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ORIGINAL RESEARCH

Single-Multiple and Recurrent Pregnancy-Related Complications and Incident Cardiovascular Disease: A Nationwide Data Linkage Study in Wales, UK

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BACKGROUND: Pregnancy-related complications are linked to increased cardiovascular disease risk, but comprehensive evaluations of diverse complications, particularly multiple or recurrent events, are limited.

METHODS: A national retrospective cohort study was conducted using the Secure Anonymised Information Linkage (SAIL) Databank in Wales. Exposures were hypertensive disorders of pregnancy, gestational diabetes, placental abruption, stillbirth, small for gestational age, fetal growth restriction, and preterm birth. Multiple complications were defined as >1 complication in the first pregnancy, and recurrent complications as the same complication in both the first and second pregnancies. Outcomes were incident ischemic heart disease, stroke, heart failure, and atrial fibrillation. Cox regression estimated hazard ratios (HRs).

RESULTS: A total of 298 515 women (mean age 27.2 years; SD 6.1) were included. Multiple pregnancy-related complications were associated with increased risk of ischemic heart disease (hazard ratio HR, 2.88 [95% CI, 2.27–3.67]), stroke (HR, 2.03 [95% CI, 1.55–2.65]), heart failure (HR, 3.18 [95% CI, 2.34–4.32]), and atrial fibrillation (HR, 1.80 [95% CI, 1.20–2.72]) compared with no complications. A dose–response relationship was observed, with progressively higher cardiovascular disease risk for multiple compared with single complications and elevated risk for both groups relative to women without complications. Recurrent pregnancy-related complications increased the risk of ischemic heart disease (HR, 1.93 [95% CI, 1.26–2.95]), stroke (HR, 1.89 [95% CI, 1.25–2.85]), heart failure (HR, 3.61 [95% CI, 2.32–5.60]), and atrial fibrillation (HR, 2.45 [95% CI, 1.38–4.37]) compared with no complication.

CONCLUSIONS: Women experiencing pregnancy-related complications encounter higher risks of cardiovascular disease, especially with multiple or recurrent complications. Comprehensive cardiovascular risks assessment and targeted prevention should be prioritized for this group.

Key Words: atrial fibrillation ■ cardiovascular disease ■ pregnancy complications ■ recurrent pregnancy complications

Although cardiovascular disease (CVD) is often considered a predominantly male condition, this misconception has led to the underestimation of CVD risk in women.[1] CVD is the leading cause of death in women globally, accounting for ~35% of all female mortality.[2] Although global mortality from ischemic heart disease (IHD) has declined over time, these reductions have been more substantial in men than

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CLINICAL PERSPECTIVE

What Is New?

- Multiple complications in the first pregnancy and recurrent complications across first and second pregnancies were associated with substantially increased long-term risks of ischemic heart disease, stroke, heart failure, and atrial fibrillation.
- A dose–response relationship was observed, with progressively higher cardiovascular risk in women with multiple compared with single complications, and elevated risk for both groups relative to women without complications.

What Are the Clinical Implications?

- Women with multiple or recurrent complications represent a particularly high-risk group who may benefit from targeted cardiovascular screening and preventive interventions.

Nonstandard Abbreviations and Acronyms

SAIL	Secure Anonymised Information Linkage Databank
WIMD	Welsh Index of Multiple Deprivation

women, particularly in younger women under the age of 55.[3,4]

Multiple systematic reviews of observational studies have indicated that pregnancy-related complications are associated with a higher risk of incident CVD.[5–8] Although studies have explored the associations between pregnancy-related complications and incident CVD,[5–8] few have evaluated atrial fibrillation (AF), the commonest heart rhythm disorder, as a CVD outcome.[9] Moreover, the association between >1 pregnancy-related complication and incident CVD has been insufficiently investigated. For example, a recent large cohort study suggested that the coexistence of multiple pregnancy-related complications was associated with a higher risk of IHD, with adjusted hazard ratios (HR) linked with encountering 1, 2, or ≥3 pregnancy-related complications being 1.29 (95% CI, 1.19–1.39), 1.80 (95% CI, 1.59–2.03), and 2.26 (95% CI, 1.89–2.70), respectively.[10]

In addition, recurrent pregnancy-related complications have been associated with a higher risk of CVD compared with nonrecurrent pregnancy-related complications.[11,12] However, there has been limited research exploring the associations between the broad spectrum of recurrent pregnancy-related complications and incident CVD.

Using population-scale national-level data linkage available in Wales, UK, the study aims to examine associations between single pregnancy-related complications, multiple pregnancy-related complications or recurrent pregnancy-related complications and risk of incident IHD, stroke, heart failure (HF), and AF.

METHODS

Data Sharing Statement

The data used in this study are available from the Secure Anonymised Information Linkage (SAIL) Databank at Swansea University, but access requires application to SAIL due to data governance restrictions.

Data Sources

This project used data from the SAIL Databank, the national trusted research environment for Wales, which contains population-scale, individual-level anonymized linkable data from various routinely-collected data sources in Wales.[13] Within the SAIL Databank, each individual is assigned a unique identifier for a particular study using an anonymous linking field.[13,14] Using the anonymous linking field, individual-level health-related information was linked from multiple sources, including the Office for National Statistics birth and death extracts, hospital admissions, outpatient attendances, and emergency department and primary care records. Further details about record linkage are given in the Supplementary materials (Table S1). The study was approved by the SAIL Databank Information Governance Review Panel (project 1136). The research used anonymized routinely collected health data; therefore, individual informed consent was not required.

Study Population

The study population included all women who were aged 16 to 45 years at the time of their first childbirth, with the first birth occurring in Wales between January 1, 2000 and December 31, 2018. Birth and maternity records were identified using the National Community Child Health data, Annual District Birth Extract, and Maternity Indicators Data Set, which have collectively recorded birth data in Wales since 1987.[15] To establish the cohort, women were excluded if they:

1. had a maternity or birth record between January 1, 1990 and December 31, 1999 to increase the likelihood of capturing women's first recorded births within the study period and approximate a predominantly nulliparous baseline cohort, as national and cohort data indicate median birth intervals of ~3 years, making unrecorded earlier births unlikely;

2. had <1 year recorded medical history, to ensure adequate ascertainment of baseline comorbidities and exposures and reduce bias from incomplete or fragmented medical records;
3. were aged <16 years or >45 years at the time of first birth;
4. had a history of IHD, AF, HF, or stroke before first pregnancy;
5. had first birth after December 31, 2018; or
6. had missing gestational age (GA) or <20 weeks pregnancy at the first birth. GA was excluded rather than imputed because it was central to defining key exposures (preterm birth, small for GA [SGA], and fetal growth restriction [FGR]) and to validate the timing of diagnostic codes. Following the cohort creation, duplicate records were checked. Details of the identification process are available in Figure S1.

To evaluate the role of recurrent pregnancy-related complications, a subset cohort was created, including only women who had >1 birth during the study period. The previous exclusion criteria were applied to the second birth. Additionally, women with an implausible birth interval, defined as a birth interval between the first and second birth being shorter than the GA of the second pregnancy, were excluded. For consistency, pregnancy complications were defined according to the first recorded pregnancy, which served as the primary exposure of interest. Subsequent pregnancies were not included in the main analysis; however, in the recurrence analysis, complications across both the first and second pregnancies were considered. The time for data extraction was determined from January 1, 2000 until December 31, 2018 to maximize the data accuracy and to allow for a minimum of 1-year follow-up. The study end date was December 31, 2019 to exclude secular trends of CVD morbidity and mortality related to the COVID-19 pandemic.[16]

Exposures

The exposures of interest were the following pregnancy-related complications: hypertensive disorders of pregnancy (HDP), gestational diabetes, placental abruption, stillbirth, SGA, FGR and preterm birth. HDP, gestational diabetes, placental abruption, and stillbirth were defined using *International Classification of Diseases, Tenth Revision* (*ICD-10*) and Read codes from the Patient Episode Database for Wales and the Wales Longitudinal General Practice data during the pregnancy period (refer to Tables S2 and S3). Preterm birth was defined as birth of a baby before 37+0 weeks of gestation. SGA and FGR were inferred from birth weight and the GA data from the National Community Child Health and the Maternity Indicators Data Set. SGA was defined as birth weight <10th percentile for sex and GA, and FGR was defined as a birth weight below the third percentile for sex and GA.[17] The birth weight percentiles were calculated using the 'zanthro' command in Stata 17, which computes *Z* scores for anthropometric measures using the 1990 UK-World Health Organization growth reference charts.[18] *Z* scores were then transformed to percentiles, which were used to define SGA and FGR. External evaluations have confirmed the accuracy of maternity and birth data within Welsh national sources linked to the SAIL Databank.[19,20]

History of any pregnancy-related complication was defined as presence of any of the previously mentioned complications during the first pregnancy. Single pregnancy-related complication was defined as presence of only 1 pregnancy-related complication during the first pregnancy. Multiple pregnancy-related complications were defined as presence of >1 of the following conditions: gestational diabetes, placental abruption, stillbirth, SGA, or preterm birth during the first pregnancy. History of FGR was excluded from this definition because all FGR cases are SGA by the study definition. Recurrent pregnancy-related complications were defined as presence of a history of occurrences of the same pregnancy-related complication in the first and second pregnancy. Nonrecurrent pregnancy-related complications were defined as a history of occurrence of any pregnancy-related complication in either the first or second pregnancy only or a history of occurrence of different pregnancy-related complications in the first and second pregnancy.

Outcomes

The outcomes of interest were incident IHD, stroke, HF, and AF. The diagnosis of these outcomes was based on related *ICD-10* and Read codes. A search for the related codes, provided in Tables S2 and S3, was undertaken in the Wales Longitudinal General Practice, Patient Episode Database for Wales, the Outpatient Dataset for Wales, the Emergency Department Data Set, and the Annual District Death Extract data sources. To accurately identify incident events, we selected the first recorded instance of the outcome across any of the available data sets. In cases where the same event was recorded in >1 data set, the earliest occurrence was retained. Algorithm and codes used in this study have been validated in other UK electronic health record systems.[21,22]

Covariates

The variables included in this project were chosen based on clinical knowledge regarding their association with CVD (Figure S2). The list and definition of variables, which included demographic characteristics

and medical conditions, are summarized in (Table S4). Covariates included prepregnancy maternal medical conditions (hypertension, diabetes, hyperlipidemia, congenital heart disease, and valvular heart disease), quintiles of the Welsh Index of Multiple Deprivation (WIMD2011 version), race/ethnicity, multifetal pregnancy (yes/no), maternal age at first delivery, and calendar year of first birth categorized as 5-year interval.

Statistical Analysis

Descriptive statistics were provided to describe the baseline characteristics of individuals with history of any pregnancy-related complications, and no pregnancy-related complication at the end of first pregnancy.

For analyses evaluating histories of any pregnancy complication and multiple-single pregnancy complications, the follow-up period was taken from the first birth date, whereas for recurrent pregnancy complications, follow-up began at the second birth. Participants were censored at the earliest date of the following: loss of follow up, death, development of outcome of interest, or the study end date. For recurrent pregnancy complications, women were also censored if they reached 10 years of follow-up. This restriction was applied because the recurrent cohort (limited to women with ≥2 births) became sparse at longer durations, leading to instability in cumulative incidence estimates, particularly for rarer outcomes such as HF and AF. It also ensured compliance with SAIL Databank disclosure controls, which prohibit the export of results that could risk reidentification of anonymized data. Survival analyses were conducted using Cox proportional hazards regression models to estimate HRs and 95% CIs for each study outcome. The proportionality of hazards was investigated using global Schoenfeld residuals test and by assessing log–log survival plots. Competing risk methods were not applied due to the very low mortality rate in this young cohort, making informative censoring by death was unlikely to affect results. Adjustment for potential confounders were conducted by including information regarding prior chronic conditions: prepregnancy hypertension, pregestational diabetes, hyperlipidemia, maternal congenital heart disease, and valvular heart disease, which were included as dichotomous variables (yes/no). Race/ethnicity (White and not White [race/ethnicity was analyzed as White versus combined minoritized ethnic groups (Black/Black British, Asian/Asian British, Mixed, and Other)]) and multifetal pregnancy (yes/no) were also included as dichotomous variables. WIMD quintiles (first—least deprived, fifth—most deprived) and the calendar year of the first birth (2000–2004, 2005–2009, 2010–2014, and 2015–2018) were included as categorical variables. Maternal age at first birth was included as a continuous variable. In analyses evaluating recurrent pregnancy complications, the same set of confounders were used at the second birth. Statistical analyses were conducted using Stata (version 17; Stata Corp LLC, College Station, TX) and R (version 4.0.2). Results are presented as main effects with 95% CIs unless otherwise stated.

Secondary Analysis

Secondary analyses were undertaken to assess the association between individual pregnancy-related complications and incident IHD, stroke, HF, and AF. Additionally, the analysis explored the influence of hypertension, diabetes, and maternal age on the relationship between a history of any pregnancy-related complication and incident composite CVD.

To evaluate individual pregnancy-related complications with incident CVD, 3 Cox proportional hazards models were employed. The first model compared women with each specified pregnancy-related complication with women who did not experience that complication, while adjusting for covariates. The second model further adjusted for a history of other pregnancy-related complications. The third model compared women with each specified pregnancy-related complication with women who had no pregnancy-related complications, while adjusting for covariates. Additional analyses explore the association between individual recurrent pregnancy-related complications and incident CVD.

For hypertension, diabetes, and maternal age, interaction analyses were performed to examine whether these factors modified the association between pregnancy-related complication and incident composite CVD. Prepregnancy hypertension was defined as the presence of hypertension-related codes before 20 weeks' gestation, and pregestational diabetes as the presence of diabetes-related codes before pregnancy. Incident postpartum hypertension was defined as the presence of hypertension-related codes after the first birth and before the diagnosis of CVD and incident postpartum diabetes as the presence of diabetes-related codes after the first birth and before the diagnosis of CVD. The *P* value for interaction was tested using the likelihood ratio test.

Further, mediation analyses were conducted to determine the impact of incident postpartum hypertension or diabetes on the association between pregnancy-related complications and incident CVD using a 4-way decomposition method.[23] Based on this approach, the effect of pregnancy-related complications on incident CVD in relation with incident postpartum hypertension or diabetes after birth, can be decomposed into 4 components: (1) *controlled direct effects* (the direct effect of pregnancy-related complications on incident CVD that was not explained by incident postpartum hypertension or diabetes); (2) *reference interaction effect* (the effect of pregnancy-related complications on incident CVD due

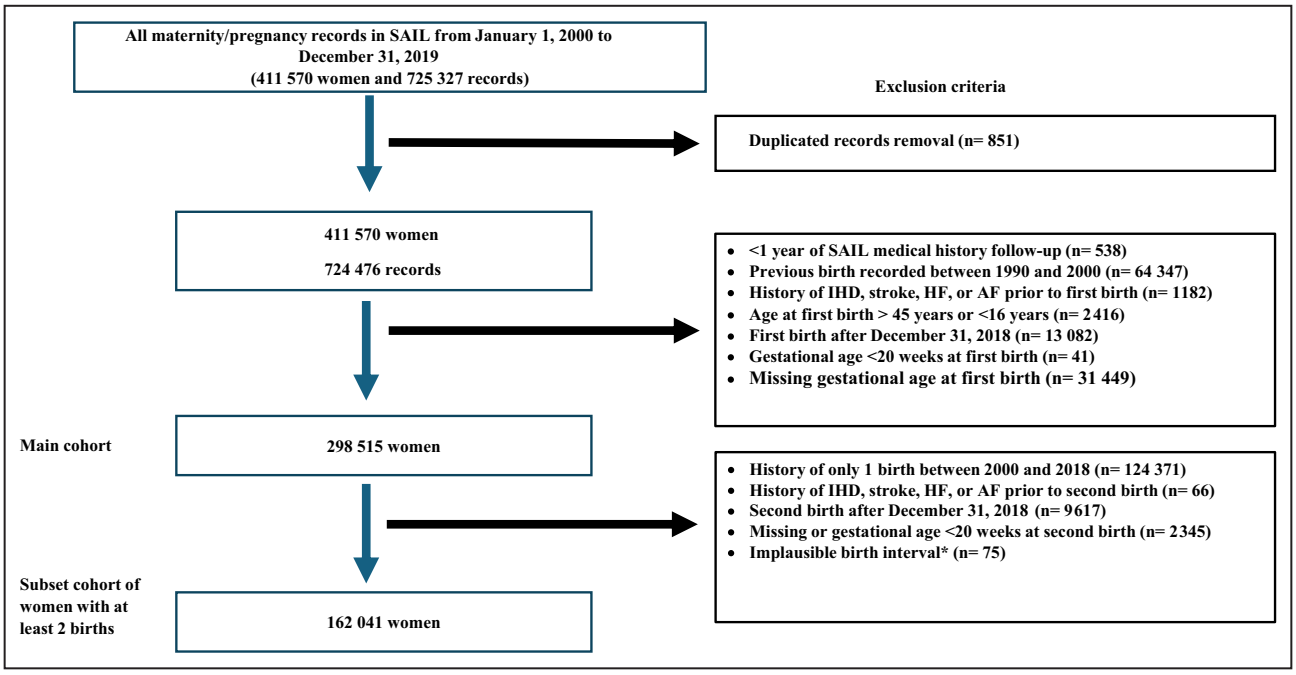

Figure 1. Flow diagram depicting the cohort construction.
AF indicates atrial fibrillation; HF, heart failure; IHD, ischemic heart disease; and SAIL, Secure Anonymised Information Linkage Databank. *Implausible birth interval: birth interval is lower than the gestational age of the second pregnancy.

to interaction with incident postpartum hypertension or diabetes); (3) *mediated interaction effect* (the effect of pregnancy-related complications on incident CVD due to both interaction and mediation with incident postpartum hypertension or diabetes); and (4) *pure indirect effect* (the effect of pregnancy-related complications on incident CVD through incident postpartum hypertension or diabetes). Stata command med4way was used to compute the 4-way decompositions.[24] Further details regarding the secondary analyses are provided in the Supplementary materials.

Sensitivity Analysis

Four sensitivity analyses were conducted. First, women with preexisting congenital or valvular heart diseases were excluded. Second, the cohort entry was delayed to 12 weeks postnatally to evaluate the impact of exposure and outcome misclassification because HDP may persist or manifest de novo after birth, and CVD developing during this period could be related to pregnancy rather than pregnancy-related complications. Third, the roles of missing data in the WIMD were evaluated using multiple scenarios. Scenario 1: All missing in WIMD are considered the lowest value and all missing in race/ethnicity are considered White; Scenario 2: all missing in WIMD are considered the lowest value and all missing in race/ethnicity are considered non-White; Scenario 3: all missing in WIMD are considered the highest value and all missing in race/ethnicity are considered White; Scenario 4: all missing in WIMD are considered the highest value and all missing in race/ethnicity are considered non-White.

RESULTS

Demographic Characteristics

The study cohort included 298 515 women (mean±SD age 27.2, [6.1]) with 541 581 unique pregnancies (Figure 1). The median follow-up time was 9.7 years (interquartile range 4.4–14.9 years). Maternal demographic and pregnancy characteristics are shown in Table 1 for the entire cohort after the first birth. Any pregnancy-related complications were present in 74 832 (25.1%) women during the first pregnancy. Compared with women with no pregnancy-related complications, women with any pregnancy-related complication tended to live in more deprived areas (lowest quintile 25.1% versus 22.4%) and had higher rates of multifetal pregnancy (4% versus 0.8%) and chronic diseases including prepregnancy hypertension (1.4% versus 0.4%) and pregestational diabetes (1% versus 0.3%). The incidence of various pregnancy-related complications, including individual, single, and multiple occurrences (individual pregnancy-related complications refer to specific types of complications [eg, gestational diabetes, preterm birth], each analyzed separately as an exposure whereas single and multiple pregnancy-related complications refer to the number of complications experienced during the first pregnancy, irrespective of type), as well as recurrent and

Table 1. Baseline Characteristics of Pregnant Women Who Had Their First Birth in Wales During 2000 to 2018 Grouped by a History of Any Pregnancy-Related Complication During the First Pregnancy

Characteristic No. (%)	Any pregnancy complication (n=74 832)	No pregnancy complication (n=223 683)
Maternal age, y, mean±SD	27.29±6.2	27.14±5.9
Male sex infant*	37 748 (52.6)	113 598 (51.2)
Gestational age, wks	37.85 (3.5)	39.79 (1.3)
Race/ethnicity		
White	62 636 (83.7)	187 816 (84.0)
Not White†	7907 (10.6)	21 527 (9.6)
Unknown	4289 (5.7)	14 340 (6.4)
Birth weight, g* mean±SD	2832±701	3483±428
Welsh index of multiple deprivation		
1st (least deprived)	18 745 (25.0)	50 149 (22.4)
2nd	15 885 (21.2)	45 949 (20.5)
3rd	14 330 (19.1)	43 931 (19.6)
4th	12 366 (16.5)	39 760 (17.8)
5th (most deprived)	11 305 (15.1)	37 890 (16.9)
Unknown	2201 (2.9)	5953 (2.7)
Multifetal pregnancy	3008 (4.0)	1700 (0.8)
Hypertension	1046 (1.4)	951 (0.4)
Diabetes	763 (1.0)	706 (0.3)
Hyperlipidemia	563 (0.8)	1144 (0.5)
Congenital heart disease	238 (0.3)	706 (0.3)
Valvular heart disease	166 (0.2)	420 (0.2)
Calendar birth year		
2000–2004	19 676 (26.3)	56 859 (25.4)
2005–2009	21 030 (28.1)	64 070 (28.6)
2010–2014	20 473 (27.4)	59 438 (26.6)
2015–2018	13 653 (18.2)	43 316 (19.4)

All numbers are n (%), unless otherwise stated.
*Excluding multifetal pregnancy.
†Race/ethnicity was analyzed as White vs combined minoritized ethnic groups (Black/Black British, Asian/Asian British, Mixed, and Other).

nonrecurrent cases, are presented in the Tables S5 through S7.

Any Pregnancy Complication, Single, and Multiple Pregnancy Complications

After adjusting for potential confounders, women with a history of any pregnancy-related complications at their first pregnancy exhibited a higher risk of incident HF (HR, 1.93 [95% CI, 1.61–2.31]), IHD (HR, 1.82 [95% CI, 1.58–2.10]), stroke (HR, 1.39 [95% CI, 1.20–1.61]), and AF (HR, 1.33 [95% CI, 1.08–1.65]), compared with women with no history of any complications (Table 2).

Women with a history of multiple pregnancy-related complications had the highest risk for incident HF compared with women with no history of pregnancy-related complications (HR, 3.18 [95% CI, 2.34–4.32]). Although the association was attenuated, it remained statistically significant when comparing women with a single pregnancy-related complication to those without complications (HR, 1.73 [95% CI, 1.43–2.10]). Similar patterns were observed for stroke, IHD, and AF, with women in the multiple complications group having higher risks compared with those in the single complications group and those with no pregnancy-related complications.

A history of HDP alone was associated with a higher risk of IHD, stroke, and HF. A history of gestational diabetes alone was significantly associated with an increased risk of IHD and HF. A history of preterm birth alone was linked to elevated risks of IHD, stroke, HF, and AF, whereas a history of SGA alone was primarily associated with an increased risk of IHD (Figure 2). Due to low event rates, placental abruption, FGR, and stillbirth were not analyzed independently.

Recurrent and Nonrecurrent Pregnancy Complications

Compared with women with no history of pregnancy-related complications, women with a history of recurrent pregnancy-related complications had a higher risk of incident HF (HR, 3.61 [95% CI, 2.32–5.60]), AF (HR, 2.45 [95% CI, 1.38–4.37]), IHD (HR, 1.93 [95% CI, 1.26–2.95]), and stroke (HR, 1.89 [95% CI, 1.25–2.85]) (Table 3). The associations were attenuated but remained statistically significant when comparing women with nonrecurrent pregnancy-related complications (defined as complications occurring in only 1 pregnancy or as different complications across pregnancies) to women without any history of pregnancy-related complications (HR, 1.64 [95% CI, 1.16–2.32] for incident HF, 1.61, [95% CI, 1.11–2.34] for incident AF, 1.59, [95% CI, 1.24–2.04] for incident stroke, and 1.46, [95% CI, 1.10–1.92] for incident IHD) (Table 3).

Secondary Analysis

Individual Pregnancy Complications

Women with a history of HDP and preterm birth had elevated risks across all 4 CVD outcomes. Gestational diabetes was associated with increased risks of IHD, stroke, and HF, albeit with wide 95% CIs. FGR showed significant associations with IHD and HF, but when accounting for other pregnancy complications, the association with IHD was not statistically significant. SGA was primarily associated with an increased risk of IHD (Figure S3). Analysis of recurrent pregnancy-related complications revealed that HDP increased the risk of IHD, stroke, HF, and AF. Recurrent preterm birth was associated with a higher risk of IHD and HF, whereas recurrent FGR was linked to stroke. No significant association was observed between recurrent gestational diabetes and SGA (Figure S4).

Table 2. The Association Between History of any Pregnancy Complication, Single or Multiple at the First Pregnancy and Incident Cardiovascular Diseases Among 298515 Pregnant Women Who Have Their First Birth in Wales From 2000 to 2018: Complete Cases Analysis

Cardiovascular diseases	Events	Person-years	Incidence rate (95% CI) per 10000 person-years	Unadjusted		Adjusted*	
	No.			HR (95% CI)	*P* value	HR (95% CI)	*P* value
Ischemic heart disease							
No pregnancy complication	525	2183662	2.40 (2.20–2.61)	1		1	
Any pregnancy complication	363	742984	4.88 (4.40–5.41)	2.09 (1.82–2.40)	<0.001	1.82 (1.58–2.10)	<0.001
Single pregnancy complication	274	644805	4.24 (3.77–4.78)	1.79 (1.54–2.09)	<0.001	1.64 (1.41–1.92)	<0.001
Multiple pregnancy complications	89	98178	9.06 (7.36–11.15)	4.08 (3.24–5.14)	<0.001	2.88 (2.27–3.67)	<0.001
Stroke							
No pregnancy complication	581	2183526	2.66 (2.45–2.88)	1		1	
Any pregnancy complication	313	743200	4.21 (3.76–4.70)	1.57 (1.37–1.80)	<0.001	1.39 (1.20–1.61)	<0.001
Single pregnancy complication	244	644986	3.78 (3.33–4.28)	1.38 (1.18–1.61)	<0.001	1.29 (1.10–1.50)	<0.001
Multiple pregnancy complications	69	98214	7.02 (5.54–8.89)	2.56 (1.97–3.32)	<0.001	2.03 (1.55–2.65)	<0.001
Heart failure							
No pregnancy complication	313	2184761	1.43 (1.28–1.60)	1		1	
Any pregnancy complication	233	743705	3.13 (2.75–3.56)	2.13 (1.79–2.55)	<0.001	1.93 (1.61–2.31)	<0.001
Single pregnancy complication	174	645352	2.69 (2.32–3.12)	1.86 (1.53–2.25)	<0.001	1.73 (1.43–2.10)	<0.001
Multiple pregnancy complication	59	98352	5.99 (4.64–7.74)	3.99 (2.97–5.36)	<0.001	3.18 (2.34–4.32)	<0.001
Atrial fibrillation							
No pregnancy complication	286	2184721	1.30 (1.16–1.46)	1		1	
Any pregnancy complication	145	743957	1.94 (1.65–2.29)	1.43 (1.16–1.76)	0.001	1.33 (1.08–1.65)	0.007
Single pregnancy complication	116	645512	1.79 (1.49–2.15)	1.32 (1.05–1.65)	0.014	1.26 (1.01–1.58)	0.044
Multiple pregnancy complications	29	98444	2.94 (2.04–4.23)	2.15 (1.44–3.22)	<0.001	1.80 (1.20–2.72)	0.005

HR indicates hazard ratio.

*Adjusted for hypertension, diabetes, hyperlipidemia, congenital, and valvular heart disease and multifetal pregnancy (yes/no), race/ethnicity (White/not White [race/ethnicity was analyzed as White vs combined minoritized ethnic groups (Black/Black British, Asian/Asian British, Mixed, and Other)]), maternal age, calendar year of first birth categorized as 5-y interval, Welsh index of multiple deprivation: categorized as quintiles at first birth.

Role of Hypertension, Diabetes, and Maternal Age

In comparison to women without a history of pregnancy-related complications and without prepregnancy hypertension or pregestational diabetes, women with both conditions had the highest risk of incident CVD (HR, 7.66 [95% CI, 6.25–9.40]) followed by women with prepregnancy hypertension or pregestational diabetes only (HR, 4.36 [95% CI, 3.33–5.70]) and women with pregnancy-related complications only (HR, 1.58 [95% CI, 1.45–1.73]) Table S8.

A history of pregnancy-related complications was associated with a higher risk of incident CVD (HR, 1.58 [95% CI, 1.45–1.73] and 1.66 [95% CI, 1.20–2.31]) among women with and without prepregnancy hypertension or pregestational diabetes, respectively (Table S8). There was no interaction between pregnancy-related complications and prepregnancy hypertension or pregestational diabetes ($P_{interaction}$=0.55). Evaluating prepregnancy hypertension or pregestational diabetes separately revealed similar patterns (Tables S9 and S10). When investigating the role of maternal age at the

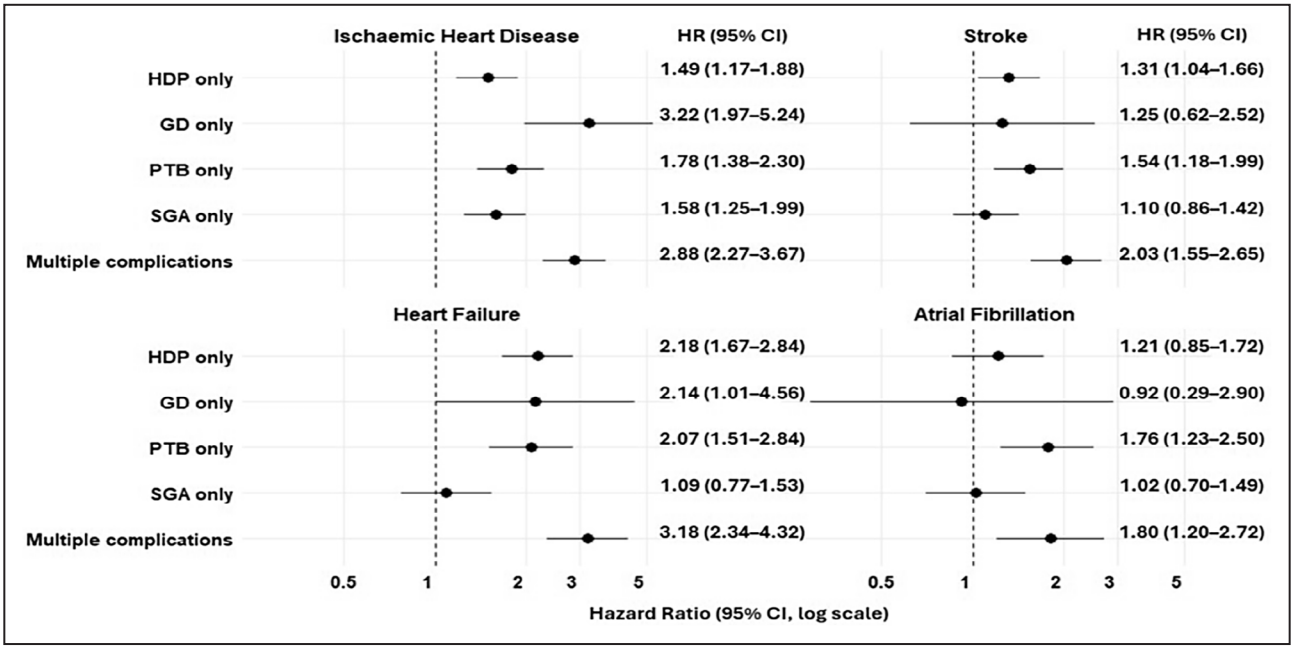

Figure 2. Adjusted hazard ratios for incident cardiovascular disease among women with a history of prespecified single pregnancy-related complication at first pregnancy compared with women without a history of pregnancy-related complication.

GD indicates gestational diabetes; HDP, hypertensive disorders of pregnancy; HR, hazard ratio; PTB, preterm birth; and SGA, small for gestational age.

first birth there was a consistent trend toward a higher risk of CVD with pregnancy-related complications and older age ($P_{interaction}$=0.026) (Table S11).

Mediation analysis revealed that pregnancy-related complications were associated with a higher risk of incident CVD, even after accounting for incident postpartum hypertension or diabetes (HR, 1.41 [95% CI, 1.26–1.56]) (Table S12). A history of pregnancy-related complications was associated with a higher risk of incident postpartum hypertension or diabetes (odds ratio [OR], 2.91 ([95% CI, 2.80–3.03]) (Table S13).

The 4-way decomposition demonstrated that 54.2% (37%–71%) of the association between pregnancy-related complications and incident CVD was due to the direct effect of pregnancy-related complications. The overall mediation of incident postpartum hypertension or diabetes accounted for 43.9% (29.5%–58.3%) of the observed association (Table S14). Similar patterns were observed for incident postpartum hypertension or diabetes individually.

Sensitivity Analysis

Sensitivity analysis, which excluded women with preexisting congenital or valvular heart diseases, did not reveal any significant differences in the point estimate or the 95% CIs when compared with the main analysis (Tables S15 and S16). Similar results were observed when the start of follow-up commenced 12 weeks postnatally, rather than immediately after birth (Tables S15 and S16), or when evaluating missing data on WIMD and race/ethnicity (Tables S17 and S18).

DISCUSSION

In this retrospective analysis of 298 515 women, any pregnancy-related complication at the first pregnancy was associated with a higher risk of IHD, stroke, AF, and HF. This risk was further increased with coexistence of multiple pregnancy-related complications. Second, in women with >1 birth, recurrent pregnancy-related complications were also associated with a higher risk of incident IHD, stroke, AF, and HF. Third, incident postpartum hypertension or diabetes may partially mediate the relationship between pregnancy-related complications and CVD. Finally, there was an interaction between maternal age and pregnancy-related complications in relation to the risk of incident CVD.

Any Pregnancy-Related Complication and CVD

The current findings align with previous research linking pregnancy-related complications and CVD.[25,26] For example, a study used the Ontario Health Insurance Plan reported that a history of any pregnancy-related complications (HDP, FGR, and placental abruption) during the first pregnancy was associated with double the risk of IHD and cerebrovascular events.[25] Another study using the same data found a higher risk of HF

Table 3. The Association Between History of Recurrent Pregnancy Complication at the Second Pregnancy and Incident Cardiovascular Diseases Among 162041 Pregnant Women Who Have Their First Birth in Wales From 2000 to 2018: Complete Cases Analysis

Cardiovascular diseases	Events No.	Person-years	Incidence rate (95% CI) per 10000 person-year	Unadjusted HR (95% CI)	Unadjusted *P* value	Adjusted* HR (95% CI)	Adjusted* *P* value
Ischemic heart disease							
No pregnancy complication	133	758193	1.75 (1.47–2.08)	1		1	
Non-recurrent pregnancy complication	89	316715	2.89 (2.34–3.56)	1.65 (1.25–2.16)	<0.001	1.46 (1.10–1.92)	0.007
Recurrent pregnancy complication	29	63514	4.65 (3.21–6.74)	2.63 (1.75–3.97)	<0.001	1.93 (1.26–2.95)	0.002
Stroke							
No pregnancy complication	160	758132	2.12 (1.81–2.48)	1		1	
Non-recurrent pregnancy complication	113	316603	3.58 (2.97–4.33)	1.69 (1.33–2.15)	<0.001	1.59 (1.24–2.04)	<0.001
Recurrent pregnancy complication	33	63497	4.65 (3.21–6.74)	2.45 (1.68–3.56)	<0.001	1.89 (1.25–2.85)	0.002
Heart failure							
No pregnancy complication	79	758387	1.07 (0.86–1.34)	1		1	
Non-recurrent pregnancy complication	64	316754	1.92 (1.48–2.49)	1.79 (1.27–2.51)	0.001	1.64 (1.16–2.32)	0.004
Recurrent pregnancy complication	30	63526	4.98 (3.48–7.13)	4.62 (3.03–7.04)	<0.001	3.61 (2.32–5.60)	<0.001
Atrial fibrillation							
No pregnancy complication	73	758424	0.97 (0.77–1.23)	1		1	
Non-recurrent pregnancy complication	51	316802	1.59 (1.17–2.07)	1.59 (1.10–2.30)	0.013	1.61 (1.11–2.34)	0.011
Recurrent pregnancy complication	17	63554	2.32 (1.37–3.92)	2.36 (1.33–4.19)	0.003	2.45 (1.38–4.37)	0.002

HR indicates hazard ratio.

*Adjusted for hypertension, diabetes, hyperlipidemia, congenital, and valvular heart disease and multifetal pregnancy (yes/no), race/ethnicity (White/not White [race/ethnicity was analyzed as White vs combined minoritized ethnic groups (Black/Black British, Asian/Asian British, Mixed, and Other)]), maternal age, calendar year of first birth categorized as 5-y interval, Welsh index of multiple deprivation: categorized as quintiles at second birth.

(HR, 1.80 [95% CI, 1.42–2.29]), and AF (HR, 1.48 [95% CI, 1.10–1.98]).[26] However, these studies were limited by their reliance on a single data source and defined incident CVD based solely on hospital admissions.[25,26] In contrast, the current study used multisource, national-level data for Wales.

Single and Multiple Pregnancy-Related Complication and CVD

Although previous studies have primarily focused on individual pregnancy-related complications,[4,6] there is a paucity of research that has comprehensively evaluated a broad range of these complications and their association with the risk of incident CVD.[10,27–29] Consistent with these studies, the current research suggests that experiencing single or multiple pregnancy-related complications is associated with a higher risk of incident CVD.[27–29] For instance, a retrospective cohort study in Florida involving 302686 women with a median follow-up of 4.9 years found that any placental syndrome (HDP, placental abruption, or infarction) was linked to an increased risk of composite CVD outcomes (HR, 1.19 [95% CI, 1.07–1.32]).[29] The risk was further increased among women with >1 placental syndrome (HR, 1.43 [95% CI, 1.20–1.70]).[29] Interestingly, the present study observed a potentially stronger association between multiple pregnancy-related complications and incident CVD compared with the previous study, possibly due to a longer follow-up period (median 9.7 versus 4.9 years).[29]

Previous studies have shown a dose–response relationship between the number of pregnancy-related complications and the risk of IHD.[10,30] For instance, data from the Scottish Morbidity Record indicated that a single complication, such as preeclampsia, low

birthweight, or preterm birth, doubled the risk of IHD. This risk increased to 3.3 to 4.5 times with 2 complications and up to 7 times with 3 complications. These findings were reinforced, albeit with an attenuated association, by a recent large Swedish study (n=2 195 266) with a 24.8-year follow-up.[10] However, it remains unclear whether multiple complications have an additive effect on CVD.

Recurrent Pregnancy-Related Complication and CVD

Although the current study evaluated recurrent pregnancy-related complications as a composite, most previous research has focused on specific complications such as recurrent HDP,[12,28,31,32] preterm birth,[11,33–35] or placental abruption[36,37] and their individual associations with incident CVD morbidity or mortality. Consistent with earlier studies, our findings suggest that recurrent pregnancy-related complications increase the risk of CVD,[28,31] IHD,[38,39] stroke,[11] and HF.[12]

For example, a study using data from Norway's Medical Birth Registry, Cardiovascular Disease in Norway project, and Cause of Death Registry, involving 508 422 women demonstrated that compared with women without history of preeclampsia, women with a history of preeclampsia during the first pregnancy and no HDP during the second pregnancy had no higher risk of HF (HR, 1.46 [95% CI, 0.90–2.39]).[12] However, women with a history of preeclampsia during the first pregnancy and HDP during the second pregnancy or a subsequent pregnancies had a higher risk of HF (HR, 3.47 [95% CI, 2.10–5.75]).[12] Similarly, one UK study (n=2 359 386) showed that the risk of incident CVD was higher for those with multiple episodes of preeclampsia (HR, 2.23 [95% CI, 1.67–2.99]) compared with a single episode (HR, 1.65 [95% CI, 1.51–1.79]), with consistent trends for other CVD outcomes such as incident coronary heart disease and stroke.[31] However, no statistically significant association was found for incident AF, likely due to the shorter follow-up period (2.3 years[31]) and the reliance on hospital admission data, which may have excluded less severe cases managed in primary care.

Hypertension, Diabetes, and Maternal Age

Previous studies have indicated no interaction between pregnancy-related complications and prepregnancy hypertension or diabetes, which is supported by the current study findings.[40,41] However, there may be interactions between smoking[42] or body mass index[43] and pregnancy-related complications in relation to the risk of incident CVD. This study has also identified an interaction between maternal age and pregnancy-related complications in the development of CVD.

Additionally, previous work has highlighted the mediating role of hypertension and diabetes in the association between pregnancy-related complications and incident CVD.[43,44] For example, a Danish study using multiple national registers found that 23.3% (15.4%–32.8%) of the associations between gestational diabetes and incident CVD could be eliminated by the hypothetical prevention of incident diabetes, consistent with the current results.[43] Another study from Norway demonstrated that last recorded systolic blood pressure and blood glucose levels mediated 60% and 25% of the excess CVD risk associated with HDP.[45] Overall, these findings, along with those from the current study, suggest that incident postpartum hypertension and diabetes play major mediating roles in the relationships between pregnancy-related complications and incident CVD.

Nevertheless, the validity of mediation models depends on strong assumptions that are difficult to verify using electronic health records from observational studies. In the present study, residual confounding by unmeasured or incompletely captured factors, such as smoking and obesity, cannot be excluded. Accordingly, the mediation results should be interpreted as exploratory and hypothesis generating rather than causal estimates.

Mechanisms

The mechanisms linking pregnancy-related complications and incident CVD are still debated, with 2 main theories proposed.[46] One theory suggests that pregnancy-related complications and CVD share common risk factors, such as hypertension and obesity.[46,47] This study supports this hypothesis, as prepregnancy CVD risk factors, including hypertension, diabetes, and maternal age, were associated with a higher risk of pregnancy-related complications. Additionally, pregnancy-related complications were linked to an increased risk of developing hypertension and diabetes.

The second theory posits that de novo insults to the circulatory system, such as endothelial dysfunction or cardiac remodeling, promote an increased risk of CVD.[46,48,49] This study also supports this explanation, as pregnancy-related complications were associated with a higher risk of CVD, independent of traditional CVD risk factors. Of note, we show that gestational diabetes was associated with significantly higher risks of IHD, stroke, and HF compared with other pregnancy-related complications. Further, HF was more strongly associated with pregnancy-related complications than other forms of CVD, possibly due to an underlying peripartum cardiomyopathy.

Risk Prediction With Pregnancy-Related Complications

Incorporating individual pregnancy-related complications into traditional CVD risk prediction tools has generally failed to significantly enhance the prediction of 10-year risk of CVD.[50–53] However, most studies included histories of any pregnancy-related complication regardless of which pregnancy was affected. One previous cohort study using data from Clinical Practice Research Datalink and Hospital Episode Statistics (HES) (n=502 916) showed that including HDP from the first birth provided statistically better but modest predictive accuracy (C-statistic=0.68), compared with using a random birth per or all births per woman (C-statistics=0.62 and 0.63, respectively).[54] Only 1 study, which used data from the Tehran Lipid and Glucose Study that evaluated a wide range of pregnancy-related complications, showed that reestimated CVD risk by adding adverse pregnancy outcomes to the Framingham risk score improved the accuracy of the risk estimation of CVD.[52]

Our study findings suggest a higher risk of 4 different cardiovascular conditions examined with single, multiple, and recurrent pregnancy-related complications, with a notable dose–response effect observed with the coexistence and recurrence of complications. Hence, a cumulative/adaptive risk prediction tool is worth considering including any pregnancy-related complication during the first pregnancy with risk stratification based on a history of multiple complications among young women. Furthermore, a history of recurrent pregnancy-related complications should be considered throughout women's subsequent pregnancies. Indeed, the prevalence of any pregnancy-related complication was significantly higher than that of single complications during the first pregnancy (25.1% versus 10.1% for the most frequent single complication), which could lead to the inclusion of women at higher risk of CVD. Importantly, the first pregnancy typically occurred at a young age (mean±SD 27.2 [6] years), providing ample opportunity to implement primary preventive measures. Finally, ~2.8% of women who developed CVD did so before their second pregnancy.

STRENGTHS AND LIMITATIONS

A major strength of this study is that the data were from linked nationwide data sources, which enabled the inclusion of both mild and severe exposures/outcomes, as well as access to all births in Welsh data. Further, CVD was evaluated separately instead of collectively, while including AF as a separate outcome. Another strength is that associations between a wide range of pregnancy-related complications and individual incident CVD were explored.

The major limitation is the incomplete information for important CVD-related risk factors, such as body mass index and smoking. Additionally, relying on codes to identify exposures and outcomes introduces the possibility of misclassification. Some birth characteristics, such as GA, were missing, and others, such as the type of preterm birth (spontaneous versus medically indicated), were unavailable. Moreover, the definitions of exposures and outcomes have evolved over the 20-year period covered by this study. For instance, the presence of proteinuria is no longer required for the diagnosis of preeclampsia if specific symptoms are present.[55] The definition of FGR primarily relied on GA and birthweight, which raises the possibility of misclassification bias. Multiple imputation was not performed. Missing data were modest (6.2% for race/ethnicity and 2.7% for WIMD) and related to noncentral covariates; therefore, the potential for bias is likely minimal. However, bias due to nonrandom missingness cannot be entirely excluded. Although our confounder selection was based on prior studies, adjustment for variables such as coronary heart disease or chronic hypertension may have introduced overadjustment or collider stratification bias. Nevertheless, a sensitivity analysis excluding women with coronary heart disease showed that the effect estimates remained materially unchanged, suggesting that collider bias related to coronary heart disease inclusion is unlikely to have influenced the findings. Another limitation is that population-based studies with data ascertained through registers are known to introduce misclassification of covariates. Although excluding women with previous births between 1990 and 1999 was used to approximate a predominantly primiparous cohort, true parity could not be fully verified for women who may have had births outside Wales, and this limitation should be considered when interpreting the findings. In addition, because pregnancy complications were defined based on the first recorded pregnancy, complications occurring in later pregnancies were not captured. This may introduce nondifferential exposure misclassification if some women developed complications subsequently; however, such misclassification would be expected to bias associations toward the null rather than inflate the effect estimates. The mediation analyses rely on the assumptions that all confounders of the exposure—outcome, exposure–mediator, and mediator–outcome relationships—were accounted for and that the exposure did not influence any confounder of the mediator–outcome association. Accordingly, these findings should be interpreted as exploratory and hypothesis-generating rather than causal. Finally, most women (~84%) were White, which limits the generalizability of the results to women from other racial or ethnic groups.

CONCLUSIONS

Women experiencing pregnancy-related complications encounter higher risks of CVD, especially when they have multiple or recurrent complications. Comprehensive assessment of their cardiovascular risk and implementation of preventive measures to mitigate this heightened risk are needed.

ARTICLE INFORMATION

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Supplemental Material

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