, a total of 15 401 (3247 PTD and 12 154 unexposed) and 15 601 (3274 PTD and 12 327 unexposed) participants were included in the analyses for hypertension and T2DM, respectively.

While the participant demographical characteristics were broadly similar between the two groups, the PTD group showed a higher proportion of cardiometabolic risk factors (table 1). By design the mean age of the participants was similar at 30.8 (SD 6.0) and 30.7 (SD 5.9)

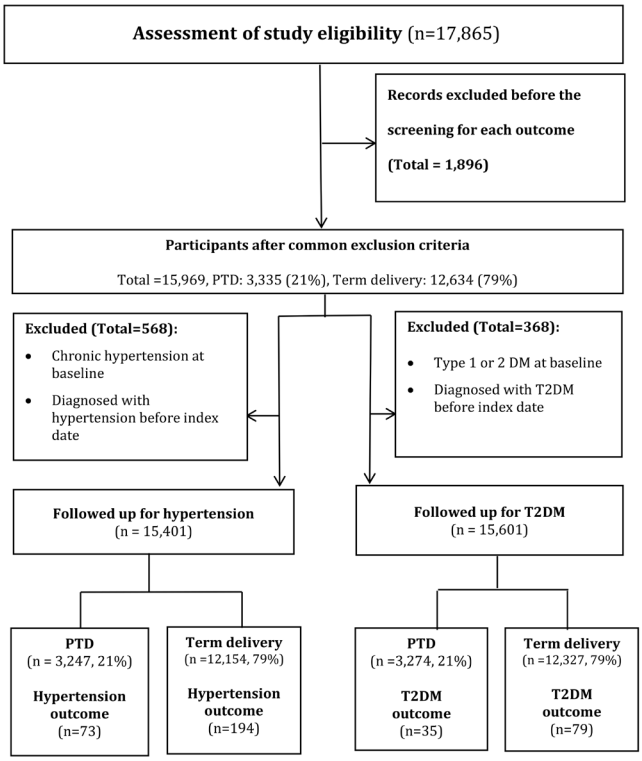

Figure 1 Flow diagram. DM, diabetes mellitus; PTD, preterm delivery; T2DM, type 2 diabetes mellitus.

years in the exposed and unexposed cohorts, respectively. The proportion of participants with baseline hypertension was higher in the PTD group than the term delivery group (hypertensive 4.7 vs 1.7%). Baseline diabetes also indicated a higher proportion in the PTD group than the term delivery group (diabetic 5.5 vs 2.6%). As expected, risk factors for PTD, as identified by previous literatures,[37–42] were more prevalent in women with preterm delivery compared with those with term delivery in the study population: women with PTD were more likely to be obese (18.6 vs 15.0%), current smokers (24.5 vs 21.5%) and South Asian (4.0 vs 2.6%). They were also more likely to be diagnosed with pregestational T2DM (1.2 vs 0.3%), GDM (3.9 vs 2.0%), migraine (12.7 vs 9.4%) and reproductive tumours (1.1 vs 0.6%).

Hypertension risk

During the follow-up period, 73 (2.2%) women in the PTD group and 194 (1.6%) women in the term delivery group developed hypertension (table 2). The incidence rate for hypertension was 36 people per 10 000 in the PTD group vs 25 people per 10 000 person-years in the term delivery group.

In the crude model, the preterm group was 42% more likely to be diagnosed with hypertension than the term delivery group (HR 1.42, 95%CI 1.09 to 1.86; p=0.011). The Nelson-Aalen cumulative hazard estimate (figure 2) shows a higher risk for hypertension in the PTD group, with the trend maintained up to the 15th year of the study.

In the model adjusting for demographical characteristics (model 1), the adjusted HR for hypertension in women who delivered preterm compared with those who delivered at term was 1.30 (95%CI 0.99 to 1.70; p=0.060), and the association became non-statistically significant. Further adjustment for clinical factors (model 2) reduced the effect estimate (aHR, 1.18; 95%CI 0.90 to 1.56; p=0.236). We identified that this reduction of effect size and significance was largely attributable to inclusion of HDP as a covariate (adjustment for covariates in model 1 plus HDP, aHR, 1.20; 95%CI 0.91 to 1.58; p=0.194).

Type 2 diabetes risk

During the follow-up period, 35 (1.1%) women in the PTD group and 79 (0.6%) women in the term delivery group developed T2DM (table 2). Incidence rate for T2DM was 17 people per 10 000 in the PTD group and 10 people per 10 000 person-years in the term delivery group.

In crude model, the preterm group was 67% more likely to be diagnosed with T2DM than the term delivery group (HR 1.67, 95%CI 1.12 to 2.48; p=0.012). The Nelson-Aalen cumulative hazard estimate (figure 3) illustrated a relatively higher risk of T2DM in the PTD group by the 14th year of the study period. In contrast, the unexposed group showed a significant increase in T2DM in the late study years and a similar risk to the PTD group by the 17th year of the study.

Attenuation of the effect estimate was observed after adjusting for baseline demographical variables (model 1, aHR, 1.35; 95%CI 0.90 to 2.02; p=0.144) and clinical factors (model 2, aHR 1.10; 95%CI 0.72 to 1.68; p=0.670), and the results became non-statistically significant. It was found that inclusion of GDM as a covariate led to a substantial reduction in effect size (adjustment for model 1 plus GDM, aHR, 1.17; 95%CI 0.78 to 1.75; p=0.457).

Sensitivity analyses

The analysis using Poisson regression instead of Cox regression produced aIRRs similar to the aHRs for both outcomes, indicating that the proportional hazards assumption violation appears to have had little impact on the findings (hypertension, aIRR 1.18, 95%CI 0.89 to 1.55; T2DM, aIRR 1.12, 95%CI 0.74 to 1.71; see online supplemental table S2). The sensitivity analysis using multiple imputation for missing BMI and smoking did not significantly change the result (hypertension, aHR 1.20, 95%CI 0.91 to 1.58; T2DM, 1.12, 95%CI 0.74 to 1.71; see online supplemental table S2).

Subgroup analyses

In the fully adjusted subgroup analysis (online supplemental table S3), comparing PTD to term delivery, the adjusted HR for hypertension was 0.92 (95%CI 0.33 to 2.60) in the subgroup of women with HDP and 1.21 (95%CI 0.91 to 1.62) in the subgroup of women without HDP. There was no significant association between preterm delivery and risk of hypertension in subgroups with/without HDP.

Table 1 Baseline characteristics of the study population

Characteristics	Total=15969	Preterm delivery n=3335 (exposed group)	Term delivery n=12634 (control group)
Age at delivery, Mean (SD), y		30.8 (SD 6.0)	30.7 (SD 5.9)
Ethnicity n (%)	White	1592 (47.7)	5711 (45.2)
	Black	185 (5.6)	544 (4.3)
	South Asian	133 (4.0)	328 (2.6)
	Others	101 (3.0)	300 (2.4)
	Missing values	1324 (39.7)	5751 (45.5)
BMI (kg/m^2) n (%)	Mean (SD)	25.8 (SD 5.9)	25.5 (SD 5.5)
	< 18.5 (underweight)	131 (3.9)	374 (3.0)
	18.5 to 24.9 (normal)	1431 (42.9)	5698 (45.1)
	25 to 29.9 (overweight)	750 (22.5)	2861 (22.7)
	>30 (obese)	621 (18.6)	1895 (15.0)
	Missing values	402 (12.1)	1806 (14.3)
Smoking status n (%)	Never	1807 (54.2)	7183 (56.9)
	Former	549 (16.5)	2040 (16.2)
	Current	816 (24.5)	2714 (21.5)
	Missing values	163 (4.9)	697 (5.5)
Baseline hypertension n (%)	Normotensive	3177 (95.3)	12429 (98.4)
	Chronic hypertension	64 (1.9)	97 (0.8)
	HDP	94 (2.8)	108 (0.9)
Baseline diabetes n (%)	Non-diabetes	3151 (94.5)	12303 (97.4)
	Pregestational type 1 DM	40 (1.2)	43 (0.3)
	Pregestational type 2 DM	13 (0.4)	31 (0.3)
	GDM	131 (3.9)	257 (2.0)
Current lipid-lowering medication, n (%)		16 (0.5)	38 (0.3)
Cardiovascular diseases, n (%)		14 (0.4)	41 (0.3)
Migraine, n (%)		422 (12.7)	1182 (9.4)
Polycystic ovarian syndrome, n (%)		131 (3.9)	420 (3.3)
Sexually transmitted diseases, n (%)		10 (0.3)	33 (0.3)
Chronic inflammatory diseases, n (%)		75 (2.3)	252 (2.0)
Reproductive tumour, n (%)		37 (1.1)	80 (0.6)

Reproductive tumours (uterine fibroids, gynaecological cancer), sexually transmitted diseases (syphilis, hepatitis C, HIV infection), chronic inflammatory diseases (adenomyosis, endometriosis, interstitial cystitis), cardiovascular diseases (ischaemic heart disease, heart failure, myocardial infarction, peripheral vein disease, stroke, transient ischaemic attack).
BMI, Body Mass Index; DM, diabetes mellitus; GDM, gestational diabetes mellitus; HDP, hypertensive disorder in pregnancy.

Likewise, comparing PTD to term delivery, the adjusted HR for T2DM was 1.38 (95%CI 0.67 to 2.82) in the subgroup of women with GDM and 0.88 (95%CI 0.50 to 1.54) in the subgroup of women without GDM. There was no significant association between preterm delivery and risk of T2DM in subgroups with/without GDM.

DISCUSSION

Main findings

In this population-based retrospective matched open cohort study, we aimed to explore whether preterm delivery is associated with long-term hypertension or T2DM in women. In the main analysis, unadjusted results suggested that women who delivered preterm were at 42% increased risk of subsequent hypertension events and 67% increased risk of subsequent T2DM events compared with the unexposed group, matched for age and region, who delivered at term. These associations were no longer statistically significant after adjustment for demographical and clinical risk factors, with much of the attenuation and loss of statistical significance appearing to be attributable hypertensive disorders of pregnancy for the hypertension outcome and GDM for the T2DM outcome, which are well-established risk factors for subsequent development

Table 2 Incidence rates and hazard ratios for hypertension and type 2 diabetes in women with and without a history of preterm delivery

	Hypertension		Type 2 diabetes mellitus	
Outcome	**Preterm delivery**	**Term delivery**	**Preterm delivery**	**Term delivery**
Population, n	3247	12154	3274	12327
Events, n (%)	73 (2.2)	194 (1.6)	35 (1.1)	79 (0.6)
Person-years	20124	74653	20565	76735
Follow-up, median (IQR), y	5.44 (2.28–9.27)	5.01 (2.13–9.62)	5.50 (2.33–9.43)	5.10 (2.16–9.74)
Crude incidence rate per 10000 person-years	36	25	17	10
Crude HR (95%CI, p value)		1.42 (1.09 to 1.86, 0.011)	1.67 (1.12 to 2.48, 0.012)	
Adjusted HR (95%CI, p value)	Model 1*	1.30 (0.99 to 1.70, 0.060)	1.35 (0.90 to 2.02, 0.144)	
	Model 2†	1.18 (0.90 to 1.56, 0.236)	1.10 (0.72 to 1.68, 0.670)	

*Model 1: adjusted for age, ethnicity, BMI, smoking status.
†Model 2: adjusted for model 1 variables plus lipid-lowering medication prescription, cardiovascular disease, migraine, sexually transmitted diseases, polycystic ovarian syndrome, chronic inflammatory diseases, reproductive tumour, hypertension for T2DM outcome, and T2DM for hypertension outcome.
BMI, Body Mass Index; T2DM, type 2 diabetes mellitus.

of the corresponding outcomes. In subgroup analysis, we attempted to explore the independent associations according to the presence of HDP or GDM. No significant association was found in these subgroup analyses; however, given the relatively small number of outcomes, statistical significance should be interpreted with caution.

We found no significant association between preterm delivery and hypertension or T2DM after adjustment for potential confounders in this study. The findings from our study are inconsistent with results from the Danish,[18 19] US[20] and Swedish[21] studies that found an association between PTD and increased risk of hypertension and T2DM. The effect estimates from previous studies were in the range of 11% to 30% increased risk for future hypertension events and from 17% to 89% increased risk for future diabetes events. In contrast, a prospective cohort study[22] of 3416 women in the UK found that preterm delivery showed a weak association with high blood pressure, but not with glucose level.

The Danish studies[18 19] showed a relatively higher risk of hypertension (27–30%) and T2DM (61–89%) compared with the other studies; however, these studies included maternal age at first birth, parity, education as confounder and missed out key confounders, including smoking, BMI and comorbidities. The US[20] and the Swedish studies[21] identified a moderate effect after they adjusted for demographical and clinical factors. They were able to adjust for pregnancy demographical conditions, such as final parity, duration of pre-pregnancy oral contraceptive use and pregnancy duration which it was not possible to include this study. However, they did not include reproductive complications which appeared to act as confounders in this study. This difference in effect size and study results could be explained by differences in the potential confounders adjusted for in the analyses.

Known or possible risk factors for hypertension and T2DM had a consistent and strong impact on effect estimates in this study.[43] An association between T2DM and

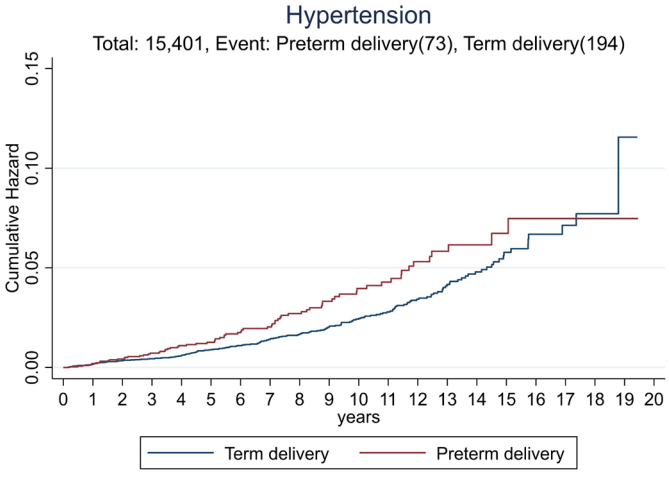

Figure 2 Nelson-Aalen plot for hypertension outcome.

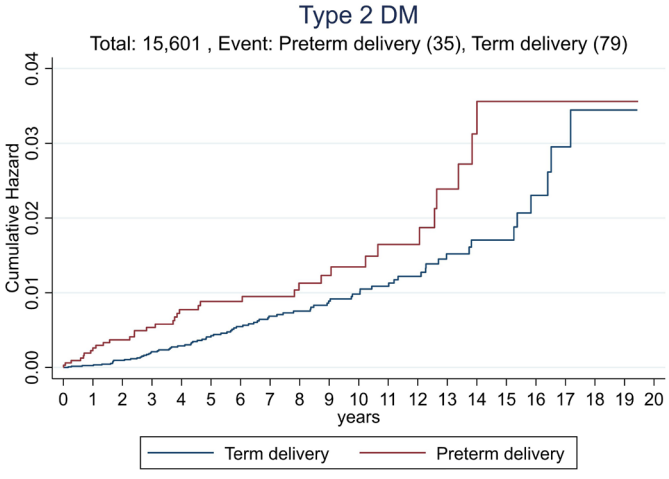

Figure 3 Nelson-Aalen plot for T2DM outcome.

reproductive complications was not observed in the multivariable models (online supplemental table S4) due to a small number of observations. While there was a significantly increased risk of hypertension events in women with health conditions linked to CID (aHR 1.87; 95%CI 1.02 to 3.44) and reproductive tumour (aHR 3.10; 95%CI 1.56 to 6.16), these findings may reflect an increase in risk of hypertension in pre-pregnancy diseases associated with chronic inflammation.[44–46] Inflammation has also been implicated to have a causal link with PTD.[47] Even though no significant association was observed in this study, these common biological factors imply that PTD may be a sign of subclinical risk of development of hypertension or T2DM in the future, rather than PTD leading to vascular and inflammatory changes. Associations with chronic inflammatory diseases support the view that inflammation may participate in hypertension, providing a pathophysiological link between these reproductive health conditions.[11 46 48]

Furthermore, hypertensive disorders of pregnancy and gestational diabetes are established risk factors for future risk of corresponding chronic health conditions.[22 49 50] The results of this study showed a strong association in the fully adjusted model (online supplemental table S4; HDP with hypertension, aHR 5.05, 95%CI 3.16 to 8.07; GDM with T2DM, aHR 18.80, 95%CI 12.05 to 29.35). These complications frequently coexist with PTD.[22] A history of PTD may be an indicator that can enable clinicians to identify women at high risk of cardiometabolic conditions which are accompanied by HDP or GDM.

Regarding perception of implication for public health, the 2021 European Society of Cardiology (ESC) guidance on CVD included PTD in the class IIb risk factors of clinical conditions, meaning that women with a history of PTD may be considered for periodic screening for hypertension and T2DM.[51] The usefulness of screening women with a history of PTD is less well established by evidence.[51] The findings of this study suggest the association observed in previous studies should be considered more carefully when applying in the UK population, as there was no significant association observed in this study, and previously observed associations could be attributable to confounding conditions. Future investigates of health conditions which accompany with PTD and the causes of PTD and their potential association with development of cardiometabolic condition would help to elucidate the complex interaction between these related conditions.

Overestimating the association may contribute to an economical burden on public health, such as inappropriate use of limited NHS resources. In addition, assessment of lower-risk patients may lead to the potential harms of prescribing unnecessary antihypertensive or diabetic medications and patient anxiety.

Strengths and limitations

Our study used a large primary care database that is generalisable to the UK. CPRD-registered participants represent the UK population regarding demographical characteristics including age, sex and ethnicity.[24] According to the Office for National Statistics,[3] the average age of mothers in England and Wales remained at 30.7 years in 2020, similar to the mean age in the study population (30.8 years). Another strength of the study is that information on a wide variety of confounders was available. Matching participants by age and region minimised confounding. Female-specific diseases or reproductive complications, such as PCOS, STD, CID and reproductive tumours, were included as potential confounders in analyses. We were also able to follow-up participants over a long period of time.

CPRD has been demonstrated to be reliable, but data is not entered into general practice systems for the purpose of research. Therefore, there were some limitations relating to data availability and data validity. The exposure variable was treated as only a dichotomous variable; differences depending on the gestational age (eg, very preterm, moderately preterm), pregnancy history, multiple pregnancy and recurrent pregnancy event could not be investigated. Also, missing values in the data on smoking, BMI and ethnicity could contribute to bias and impact the results in this study. To mitigate this issue, we conducted multiple imputation as a sensitivity analysis to see the effect of missing values on results.

Patients with undiagnosed hypertension and T2DM could have potentially been included in the unexposed cohort, resulting in misclassification. According to the Health Survey for England 2017,[52] one in five people with diabetes is undiagnosed, and this undiagnosed diabetes accounts for 1.5% of adults in the UK. Also, around half of hypertensives are unaware of their condition.[53] Although the exposure and outcomes variables were selected through a rigorous process, there are no studies that have validated the recording of PTD, hypertension or T2DM in the CPRD GOLD database. However, under the QOF scheme, reporting of hypertension and diabetes is financially rewarded; consequently, they are well documented in the CPRD. It is possible that a proportion of women in the exposed group may have experienced recurrent PTD in subsequent pregnancies. History of recurrent PTD further augments the risk of long-term maternal cardiometabolic outcomes.[19] The possibility of unmeasured confounding still exists, despite the fact that we controlled several known and potential confounders; for example, we were unable to adjust for family history of CVD, physical activity and chlamydia trachomatis infection.

The relatively short follow-up period in a population of young women and the low number of outcome events may have led to type II error in this study; therefore, the lack of statistical significance of the findings should be interpreted with caution. In this study, the overall outcome event rate was 1.7% for hypertension and 0.73% for T2DM, with a median follow-up of 5.11 (IQR 2.15–9.56) years for hypertension outcome and 5.17 (IQR 2.18–9.67) years for T2DM outcome; this was a slightly lower event rate with shorter follow-up period

than in the previous national registry-based retrospective cohort study,[19] in which overall outcome event rates were 2.4% for hypertension and 0.9% for T2DM with a median follow-up time of 14.6 years (IQR 7.61–21.8) and 12.9 years (IQR 6.86–18.9) for each cohort. Other studies appeared to have followed patients longer. Using a larger dataset such as CPRD Aurum could be considered for further research to increase the number of outcomes and address the issue of statistical power.

CONCLUSION

An independent effect of preterm delivery on subsequent development of hypertension or T2DM was not observed in this study population. While significant associations were observed in unadjusted analyses, the association was lost after adjustment and appeared to be attributable to other reproductive complications, such as HDP, GDM and chronic inflammatory diseases. Additional studies are needed to confirm these findings. This study suggests that the associations identified in previous studies should be considered more carefully when applying them to the UK population and in the context of potential confounders. Overestimating the association may result in a burden on public health and patients. Additionally, it would be of value to investigate health conditions which co-occur with PTD and the causes of PTD and their association with development of hypertension and T2DM to further elucidate the complex interplay between these related conditions.

Contributors KO and NA conceived the idea for the study. AS carried out the statistical analysis and wrote the first draft of the manuscript. KO and NA supervised the study and analysis. All authors, AS, KO and NA, reviewed and revised the manuscript. AS acts as guarantor.

Funding This is independent research carried out at the National Institute for Health and Care Research (NIHR) Birmingham Biomedical Research Centre (BRC).

Disclaimer The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval Observational research using CPRD data was approved by National Research Ethics Service Committee. This study was approved by the independent Research Data Governance Committee (reference 22_001864).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data may be obtained from a third party and are not publicly available. Data for the study were obtained under licence from CPRD; pseudonymised participant data are available from CPRD subject to Research Data Governance approval.

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