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ORIGINAL RESEARCH

Pregnancy Complications and Risk of Cardiovascular Disease Later in Life: A Nationwide Cohort Study

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BACKGROUND: The aim of this study was to investigate the associations between pregnancy complications and cardiovascular mortality and hospitalizations of cardiovascular disease (CVD) after adjustment for major confounding.

METHODS AND RESULTS: In a nationwide register-based cohort study, women with singleton births between 1973 and 2014 were included from the Swedish Medical Birth Register. Outcomes of mortality and hospitalizations of CVD were collected from the Cause of Death Register and the National Inpatient Register. The cohort was followed from the date of the first delivery until death or end of follow-up, whichever occurred first. The pregnancy complications studied were preeclampsia or eclampsia, gestational hypertension, gestational diabetes, preterm birth, small for gestational age, and stillbirth. Among the 2 134 239 women (mean age at first pregnancy, 27.0 [SD, 5.1] and mean parity 1.96 [SD, 0.9]), 19.1% (N=407 597) had 1 of the studied pregnancy complications. All pregnancy complications were associated with all-cause and cardiovascular mortality and hospitalization for CVD (ischemic heart disease, ischemic stroke, and peripheral artery disease) after adjustment for major confounding in a Cox proportional hazard regression model. The adjusted hazard ratio for cardiovascular mortality was 1.84 (95% CI, 1.38–2.44) for preterm birth and 3.14 (95% CI, 1.81–5.44) for stillbirth.

CONCLUSIONS: In this large cohort study, pregnancy complications were associated with all-cause mortality, cardiovascular mortality, and hospitalizations for CVD, also after adjusting for confounding, including overweight, smoking, and comorbidities. The study highlights that less established pregnancy complications such as preterm birth and stillbirth are also associated with cardiovascular mortality and CVD.

Key Words: cardiovascular disease ■ ischemic heart disease ■ ischemic stroke ■ peripheral artery disease ■ pregnancy complications

Pregnancy complications are established risk factors for future cardiovascular disease (CVD).[1,2] An increased risk of CVD has been described for women with a history of maternal pregnancy complications such as preeclampsia,[3–5] gestational hypertension (GHT),[6–8] and gestational diabetes.[7] The association between maternal pregnancy complications and CVD is well documented.[1,2,9] In general, the association between fetal complications and CVD are less recognized, although an increased risk of CVD has been described for preterm birth,[7,10,11] small for gestational age (SGA),[7,8] and stillbirth.[12] Several CVD prevention guidelines have highlighted the importance of pregnancy complications in terms of cardiovascular risk assessment, such as preeclampsia, gestational diabetes, preterm birth, and SGA.[1,2,9] Stillbirth has received more attention recently.[13,14]

Earlier studies have not fully elucidated the risk of separate pregnancy complications on specific CVD outcomes where especially the fetal complications are less established. Limitations of earlier studies also include the use of self-reported pregnancy complications instead of verified

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CLINICAL PERSPECTIVE

What Is New?

- Both maternal and fetal pregnancy complications are associated with cardiovascular mortality and specific hospitalizations of cardiovascular disease after adjustment for major confounding including overweight, smoking, and comorbidities.
- A history of preterm birth or stillbirth in pregnancy is associated with an increased risk of later cardiovascular disease in the mother.

What Are the Clinical Implications?

- Both maternal and fetal pregnancy complications should be addressed in cardiovascular disease risk assessment.

Nonstandard Abbreviations and Acronyms

CDR	Cause of Death Register
GHT	gestational hypertension
IHD	ischemic heart disease
MBR	Medical Birth Register
NPR	National Patient Register
SGA	small for gestational age

diagnoses and lack of adjustment for traditional risk factors for CVD.[12] It is unknown whether women with pregnancy complications have CVD earlier in life.[7] This study focused on 3 specific outcomes of atherosclerotic CVD: ischemic heart disease (IHD), ischemic stroke/transient ischemic attack (TIA), and peripheral artery disease (PAD).

The aim of the study was to determine whether different pregnancy complications are associated with general and specific outcomes of CVD, adjusting for major confounding, including overweight, smoking, and comorbidities. The general outcomes were all-cause and cardiovascular mortality. The specific outcomes of CVD were first-time hospitalization of IHD, ischemic stroke/TIA, and PAD. Our aim was also to describe whether first-time hospitalization of CVD occurred earlier in life in women with pregnancy complications compared with women without complications.

METHODS

Study Population

The data and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. According to Swedish law, data can be available only after a legal and ethical review and cannot be spread because of the integrity of the study participants. More details about analytical methods can be acquired upon request to the corresponding author. The study was approved by the regional ethics committee of Uppsala, that belongs to the Swedish Ethical Review Authority (Log. 2015/524), and was conducted in accordance with institutional guidelines. The requirement of informed consent was waived by the institutional review board.

In total, 2 152 109 women were identified in the Swedish Medical Birth Register (MBR) as having given birth to ≥1 children since the start of MBR in 1973 until the end of 2014. Multiple births and women with any missing date of delivery were excluded and the final study cohort consisted of 2 134 239 women. The study cohort was followed from the date of the first delivery until death or the end of follow-up (December 31, 2014), whichever occurred first. Women aged ≤75 years at the end of 2014 were included to focus on women at risk for earlier onset of CVD. Women who died before the end of 2014 were included if they were younger than age 76 years at the time of death.

Data Sources

Data from MBR of the study cohort were linked to 2 nationwide registers in Sweden: the Cause of Death Register (CDR) and the National Patient Register (NPR). Information about exposure to pregnancy complications were collected from MBR and enriched by information from the NPR 1 year before delivery and 6 months postpartum. Mortality outcomes were collected from the CDR. Outcome variables of hospitalizations of CVD and comorbidities were collected from the NPR and were collected for the whole lifetime of the women. Linkage of individuals was enabled by the personal identity number that identifies each Swedish resident. The National Board of Health and Welfare approved merging the data of the registers.

The MBR includes 97% to 99% of all deliveries and pregnancies in Sweden that exceed 22 weeks of pregnancy. It includes both pregnancy- and delivery-related diagnoses as well as history of disease in the mother and the condition of the infant. The information is registered from the first antenatal care visit that normally occurs in weeks 10 to 12 of pregnancy and includes the age of the mother, body mass index (BMI), smoking status, family situation, and parity. BMI and smoking were available in MBR from 1982 onward. The information is complemented after childbirth with delivery data, the gestational length of the pregnancy and the condition of the infant.[15,16] In the time span of the study from 1973 to 2014 diagnoses were registered

according to *International Classification of Diseases, Eighth Revision* (*ICD-8*), *Ninth Revision* (*ICD-9*), and *Tenth Revision* (*ICD-10*) (Table S1) in the NPR and CDR.

The NPR was founded in 1964 and includes information about hospital admissions nationwide. Since 1987 the coverage has been complete, and currently >99% of hospital admissions are registered. Each hospital discharge receives a main diagnosis, registered by the physician responsible for the hospital discharge.[17]

The CDR is a virtually complete register that includes all deaths in Sweden since 1952. Rules of the World Health Organization[18] determine the underlying cause of death from several contributed causes of death reported from the physician responsible for the medical death certificate. Residents of Sweden who died abroad are also included.[19]

Baseline Characteristics

Baseline characteristics such as maternal age, BMI, smoking status, and family situation were collected from the first registered pregnancy of the woman in the MBR. Parity was calculated from the total number of delivery dates registered in the MBR. Comorbidities such as diabetes, hypertension, chronic kidney failure, and venous thrombosis were defined as the diagnoses registered in the MBR or in NPR 1 year before and 6 months postpartum for any pregnancy.

Pregnancy Complications

We categorized pregnancy complications into maternal (preeclampsia or eclampsia, GHT, gestational diabetes) and fetal (preterm birth, very preterm birth, SGA, and stillbirth). Pregnancy complications were studied in total and separately. Multiple births were excluded since they are associated with an increased risk of complications. Multiple births were identified as mothers with ≥2 identical delivery dates. Preterm birth was defined as a gestational age of <37 weeks and very preterm birth as a gestational age of <32 weeks.[20] Birth weight for gestational age and sex were categorized as SGA when <2 SDs for weight according to the Swedish reference curve.[21] The exposures defined as *ICD* codes (preeclampsia or eclampsia, GHT, gestational diabetes, and stillbirth) were collected from the MBR and NPR, 1 year before delivery and 6 months postpartum (Table S1). The gestational age for the definition of stillbirth was reduced in the MBR in 2008, from 28 to 22 completed weeks of pregnancy.

Cardiovascular Outcomes

Mortality

Mortality was classified according to the underlying cause of death and included all-cause mortality and cardiovascular mortality with the focus on atherosclerotic cardiovascular disease (IHD, ischemic stroke/TIA, and PAD). The *ICD* codes for the outcome variables are listed in Table S1.

Hospitalization for CVD

A hospitalization for CVD was defined as the first-time hospital admission with a main diagnosis in the NPR of either IHD, ischemic stroke/TIA or PAD. Hospitalizations for the same main diagnosis with <24 hours between discharge and next admission were linked together and were treated as 1 hospital admission. In these cases, the main diagnosis of the first hospitalization defined the outcome. Time was defined as time to first outcome from the date of the first delivery and was studied for each outcome of CVD by the date of the first hospital admission with a main diagnosis of any of the CVD diagnoses studied. Comorbidities at the hospitalizations were collected from all secondary diagnoses. Diabetes, hypertension, chronic kidney failure, and venous thrombosis were considered potential confounding comorbidities.

Confounders

Maternal age, BMI, smoking, family situation, and parity were considered as potential confounders. Comorbidities in any pregnancy or at first-time hospitalization of CVD (diabetes, hypertension, chronic kidney failure, and venous thrombosis) were also considered as potential confounders. Adjustments were also performed for decade at first pregnancy, to adjust for societal and medical changes over time. Maternal age at the first antenatal care visit in first pregnancy was categorized into <18, 18 to 25, 25 to 30, and >30 years. BMI and maternal smoking were registered from 1982 onward. BMIs were categorized as <18.5 (underweight), 18 to 24.9 (normal weight), 25 to 29.9 (overweight), and >30 kg/m^2 (obese). Smoking was categorized as nonsmokers and smokers. Family situation was categorized as cohabitation/married and single parent/earlier marriage/unmarried/other.

Statistical Analysis

The study cohort was divided into women with prior exposure to at least 1 of the studied pregnancy complications in any of the registered pregnancies in the MBR and women unexposed. Each of the studied pregnancy complications were also studied separately, dividing the cohort into women exposed to the individual complication in any pregnancy versus unexposed. Pregnancy complications in the first pregnancy were studied separately as a sensitivity analysis. Women with >2 pregnancy complications were studied separately to evaluate whether this was associated with increased risk.

Categorical variables were described as frequencies and percentages, and continuous variables

were categorized or presented as means and SD. Visualization of cumulative incidence between exposed and unexposed was done by unadjusted cumulative incidence plots in Prism version 9 (GraphPad Software, La Jolla, CA). Separate analyses of the cumulative incidence between exposed and unexposed starting at maternal age of 45 years and in age categories <25, 25 to 35, and >35 years at first pregnancy were performed. Mortality and incidence rates were calculated as the number of events divided by the person-time at risk and were reported per 100 000 person-years. The associations of pregnancy complications with adverse outcome were studied using Cox regression models and reported as hazard ratios (HR) with 95% CIs. The proportionality assumption was checked by visual inspection of the Kaplan-Meier survival plot for the categories of each variable and was found fulfilled. The follow-up was started at the date of the first delivery.

Potential confounders were identified by direct acyclic graphs that were drawn after a review of the literature and based on our best assumptions. The final version was reviewed and approved by the authors (Figure S1). Adjustment was performed for the identified potential confounders: maternal age, maternal age^2, BMI, BMI^2, smoking status (smoker/nonsmoker), family situation (cohabitation/married and single parent/earlier marriage/unmarried/other), parity and comorbidities in any pregnancy or at hospitalization of CVD (diabetes, hypertension, chronic kidney failure, and venous thrombosis) and decade at first pregnancy. Preeclampsia or eclampsia in any pregnancy were considered potential confounders for the fetal complications and were added to the adjusted model. All analyses were performed with SPSS Statistics version 26 (IBM, Armonk, NY).

RESULTS

Baseline Characteristics

The study cohort consisted of 2 134 239 women with 4 177 154 registered pregnancies between 1973 and the end of 2014, as described in Figure 1. The mean age at first pregnancy for the total cohort was 27.0 (SD,

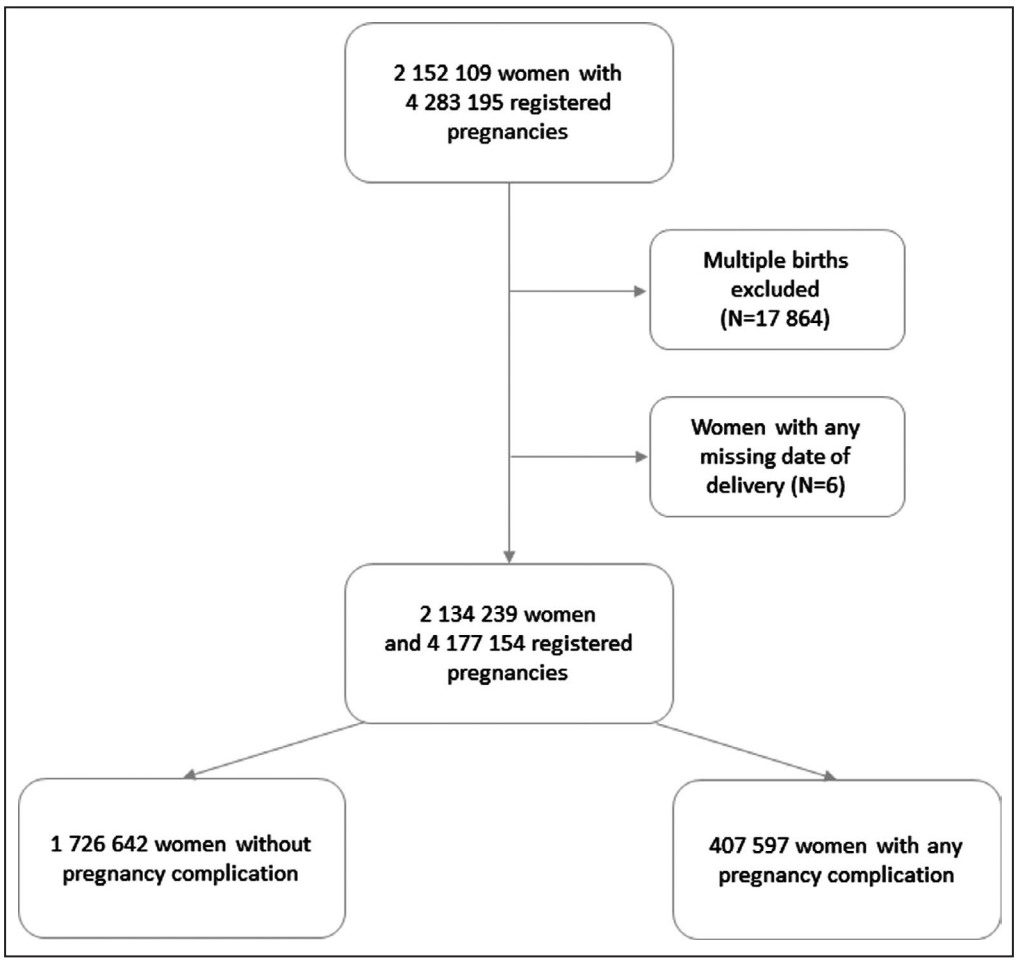


Figure 1. Flowchart of the study population with births in Sweden 1973 to 2014.

Table 1. Baseline Characteristics

	No pregnancy complication (N=1 726 642) N (%)	Pregnancy complication in at least 1 pregnancy (N=407 597) N (%)
Maternal age (y) at first pregnancy (N=2 134 236)		
<18	18 360 (1.1)	6842 (1.7)*
18–25	545 897 (31.6)	143 733 (35.3)
25–30	635 201 (36.8)	138 030 (33.9)
30–35	385 327 (22.3)	83 482 (20.5)
35–40	120 372 (7.0)	29 555 (7.2)
>40	21 482 (1.2)	5955 (1.5)
Body mass index in first pregnancy, available from 1982- (N=825 419)		
Underweight (<18.5)	68 151 (10.2)	16 963 (10.9)*
Normal weight (18.5–24.9)	397 966 (59.4)	84 368 (54.1)
Overweight (25–29.9)	145 740 (21.8)	34 987 (22.4)
Obesity (>30)	57 560 (8.6)	19 684 (12.6)
Smoking in first pregnancy, available from 1982- (N=1 421 428)		
Nonsmoker	975 226 (85.1)	225 911 (82.2)*
Smoker	171 250 (14.9)	49 041 (17.8)
Family situation in first pregnancy (N=1 981 754)		
Cohabitation/married	1 339 470 (83.3)	305 125 (81.5)*
Single parent/earlier marriage/unmarried/other	267 980 (16.7)	69 179 (18.5)
Parity (N=2 134 239)		
1	606 249 (35.1)	108 546 (26.6)*
2	774 535 (44.9)	176 408 (43.3)
3	271 952 (15.7)	84 486 (20.7)
4	56 794 (3.3)	26 448 (6.5)
≥5	17 112 (1.0)	11 709 (2.9)
Comorbidities 1 year before delivery and 6 months postpartum (N=2 134 239)		
Diabetes	5230 (0.3)	11 078 (2.7)*
Essential hypertension	6278 (0.4)	9623 (2.3)*
Chronic kidney failure	106 (0.0)	233 (0.1)*
Venous thrombosis	7429 (0.4)	2831 (0.7)*
No comorbidities	1 707 599 (98.9)	383 832 (94.2)*
Comorbidities diagnosed at hospitalization of cardiovascular disease (N=61 469)		
Diabetes	25 (0.1)	27 (0.2)*
Essential hypertension	151 (0.3)	137 (0.8)*
Chronic kidney failure	426 (0.9)	100 (0.6)
Venous thrombosis	1611 (3.6)	584 (3.6)*

Comparisons between groups by chi-square test. *P value <0.0001.

5.1) and the mean parity was 1.96 (SD, 0.9). Baseline characteristics at the first registered pregnancy in the MBR of the cohort of women with (N=407 597) and without any of the studied pregnancy complications (N=1 726 642) are described in Table 1. Obesity, smoking, and comorbidities (diabetes, hypertension, chronic kidney failure, and venous thrombosis) 1 year before delivery and 6 months postpartum were more common in women with any of the studied pregnancy complications in any pregnancy compared with women without complications (Table 1). The frequencies of comorbidities in the first pregnancy are described in Table S2.

Pregnancy Complications

Pregnancy complications were common; 19.1% (N=407 597) of the women had 1 of the studied pregnancy complications in at least 1 of the registered pregnancies in MBR. When analyzing the maternal complications, 4.9% had preeclampsia or eclampsia (N=104 322), 3.0% had GHT (N=63 730), and 1.1% had gestational diabetes (N=22 991) in 1 of the registered pregnancies. When analyzing the fetal complications, 9.4% gave birth preterm (N=200 574), 1.3% gave birth very preterm (N=27 480), 3.7% had SGA (N=78 156), and 1.6% had a stillborn (N=34 637) in 1 of the registered pregnancies. The frequency of pregnancy complications in the first pregnancy is described in Table S3. The frequencies of preeclampsia or eclampsia and fetal complications are described in Table S4.

Cardiovascular Outcomes

Mortality

During the study period, 62 788 died, 4968 of whom died of CVD. The median follow-up time was 22.7 years. Cumulative incidence for all-cause mortality and cardiovascular mortality are shown in Figure 2, with and without any of the studied pregnancy complications. In separate analyses of the cumulative incidence of all-cause mortality, cardiovascular mortality, and hospitalizations of CVD, the women were grouped according to age categories in their first pregnancy (Figure 3 and Figure S2A through S2C). The cumulative incidence of cardiovascular mortality starting at the maternal age of 45 years is described in Figures S3 and S4. The median follow-up time was 26.8 years in women aged <25 years, 20.8 years in women aged 25 to 35 years, and 13.6 years in women aged >35 years in the first pregnancy. All of the maternal complications were associated with higher cardiovascular mortality (Table 2). Cardiovascular mortality rates were higher for women exposed to the pregnancy complications studied, both maternal and fetal (Table 2). The HR was higher for cardiovascular mortality compared with all-cause mortality. The all-cause mortality rates and HRs are found in Table S5. Preeclampsia or eclampsia and gestational diabetes more than doubled the risk for cardiovascular mortality after adjustment (Table 2).

The fetal complications were associated with a slightly higher risk for all-cause mortality (Table S5). All of the fetal complications were associated with a higher risk of cardiovascular mortality (Table 2). Women

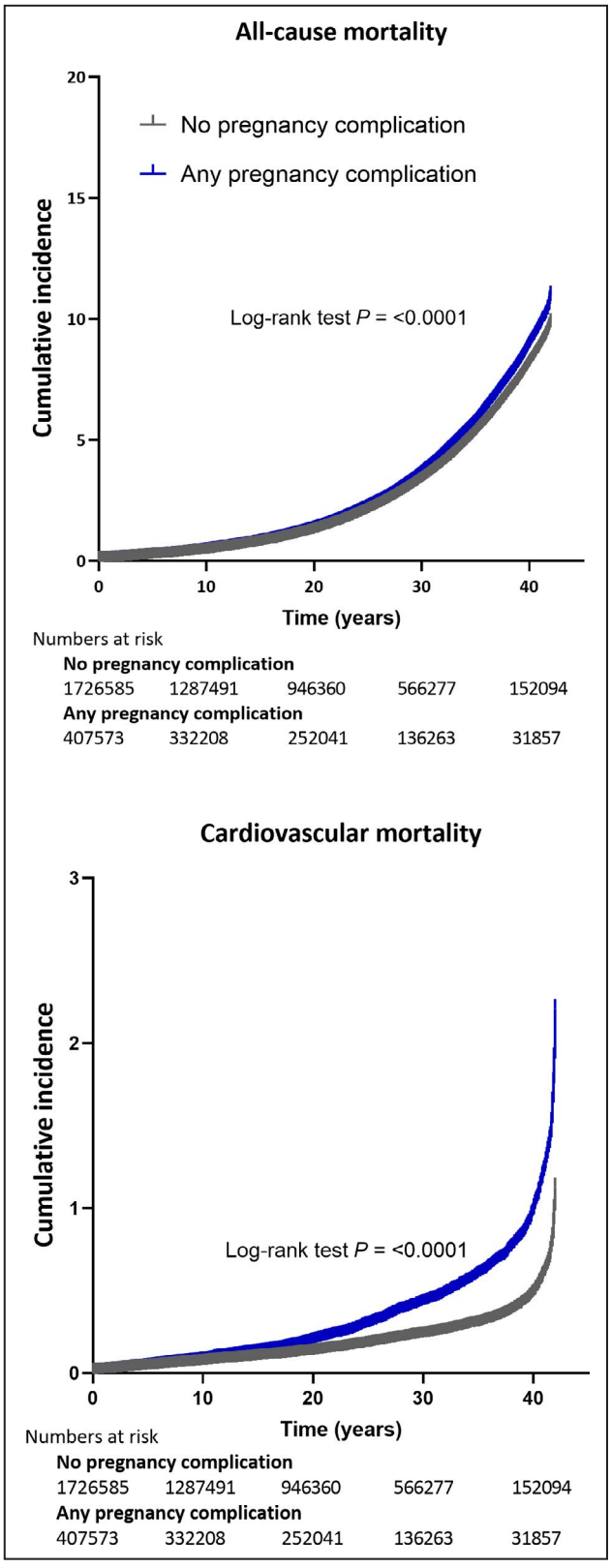


Figure 2. Unadjusted cumulative incidence plots for all-cause and cardiovascular mortality in women unexposed and exposed to pregnancy complications in any pregnancy 1973 to 2014.
Women aged ≤75 years at the end of 2014 were included.

with pregnancies in which infants were born SGA or preterm were associated with an almost doubled risk of cardiovascular mortality (Table 2). For women with pregnancies that resulted in stillbirth, the risk was more than tripled (Table 2). The results were similar when the first pregnancy was studied separately (Table S6). In women with ≥2 different pregnancy complications in any pregnancy, the adjusted HR was 3.43 (95% CI, 2.46–4.78) for cardiovascular mortality.

Hospitalization for CVD

During the study period, 27 993 women were hospitalized because of IHD, 28 514 because of ischemic stroke/TIA, and 4962 because of PAD; the median follow-up time until hospitalization was 22.5 years, 22.5 years, and 22.6 years, respectively. Incidence rates for the outcomes of hospitalizations studied were higher for all pregnancy complications studied, both maternal and fetal (Table S7).

Both the maternal and fetal complications were to a larger extent associated with hospitalization of IHD and PAD than to ischemic stroke/TIA (Figure 4). The HR increased when the very preterm births were studied separately (Figure 4).

The results were similar when the first pregnancy was studied separately (Table S8). Women with ≥2 different complications in any pregnancy had an HR of 2.48 (95% CI, 2.18–2.83) for hospitalizations for IHD, an HR of 1.90 (95% CI, 1.67–2.15) for hospitalization for ischemic stroke/TIA, and an HR of 3.10 (95% CI, 2.28–4.23) for hospitalization for PAD after adjustment. Women with pregnancy complications had an earlier onset of CVD in terms of IHD, ischemic stroke/TIA, and PAD (Figure 5 and Figure S2A through S2C).

DISCUSSION

This large cohort study of 2 134 239 women and 4 177 154 pregnancies with a median follow-up time of >22 years shows that both maternal and fetal complications are associated with increased cardiovascular mortality earlier in life; hospitalizations; and an earlier onset of IHD, ischemic stroke/TIA, or PAD after adjustment for major confounders including overweight, smoking, and comorbidities. The results of our study provide additional important information that also less established pregnancy complications such as very preterm birth and stillbirth are associated with CVD.

Comparison With Other Studies and Potential Pathophysiological Mechanisms

Our study confirms earlier findings regarding increased risk for cardiovascular mortality for both maternal and fetal pregnancy complications.[7,22] The study

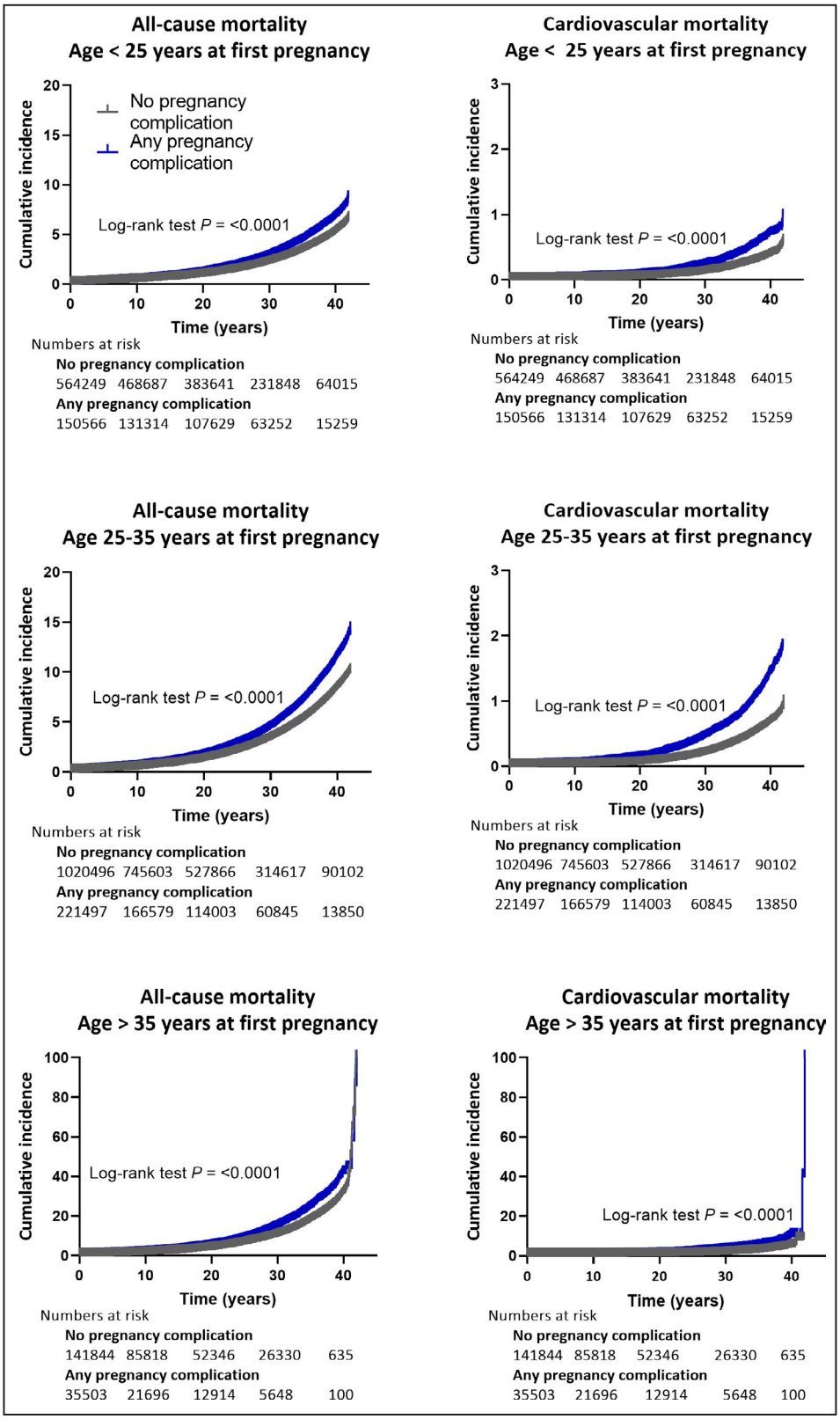


Figure 3. Unadjusted cumulative incidence plots for all-cause and cardiovascular mortality stratified into 3 age categories in women unexposed and exposed to pregnancy complications in any pregnancy.
Women aged ≤75 years at the end of 2014 were included.

Table 2. Cardiovascular Mortality Rates and Hazard Ratios in Women Unexposed and Exposed to Pregnancy Complications in Any Pregnancy

Cardiovascular mortality			
Mortality rate (N)		Hazard ratio (95% CI)	
Unexposed	Exposed	Unadjusted	Adjusted
Preeclampsia or eclampsia			
10.1 (4529)	19.9 (439)	2.30* (2.09–2.54)	2.10* (1.47–2.99)
Gestational hypertension			
10.1 (4579)	24.4 (389)	2.44* (2.20–2.70)	1.79* (1.20–2.66)
Gestational diabetes			
10.5 (4907)	19.4 (61)	4.91* (3.81–6.33)	3.03* (1.49–6.16)
Preterm birth (<37 weeks)			
9.8 (4174)	16.7 (753)	1.84* (1.70–1.98)	1.84* (1.38–2.44)
Very preterm birth (<32 weeks)			
10.3 (4802)	20.8 (125)	2.18* (1.82–2.60)	1.82 (0.89–3.72)
Small for gestational age			
10.0 (4511)	21.0 (407)	1.93* (1.74–2.13)	1.77* (1.19–2.64)
Stillbirth			
10.5 (4856)	16.4 (112)	1.96* (1.63–2.37)	3.14* (1.81–5.44)

BMI indicates body mass index.

Mortality rates per 100 000 person-years.

Adjusted for maternal age, maternal age^2, BMI, BMI^2, smoking status, family situation, comorbidities associated with pregnancy and at first-time hospitalization for cardiovascular disease (diabetes, hypertension, chronic kidney failure and venous thrombosis), parity, and decade at first pregnancy. For the fetal complications, we also adjusted for preeclampsia or eclampsia in any pregnancy.

*P-value <0.005.

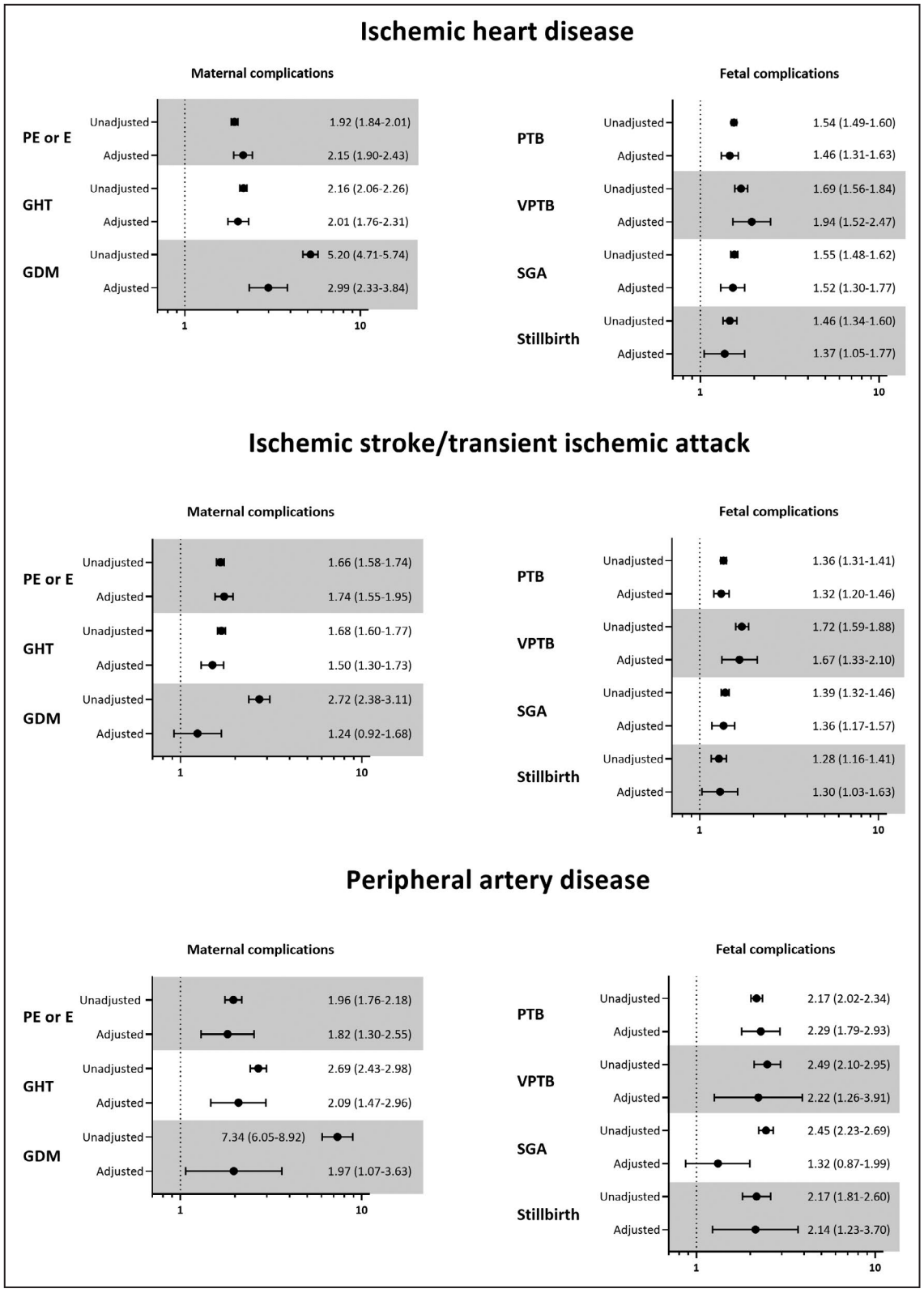
emphasizes the importance of fetal complications as risk factors for specific outcomes of CVD. Both preterm birth and very preterm birth were associated with cardiovascular mortality. Endothelial dysfunction and inflammation are potential mechanisms that preterm birth and cardiovascular disease have in common.[23] Preterm birth and very preterm birth share underlying pathophysiological mechanisms but also have different profiles. Both are multifactorial and can be either iatrogenic or spontaneous and for many women the cause remains unclear.[24] A pregnancy complicated by preeclampsia can result in both preterm birth and very preterm birth and SGA depending on the severity; however, after adjustment for preeclampsia, these fetal complications were still associated with CVD. The present study shows that the risk for cardiovascular mortality increased when very preterm birth was isolated from preterm birth. In our study, stillbirth was associated with a 3-fold increase in the risk of cardiovascular mortality, slightly higher than numbers published elsewhere.[22]

For hospitalizations for IHD, we could confirm earlier findings for the maternal complications preeclampsia or eclampsia and GHT and for the fetal complication preterm birth.[8,25] The HR for hospitalizations for ischemic stroke/TIA were in general lower for several of the pregnancy complications studied compared with those for IHD and PAD. A potential reason for this might be that ischemic stroke/TIA to a larger extent than IHD and PAD are embolic because of undiagnosed atrial fibrillation. Because of the organization of NPR, it was not possible to differentiate between embolic and atherosclerotic ischemic stroke/TIA and subgroups of IHD. An increased risk for PAD has been described for hypertension in pregnancy (preeclampsia or eclampsia[26] and GHT) both with diagnostic codes[8] and by clinical methods,[27] and we could confirm these findings. This study adds that gestational diabetes and fetal complications also increase the risk of hospitalization for PAD. The HR was more than doubled for hospitalization of PAD for preterm birth and persisted for very preterm birth. Stillbirth more than doubled the risk of hospitalization of PAD. IHD, ischemic stroke/TIA, and PAD share pathophysiological mechanisms but also have different profiles.[28] The fetal complications preterm birth, very preterm birth, and stillbirth all showed a high association to PAD after adjustment for preeclampsia. These findings emphasize that we may need to focus on selected pregnancy complications and their relations to the different cardiovascular manifestations to explore mechanisms involved. Studies focusing on proteomics and metabolomics associated with the pregnancy complications and cardiovascular manifestations might improve our knowledge of common biological pathways.

Pregnancy serves as an early stress test, challenging maternal vascular function, immunoregulation, and metabolic control, pathways that are aggravated by pregnancy complications.[29] GHT and gestational diabetes

Figure 4. Forest plots for first-time hospitalization of ischemic heart disease, ischemic stroke/transient ischemic attack, peripheral artery disease, and pregnancy complications.

Data are described as hazard ratios (HRs) calculated by Cox proportional hazard regression by and 95% CI. Adjusted for maternal age, maternal age^2, BMI, BMI^2, smoking status, family situation, comorbidities associated with pregnancy and at first-time hospitalization for cardiovascular disease (diabetes, hypertension, chronic kidney failure, and venous thrombosis), parity, and decade at first pregnancy. Beyond this, we also adjusted for preeclampsia or eclampsia in any pregnancy for the fetal complications. BMI indicates body mass index; GDM, gestational diabetes mellitus; GHT, gestational hypertension; PE or E, preeclampsia or eclampsia; PTB, preterm birth (<37 weeks); SGA, small for gestational age; VPTB, very preterm birth (<32 weeks).



seem to be early signs of a high risk of later manifestations of hypertension and type 2 diabetes.[9] A potential common denominator in the pregnancy complications studied is the placenta. Preeclampsia is associated with insufficient blood supply of the placenta, of abruption and infarction and causes SGA or stillbirth and preterm birth. Preeclampsia or eclampsia and CVD share several risk factors, and pregnancy complications have been associated with an earlier development of traditional risk factors for CVD.[30] Overweight and smoking are 2 of the

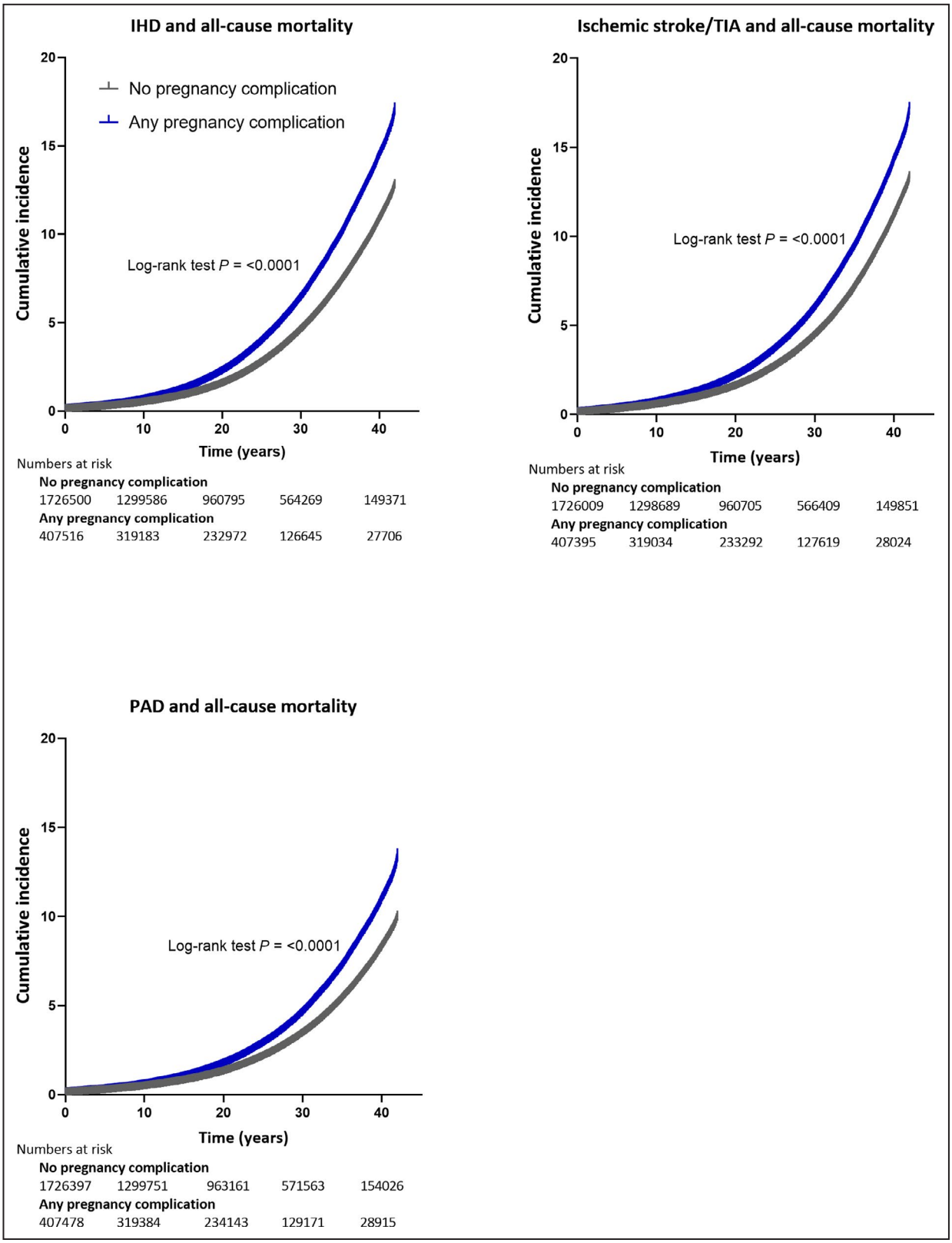


Figure 5. Unadjusted cumulative incidence plots for first-time hospitalizations of ischemic heart disease (IHD) and all-cause mortality, ischemic stroke/transient ischemic attack (TIA) and all-cause mortality and peripheral artery disease (PAD) and all-cause mortality in women unexposed and exposed to pregnancy complications in any pregnancy. Women aged ≤75 years at the end of 2014 were included.

traditional risk factors that contribute mainly to CVD in younger women.[31,32] These risk factors, identified early in life, seem important even upon admission for CVD in these women since the proportions of newly diagnosed comorbidities were low. However, whether specific interventions are beneficial in reducing cardiovascular risk needs to be evaluated. Further prospective studies are needed to find effective interventions reducing CVD risk in women with pregnancy complications, both in terms of lifestyle changes and pharmacologic aspects.

Pregnancy complications thereby unmask an excess risk of CVD in women at an early age.[33] The combination of ≥2 pregnancy complications further added to the risk of future CVD in the present study. Identifying the increased risk will enable women to become informed and engaged in CVD prevention at an early age. Whether pregnancy complications unmask a preexisting risk of CVD or actually are mediators is not clear. However, there is a difference between association and prediction. Pregnancy complications seem largely not to improve CVD risk prediction.[34,35] A recent study concluded that only preeclampsia predicted CVD after adjusting for established risk factors. Adding preeclampsia, GHT, preterm birth, and SGA made only minor improvements to CVD prediction.[36] The risk for CVD for these pregnancy complications also seems to decline with age[7,37]

Strengths and Limitations of This Study

The MBR, NPR, and CDR in Sweden are solid, nationwide registers, and almost all childbearing women in the country are included in the MBR. Information from all registered pregnancies in the MBR was taken into account, in contrast to many other studies focusing on the first pregnancy. The population of Sweden was relatively homogeneous during the study period. As with all large registers, there are limitations in quality of registration and missing data. The registers are dependent on a correct registration of diagnoses with potential misclassification bias but no recall bias. To reduce missing diagnoses, the data we collected on exposures to pregnancy complications in MBR were enriched with diagnoses from NPR, 1 year before the date of the delivery and 6 months postpartum. Comorbidities at the time of first-time hospitalization for CVD were collected only from the NPR. Information of smoking status is missing in 4% to 9% of cases in the MBR, and numbers of stillbirths are slightly underestimated.[16] There is a potential diagnostic overlap between, for example, essential hypertension, GHT, and preeclampsia. There is also a potential overlap between diabetes and gestational diabetes. Diagnostic criteria for some of the pregnancy complications studied have changed over time, such as gestational diabetes.[38] A potential underestimation of the frequency of the pregnancy complications might lead to a lower risk estimate. Another limitation is that we lack information about education and income of the women at the first antenatal care visit. Information about overweight and smoking during follow-up and about the amount of smoking at the first antenatal care visit is missing. Follow-up starts at the date of the first delivery for all women, with and without exposure of pregnancy complications. A limitation is that some women with a healthy first pregnancy will be included before exposure of pregnancy complications in a later pregnancy. We assess the impact to be small since there is a small number of events in childbearing age and since the results of the analysis in first pregnancy were similar (Tables S6 and S8). We also found similar results in cumulative incidence between exposed and unexposed starting at maternal age of 45 years (Figures S3 and S4). The differences in cumulative incidence stratified by age categories may not be clinically meaningful (Figure 3).

CONCLUSIONS

In this large cohort study, after adjusting for potential major confounders including overweight, smoking, and comorbidities, we confirm that both maternal and fetal pregnancy complications are associated with both cardiovascular mortality and hospitalizations for IHD, ischemic stroke/TIA, and PAD. The study highlights that also less established pregnancy complications such as preterm birth, very preterm birth, and stillbirth are associated with CVD. Furthermore, the study adds that women with prior pregnancy complications have an earlier onset of CVD compared with women without and addresses the importance of pregnancy complications as a risk factor for CVD.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Tables S1–S8
Figures S1–S4

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Supplemental Material

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Table S1: List of ICD codes for exposures

Exposure	ICD-8	ICD-9	ICD-10
Pregnancy complications			
Preeclampsia or eclampsia	63703–63704, 63709, 6371, 6379, 6612, 7621–7623, 76298	6424–6427	O14–O15
Gestational hypertension	63701	6420–6421, 6423, 6429, 7600	O13, O16
Gestational diabetes mellitus	7611	6480, 7750	O24, P700–P701
Stillbirth	779	6564, V235, V271	O312, O366, P95, Z371
Comorbidities one year before delivery and six months postpartum and at hospitalizations for CVD			
Diabetes mellitus	250	250	E10–E14, I10
Hypertension	400–404, 7602	401–405, 6422	I11–I13, I15, O10–O11
Chronic kidney failure	403, 582, 584	403, 585	I12, N18
Venous thrombosis	321, 450–453, 671, 673	325, 4151, 451–453, 4591, 6712, 6713, 6714, 6715, 6718, 6719, 6732	I26, I676, I80–I82, I870, O222, O223, O225, O228, O229, O870, O871, O873, O878, O8799
Outcome			
Ischemic heart disease	410–414	410–414	I20–I25
Ischemic stroke /transient ischemic attack	432–438	433–438	G45–46, I63, I65–67, I69
Peripheral artery disease	4439, 440, 444–445	4439, 440, 444	I70, I739, I74
Cardiovascular mortality (Ischemic heart disease, ischemic stroke/transient ischemic attack, peripheral artery disease)	410–414, 427–429, 432–438, 4439, 440, 444-445	410–414, 429, 433–438, 4439,440, 444,	I20–I25, I51, G45–G46, I63, I65–I67, I69, I70, I739, I74

ICD=International Classification of Disease, CVD=Cardiovascular disease

Table S2: Baseline characteristics in first pregnancy

Comorbidities one year before delivery and six months postpartum in first pregnancy (N = 2 134 239)	
Diabetes mellitus	9627 (0.5)
Essential hypertension	7691 (0.4)
Chronic kidney failure	197 (0.0)
Venous thrombosis	4498 (0.2)
No comorbidities	2 112 226 (98.9)

Table S3: Pregnancy complications in any pregnancy and in first pregnancy

Pregnancy complications	Pregnancy complication in any pregnancy	Pregnancy complication in first pregnancy
Any complication	407 597 (19.1)	285 910 (13.4)
Preeclampsia or eclampsia	104 322 (4.9)	78 972 (3.7)
Gestational hypertension	63 730 (3.0)	41 010 (1.9)
Gestational diabetes mellitus	22 991 (1.1)	12 875 (0.6)
Preterm birth (<37 weeks)	200 574 (9.4)	128 729 (6.0)
Very preterm birth (<32 weeks)	27 480 (1.3)	19 120 (0.9)
Small for gestational age	78 156 (3.7)	55 011 (2.6)
Stillbirth	34 637 (1.6)	16 876 (0.8)

Table S4: Women with preeclampsia or eclampsia and fetal complications

Pregnancy complications	Preeclampsia or eclampsia in any pregnancy (N=104 322)	Preeclampsia or eclampsia in first pregnancy (N= 78 972)
Preeclampsia or eclampsia and preterm birth (<37 weeks)	27 234 (8.9)	16 261 (7.0)
Preeclampsia or eclampsia and small for gestational age	9298 (26.1)	5494 (20.6)
Preeclampsia or eclampsia and stillbirth	2978 (2.9)	975 (1.2)

Table S5: All-cause mortality in women unexposed and exposed to pregnancy complications in any pregnancy, mortality rates and hazard ratios

All-cause mortality			
Mortality rate (N)		**Hazard ratio (CI)**	
Unexposed	Exposed	Unadjusted	Adjusted
Preeclampsia or eclampsia			
133.2 (59 845)	133.6 (2943)	1.12 (1.08–1.16)	1.04 (0.94–1.16)
Gestational hypertension			
132.0 (60 114)	168.0 (2674)	1.27 (1.22–1.32)	1.15 (1.02–1.29)
Gestational diabetes mellitus			
133.4 (62 457)	105.1 (331)	1.52 (1.37–1.70)	1.29 (1.02–1.62)
Preterm birth (<37 weeks)			
129.5 (55 154)	163.3 (7370)	1.33 (1.30–1.36)	1.43 (1.33–1.54)
Very preterm birth (<32 weeks)			
131.9 (61 328)	198.9 (1196)	1.59 (1.50–1.68)	1.75 (1.46–2.08)
Small for gestational age			
129.7 (58 496)	203.8 (3957)	1.47 (1.42–1.52)	1.28 (1.15–1.43)
Stillbirth			
133.1 (61 834)	139.8 (954)	1.24 (1.16–1.32)	1.59 (1.34–1.88)

BMI=Body Mass Index, CI=Confidence interval, CVD=Cardiovascular disease

Adjusted for: Maternal age, maternal age^2, BMI, BMI^2, smoking status, family situation, comorbidities associated to pregnancy and at first-time hospitalization for cardiovascular disease (diabetes mellitus, hypertension, chronic kidney failure and venous thrombosis), parity and decade at first pregnancy. For the fetal complications, we also adjusted for preeclampsia or eclampsia in any pregnancy.

Table S6: All-cause and cardiovascular mortality for pregnancy complications in first pregnancy, hazard ratios

	All-cause mortality Hazard ratio (CI)		**Cardiovascular mortality Hazard ratio (CI)**	
Pregnancy complications	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Preeclampsia or eclampsia	1.24 (1.19–1.29)	1.07 (0.95–1.20)	2.53 (2.25–2.83)	2.06 (1.39–3.04)
Gestational hypertension	1.51 (1.45–1.59)	1.14 (0.99–1.30)	2.93 (2.59–3.31)	1.65 (1.04–2.63)
Gestational diabetes mellitus	2.55 (2.19–2.96)	1.61 (1.23–2.11)	9.83 (6.84–14.13)	3.43 (1.52–7.73)
Preterm birth (<37 weeks)	1.53 (1.48–1.57)	1.34 (1.23–1.47)	2.36 (2.16–2.58)	1.87 (1.36–2.59)
Very preterm birth (<32 weeks)	1.78 (1.67–1.91)	1.32 (1.04–1.68)	2.76 (2.26–3.37)	1.64 (0.67–3.99)
Small for gestational age	1.63 (1.57–1.69)	1.18 (1.04–1.35)	2.27 (2.03–2.54)	1.86 (1.19–2.91)
Stillbirth	1.51 (1.40–1.64)	1.22 (0.96–1.57)	2.60 (2.08–3.25)	2.55 (1.20–5.41)

BMI=Body Mass Index, CI=Confidence interval

*= Parity excluded from the model

Adjusted for: Maternal age, maternal age^2, BMI, BMI^2, smoking status, family situation, comorbidities associated to pregnancy and at first-time hospitalization for cardiovascular disease (diabetes mellitus, hypertension, chronic kidney failure and venous thrombosis) and decade at first pregnancy. For the fetal complications, we also adjusted for preeclampsia or eclampsia in first pregnancy.

Table S7: Incidence rates for first time hospitalizations of ischemic heart disease, ischemic stroke/transient ischemic attack or peripheral artery disease in women unexposed and exposed to pregnancy complications in any pregnancy

Ischemic heart disease		**Ischemic stroke/TIA**		**Peripheral artery disease**	
Incidence rate (N)		**Incidence rate (N)**		**Incidence rate (N)**	
Unexposed	Exposed	Unexposed	Exposed	Unexposed	Exposed
Preeclampsia or eclampsia					
57.8 (25860)	97.6 (2133)	59.5 (26627)	86.2 (1887)	10.2 (4559)	18.3 (403)
Gestational hypertension					
57.4 (26012)	125.8 (1981)	59.4 (26950)	99.0 (1564)	10.0 (4536)	26.8 (426)
Gestational diabetes mellitus					
59.2 (27581)	132.1 (412)	60. 7 (28285)	73.1 (229)	10.4 (4851)	35.3 (111)
Preterm birth (<37 weeks)					
57.1 (24177)	83.3 (3734)	59.1 (25050)	75.3 (3378)	9.6 (4068)	19.6 (882)
Very preterm birth (<32 weeks)					
59.1 (27349)	94.2 (562)	60.2 (27847)	97.4 (581)	10.3 (4804)	24.3 (146)
Small for gestational age					
57.9 (26013)	97.0 (1867)	59.5 (26713)	87.8 (1693)	9.9 (4459)	25.2 (489)
Stillbirth					
59.5 (27506)	71.8 (487)	60.7 (28082)	63.6 (432)	10.4 (4837)	18.4 (125)

TIA=Transient ischemic attack

Incidence rates (IR) per 100 000 person-years (PY)

Table S8: First time hospitalizations of ischemic heart disease, ischemic stroke/transient ischemic attack and peripheral artery disease in women unexposed and exposed to pregnancy complications in first pregnancy

	Ischemic heart disease Hazard ratio (CI)		**Ischemic stroke/TIA Hazard ratio (CI)**		**Peripheral artery disease Hazard ratio (CI)**	
Pregnancy complications	Unadjusted	Adjusted*	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Preeclampsia or eclampsia	1.96 (1.86–2.07)	2.16 (1.88–2.48)	1.77 (1.67–1.87)	1.81 (1.59–2.06)	2.03 (1.79–2.30)	1.79 (1.23–2.62)
Gestational hypertension	2.22 (2.10–2.35)	1.95 (1.67–2.28)	1.87 (1.76–2.00)	1.57 (1.33–1.85)	3.14 (2.78–3.54)	2.33 (1.59–3.41)
Gestational diabetes mellitus	11.15 (9.72–12.78)	3.25 (2.39–4.42)	4.68 (3.87–5.66)	1.28 (0.87–1.89)	15.32 (11.92–19.69)	2.98 (1.53–5.79)
Preterm birth (<37 weeks)	1.67 (1.60–1.74)	1.40 (1.23–1.60)	1.48 (1.41–1.54)	1.30 (1.15–1.46)	2.56 (2.35–2.80)	2.48 (1.89–3.27)
Very preterm birth (<32 weeks)	2.03 (1.85–2.24)	2.32 (1.77–3.04)	1.96 (1.77–2.16)	1.66 (1.25–2.19)	3.06 (2.52–3.72)	2.58 (1.36–4.89)
Small for gestational age	1.65 (1.57–1.75)	1.58 (1.32–1.89)	1.50 (1.41–1.58)	1.38 (1.16–1.64)	2.87 (2.58–3.18)	1.51 (0.96–2.38)
Stillbirth	1.82 (1.62–2.03)	1.65 (1.18–2.30)	1.39 (1.22–1.58)	1.28 (0.91–1.79)	2.85 (2.29–3.54)	1.79 (0.80–4.02)

BMI=Body Mass Index, CI=Confidence interval, TIA=Transient ischemic attack

*= Parity excluded from the model

Adjusted for: Maternal age, maternal age^2, BMI, BMI^2, smoking status, family situation, comorbidities associated to pregnancy and at first-time hospitalization for cardiovascular disease (diabetes mellitus, hypertension, chronic kidney failure and venous thrombosis) and decade at first pregnancy. For the fetal complications, we also adjusted for preeclampsia or eclampsia in first pregnancy.

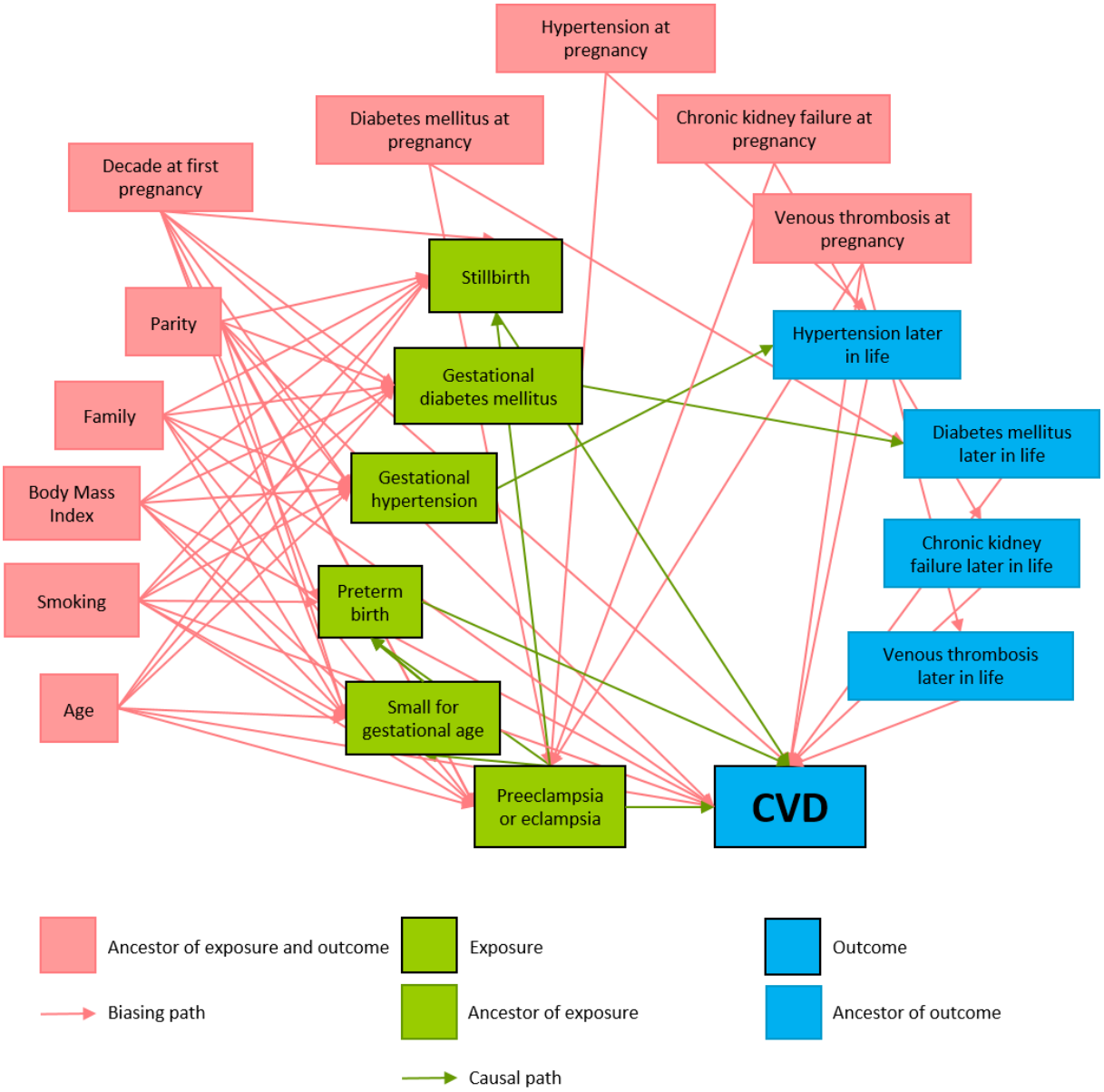


Figure S1: Directed acyclic graph (DAG)

CVD=Cardiovascular disease

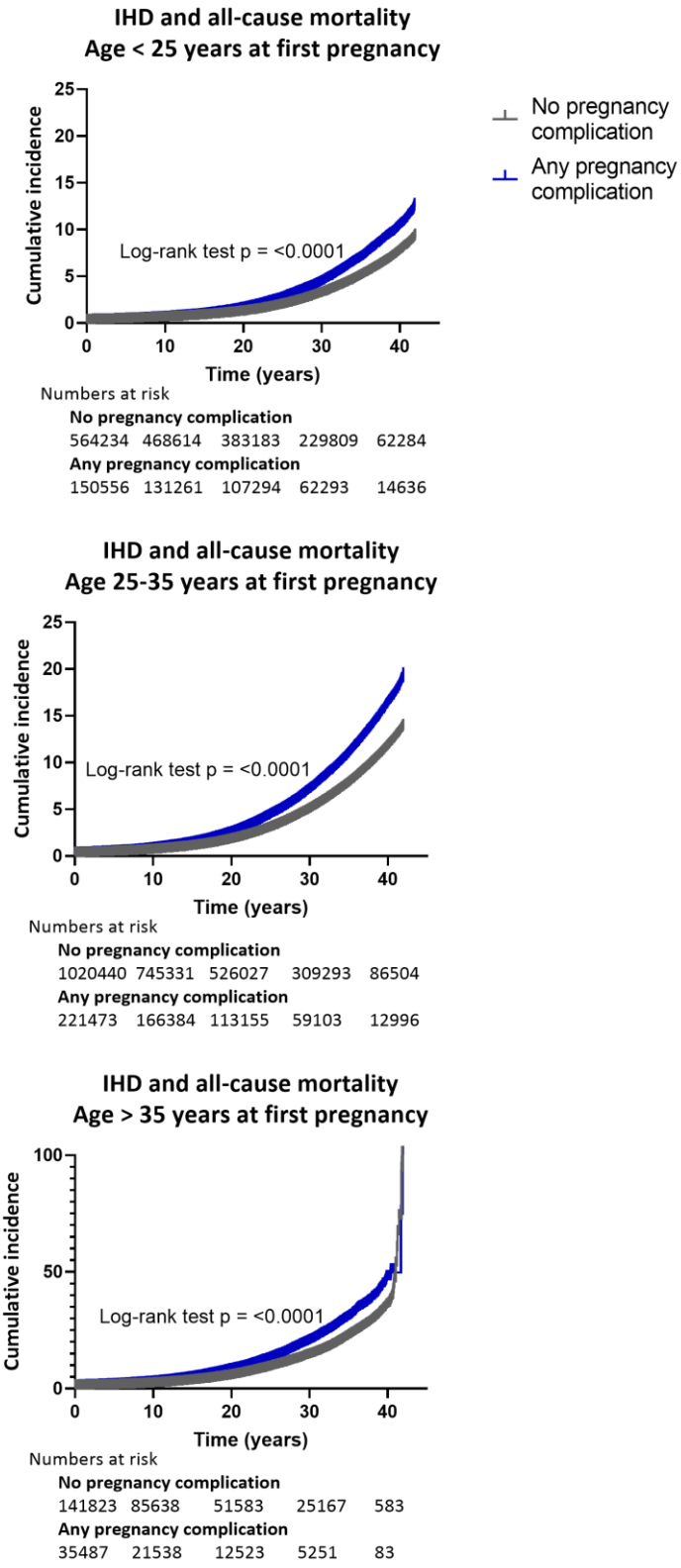


Figure S2a: Unadjusted cumulative incidence plots for first time hospitalizations of ischemic heart disease (IHD) and all-cause mortality, stratified into three age categories in women unexposed and exposed to pregnancy complications in any pregnancy. Women at age 75 years and younger at the end of 2014 were included.

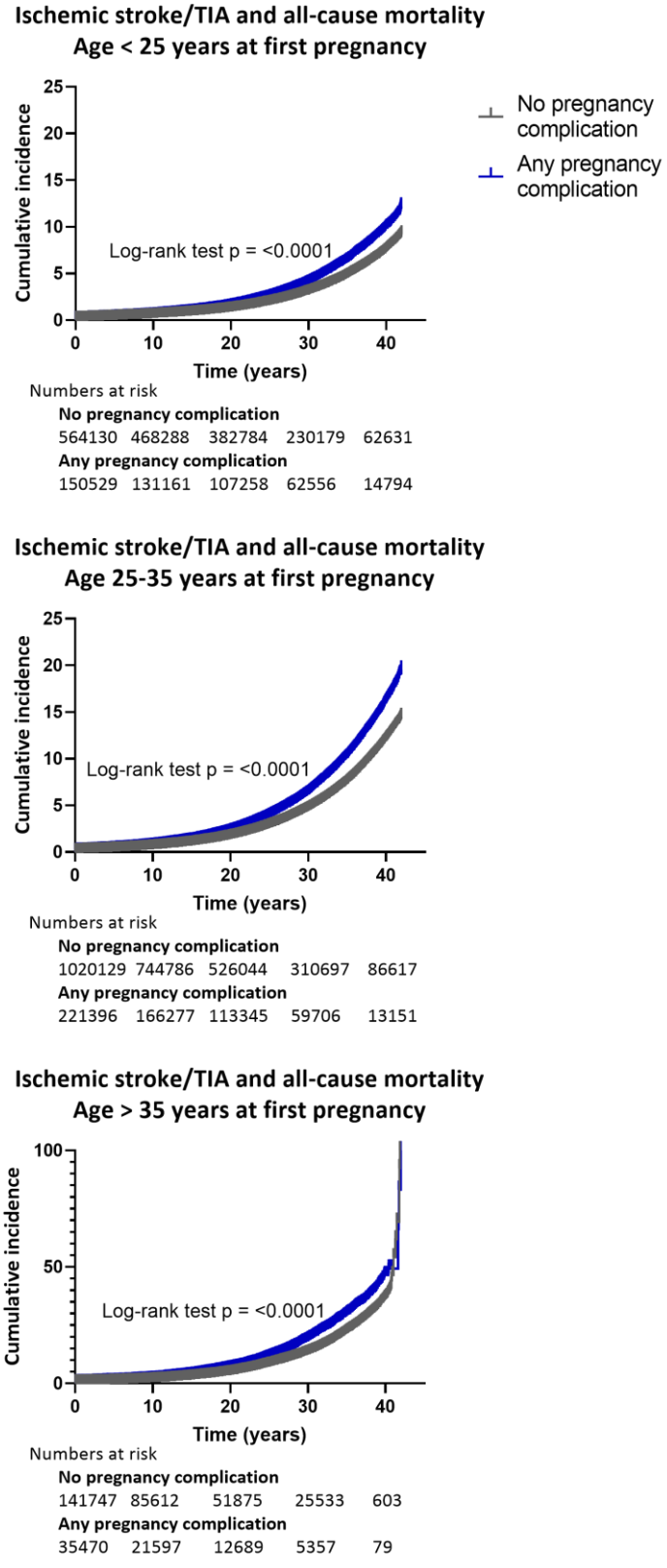


Figure S2b: Unadjusted cumulative incidence plots for first time hospitalizations of ischemic stroke/transient ischemic attack (TIA) and all-cause mortality, stratified into three age categories in women unexposed and exposed to pregnancy complications in any pregnancy. Women at age 75 years and younger at the end of 2014 were included.

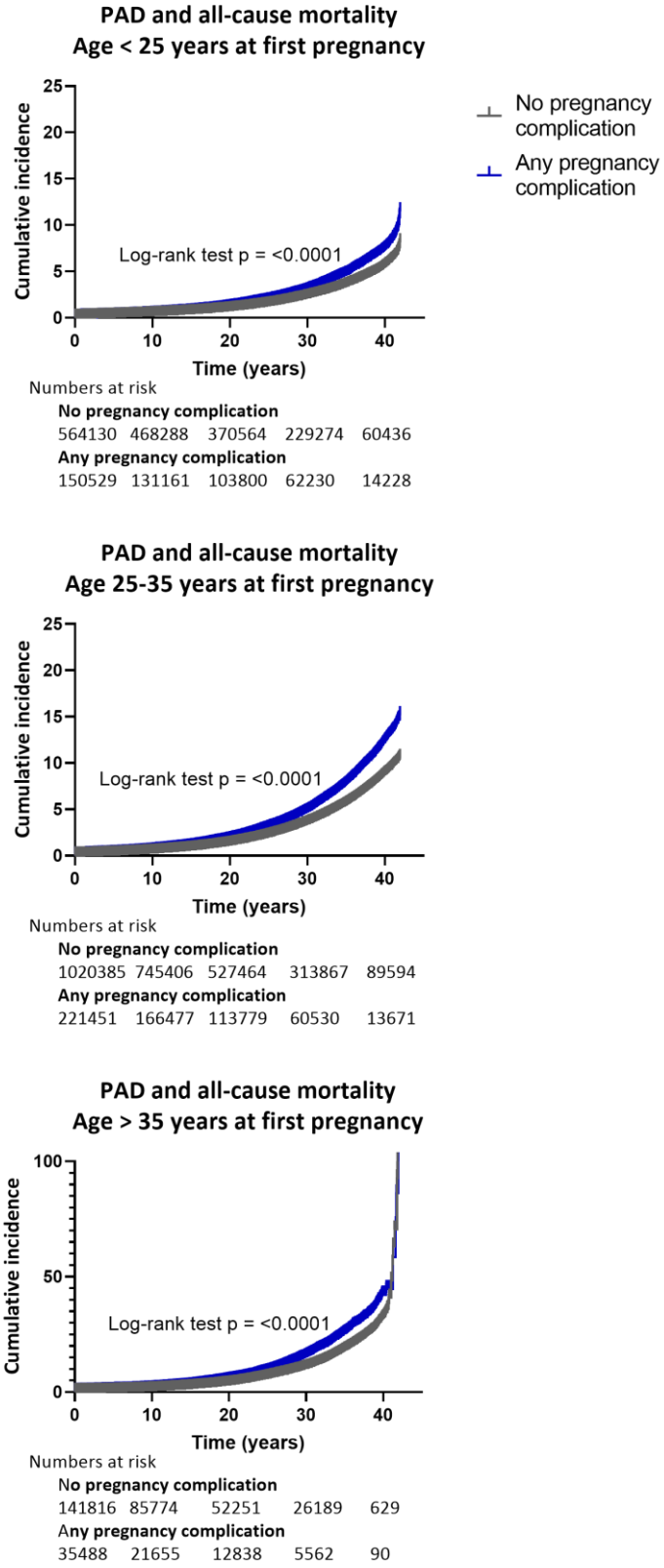
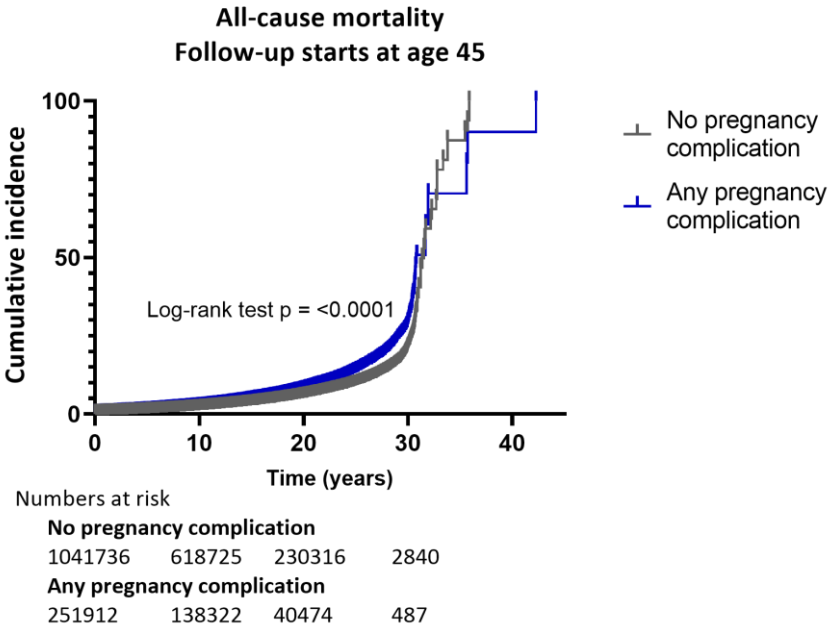


Figure S2c: Unadjusted cumulative incidence plots for first time hospitalizations of peripheral artery disease (PAD) and all-cause mortality, stratified into three age categories in women unexposed and exposed to pregnancy complications in any pregnancy. Women at age 75 years and younger at the end of 2014 were included.



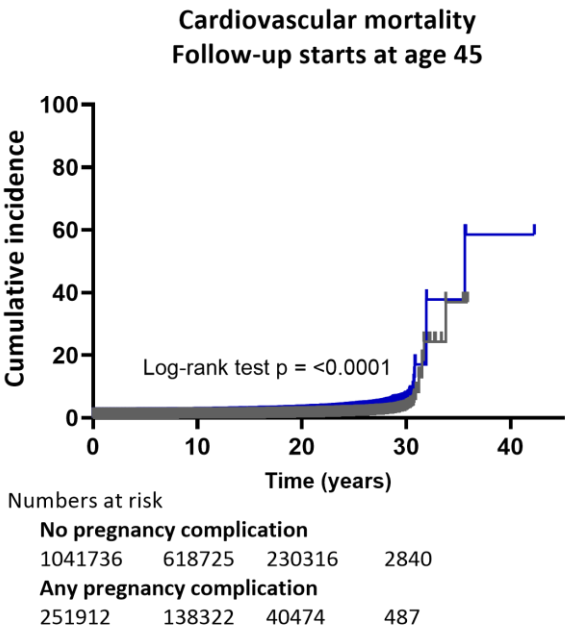


Figure S3: Unadjusted cumulative incidence plots for all-cause and cardiovascular mortality in women unexposed and exposed to pregnancy complications in any pregnancy starting at maternal age of 45. Women at age 75 years and younger at the end of 2014 were included.

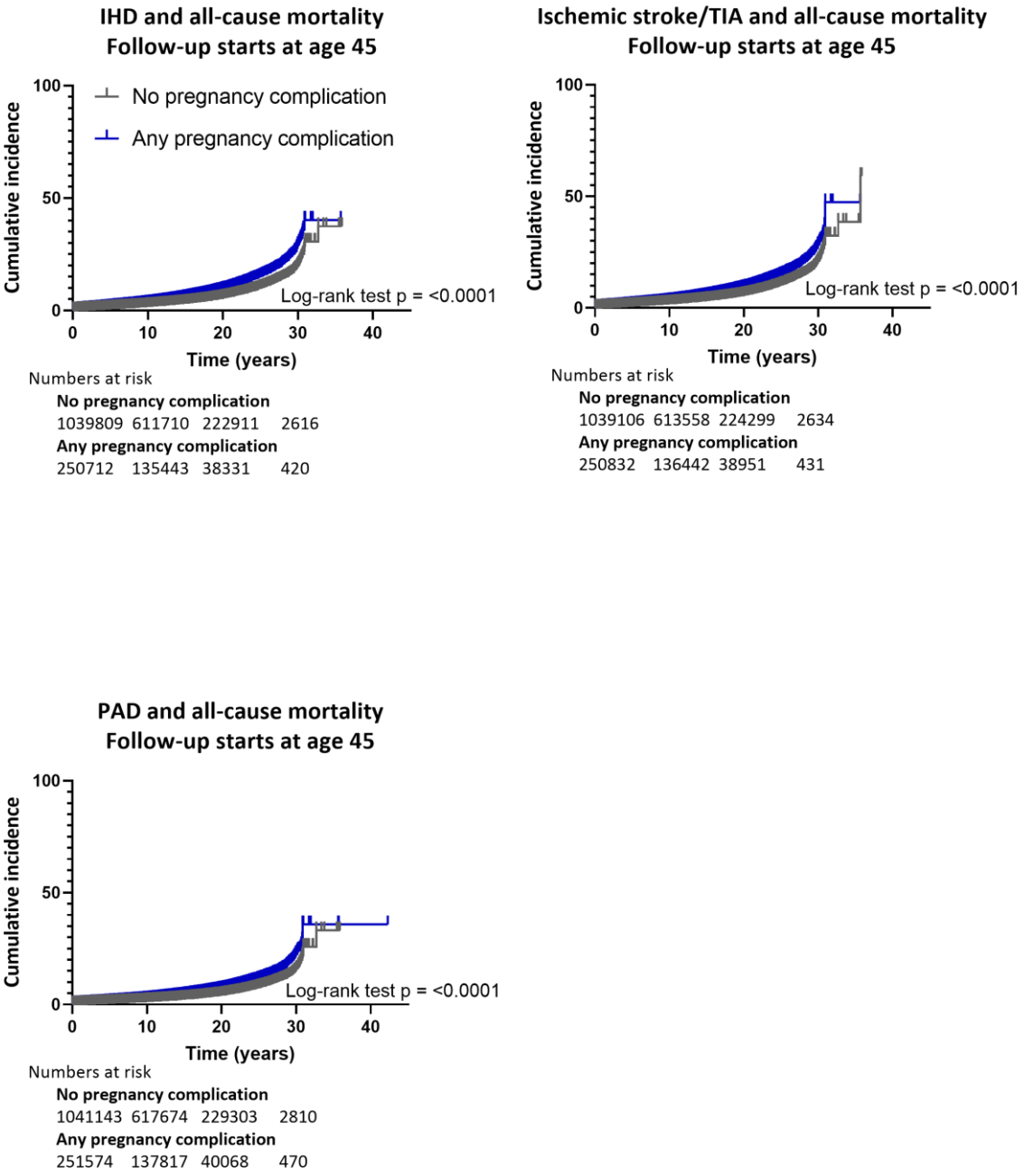


Figure S4: Unadjusted cumulative incidence plots for first time hospitalizations of ischemic heart disease (IHD) and all-cause mortality, ischemic stroke/transient ischemic attack (TIA) and all-cause mortality and peripheral artery disease (PAD) and all-cause mortality in women unexposed and exposed to pregnancy complications in any pregnancy starting at maternal age of 45. Women at age 75 years and younger at the end of 2014 were included.