Received: 7 April 2022 | Revised: 30 August 2022 | Accepted: 13 September 2022

DOI: 10.1111/ppe.12928

ORIGINAL ARTICLE

Paediatric and Perinatal Epidemiology WILEY

Long-term cardiovascular mortality in women with twin pregnancies by lifetime reproductive history

Prativa Basnet[1] | Rolv Skjærven[1,2] | Linn Marie Sørbye[1,3] | Nils-Halvdan Morken[1,4,5] | Kari Klungsøyr[1,6] | Aditi Singh[1] | Janne Mannseth[1] | Quaker E. Harmon[7] | Liv Grimstvedt Kvalvik[1]

[1]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[2]Centre for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

[3]Norwegian Research Centre for Women's Health, Oslo University Hospital, Rikshospitalet, Oslo, Norway

[4]Department of Clinical Science, University of Bergen, Bergen, Norway

[5]Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway

[6]Division for Mental and Physical Health, Norwegian Institute of Public Health, Bergen, Norway

[7]Epidemiology Branch, National Institute of Environmental Health Sciences, Durham, North Carolina, USA

Correspondence
Prativa Basnet, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.
Email: prativa.basnet@uib.no

Funding information
H2020 European Research Council, Grant/Award Number: 833076; The Intramural Research Program of the NIH National Institute of Environmental Health Sciences; Norwegian Research Centre for Women's Health at Oslo University Hospital

Abstract

Background: Women with one lifetime singleton pregnancy have increased risk of cardiovascular disease (CVD) mortality compared with women who continue reproduction particularly if the pregnancy had complications. Women with twins have higher risk of pregnancy complications, but CVD mortality risk in women with twin pregnancies has not been fully described.

Objectives: We estimated risk of long-term CVD mortality in women with naturally conceived twins compared to women with singleton pregnancies, accounting for lifetime number of pregnancies and pregnancy complications.

Methods: Using linked data from the Medical Birth Registry of Norway and the Norwegian Cause of Death Registry, we identified 974,892 women with first pregnancy registered between 1967 and 2013, followed to 2020. Adjusted hazard ratios (aHR) with 95% confidence intervals (CI) for maternal CVD mortality were estimated by Cox regression for various reproductive history (exposure categories): (1) Only one twin pregnancy, (2) Only one singleton pregnancy, (3) Only two singleton pregnancies, (4) A first twin pregnancy and continued reproduction, (5) A first singleton pregnancy and twins in later reproduction and (6) Three singleton pregnancies (the referent group). Exposure categories were also stratified by pregnancy complications (pre-eclampsia, preterm delivery or perinatal loss).

Results: Women with one lifetime pregnancy, twin or singleton, had increased risk of CVD mortality (adjusted hazard [HR] 1.72, 95% confidence interval [CI] 1.21, 2.43 and aHR 1.92, 95% CI 1.78, 2.07, respectively), compared with the referent of three singleton pregnancies. The hazard ratios for CVD mortality among women with one lifetime pregnancy with any complication were 2.36 (95% CI 1.49, 3.71) and 3.56 (95% CI 3.12, 4.06) for twins and singletons, respectively.

Conclusions: Women with only one pregnancy, twin or singleton, had increased long-term CVD mortality, however highest in women with singletons. In addition, twin mothers who continued reproduction had similar CVD mortality compared to women with three singleton pregnancies.

KEYWORDS
CVD mortality, maternal survival, Norway, population-based study, twin pregnancy

1 | BACKGROUND

Cardiovascular disease (CVD) mortality risk is increased among women with one lifetime singleton births compared to women who continue reproduction.[1] Pregnancy complications including pre-eclampsia, preterm delivery and perinatal loss are also associated with elevated risk of CVD morbidity and mortality in singleton pregnancies.[2–8] Women with twin pregnancies have an increased risk of pregnancy complications[9–11] and may potentially stop reproduction after a first pregnancy with twins because two children are a common desired family size.[12,13] Twin pregnancies also have a greater biological demand on the mothers, which might impact their later health. However, the influence and interaction between lifetime number of pregnancies and pregnancy complications on maternal long-term CVD mortality have not been fully explored for twin pregnancies.

Due to the difficulty in linking pregnancies across a woman's reproductive lifetime, many previous studies have focused on associations between complications in the first pregnancy and later maternal health. However, analyses restricted to outcomes in first pregnancies do not account for possible heterogeneity in risk by the number of children.[14] To the best of our knowledge, no previous research has investigated long-term CVD mortality in women considering both plurality and complications in successive pregnancies across womens' reproductive period.

In Norway, a unique national identification number, provided to all residents, enables linkage of all pregnancies to a woman. With data on pregnancies since 1967, the Medical Birth Registry of Norway (MBRN) provides an opportunity to analyse women's complete reproductive history. Further linkage with the Norwegian Cause of Death Registry, allows an evaluation of the association between reproductive history and maternal cause-specific mortality. In linked pregnancy data (with the mother as the observational unit), we aimed to estimate long-term CVD mortality in women with twins by lifetime number of pregnancies compared to women with singleton pregnancies. We also assessed associations with long-term mortality by presence of pre-eclampsia, preterm delivery, perinatal loss as pregnancy complications are more common in twin pregnancies.[10,11] Findings may identify high-risk women for appropriate follow-up with interventions to lower their long-term risk of CVD related deaths.

Synopsis

Study question

Do women with twin pregnancies have increased risk of long-term cardiovascular disease (CVD) mortality?

What's already known

CVD mortality is increased among women with one lifetime singleton birth. Several complications in singleton pregnancies are associated with increased CVD mortality. Women with twin pregnancies have increased risk of pregnancy complications, such as pre-eclampsia, preterm delivery and perinatal loss, compared to singleton pregnancies.

What this study adds

In a population-based cohort study, women with only one pregnancy, twin or singleton, had increased risk of Atherosclerotic cardiovascular disease (ASCVD) mortality, compared to women with three singleton pregnancies. The increase was highest in women with singletons. Women with a first twin pregnancy and continued reproduction had similar ASCVD mortality compared to women with three singleton pregnancies.

2 | METHODS

2.1 | Data sources

The MBRN is a population-based registry, established in 1967, primarily to monitor birth defects and other maternal and perinatal health problems and to provide data for epidemiological research on causes and consequences of perinatal health problems.[15] The MBRN is based on mandatory notification of all live births, stillbirths and pregnancy losses from 16 weeks of gestation. The registry records prospectively collected information on women's health before and during pregnancy, the delivery and the immediate postpartum period, including demographic information, complications and interventions during delivery and infant outcomes. The attending midwife and obstetrician record data using a standardised notification form, either as free text or, since 1999, by predefined variables or check boxes in addition to free text. Since 2006, a gradual transition to electronic birth notification took place (complete in 2014), and the notifications are now based on pre-specified extractions from the medical records at the delivery units. Every live-born infant in Norway, as well as all immigrants who become Norwegian inhabitants, are provided with a unique national identification number by the National Population Register. The MBRN is routinely matched with the National Population Register and receives all national identification numbers and all dates of death and emigration through this linkage. The unique identification number was used to link all pregnancies to their mother in maternal pregnancy files, and linkage

with the Cause of Death Registry provided information on mother's causes of death. The Cause of Death Registry, established in 1954, contains information on the underlying and contributing causes of death, registered using ICD codes. The form is filled out by a medical doctor and is quality-assured using other national registries. Information on highest attained level of education by 2020 was obtained from the National Education Database at Statistics Norway.

We restricted our study population to women with their first pregnancy registered in the MBRN during 1967–2013 (Figure 1). This provided enough follow-up time for women to have a second pregnancy by 2020 as 95% of Norwegian women with two or more pregnancies have their second pregnancy within 7 years.[1] All women were followed until 2020 for deaths before 70 years of age.

There have been changes in the data quality of MBRN during the 50 years since its establishment, mainly due to the change of the notification form in 1999 from being based solely on free text to adding check boxes. These changes are unlikely to impact the reporting of singleton or multiple gestations over time. Reporting of some pregnancy complications including mild pre-eclampsia and late spontaneous abortions have improved over time. Registry-based research depends on valid information, and over the years, several MBRN variables have been validated with mostly acceptable results.[16] Pre-eclampsia was for example found to have a positive predictive value of 88.3% (births 1967–2002) in one study, using the diagnostic criteria at that time.[17] In a study of births 1999–2010, the positive predictive value of pre-eclampsia was 83.9%.[18]

2.2 | Lifetime successive pregnancies approach

By linking data on a woman's successive pregnancies through her lifetime to later health outcomes allows a more comprehensive study of possible associations between reproductive events and long-term health.[19] In this study, we linked consecutive pregnancies (as registered in the MBRN) to the women, to compare women with twin and singleton pregnancies accounting for their lifetime number of pregnancies.

2.3 | Exposure variables

Lifetime reproductive history, ascertained at the end of reproduction or 2020, consisting of six mutually exclusive categories were used as exposure: (1) Women with only one twin pregnancy, (2) Women with only one singleton pregnancy, (3) Women with only two singleton pregnancies, (4) Women with a first twin pregnancy and continued reproduction, (5) Women with a first singleton pregnancy and twins in later reproduction and (6) Women with three singleton pregnancies as the referent group (Figure 1). Given that two pregnancies are a common pregnancy pattern among singletons, we chose three pregnancies as the referent so that three children (two pregnancies for those that start with twins or three pregnancies for those who start with a singleton) were a possible stopping point for both twin and singleton first births.

Complications in each pregnancy were obtained from the MBRN. A diagnosis of pre-eclampsia is based on the definition provided by the Norwegian Gynaecological Association and aligned with the criteria recommended by the American College of Obstetricians and Gynaecologists (see further definition in Appendix S1). Preterm delivery was defined as births before 37 completed weeks of gestation. Perinatal loss included losses between 16 and 22 weeks, stillbirths and neonatal deaths during the first week after birth (one or both infants in case of twins). The six categories of reproductive history were further stratified by occurrence of pregnancy complications: pre-eclampsia, preterm delivery, perinatal loss in any pregnancy. This resulted in 12 exposure categories with women who had three singletons and no complication in any pregnancy as the referent.

2.4 | Outcome

The main outcome variable was Atherosclerotic Cardiovascular Disease (ASCVD) mortality defined as death from ischaemic heart disease or cerebrovascular disease or peripheral arterial disease in women before 70 years of age. We used codes from the International Statistical Classification of Diseases and Related Health Problems (ICD) to define our outcome as shown in Appendix S1. In addition, results using more expansive definition of CVD are presented in Appendix S1.

2.5 | Covariates

Estimates were adjusted for calendar year of first delivery, mother's age at first birth, maternal education: <9 years, 10–12 years and ≥13 years (reference) and chronic medical conditions available in the MBRN (Type 1 or Type 2 diabetes mellitus, hypertension, kidney disease and rheumatoid arthritis).

2.6 | Exclusions

Pregnancies conceived by assisted reproductive technologies (ART) were excluded from the main analyses as infertility/subfertility could be associated with underlying factors predisposing women for cardiovascular disease.[20,21] In addition, information on ART was not available for the whole study period in the MBRN. We also excluded women with any higher order multi-foetal pregnancies (≥triplets), as these pregnancies are rare and associated with specific obstetric challenges. Further, we excluded women with four singleton pregnancies ($n = 63{,}756$).

2.7 | Statistical methods

All data were analysed using STATA version 17. Descriptive statistics were presented as number and percentages. To estimate hazard ratios with 95% confidence intervals (CI) for ASCVD mortality by

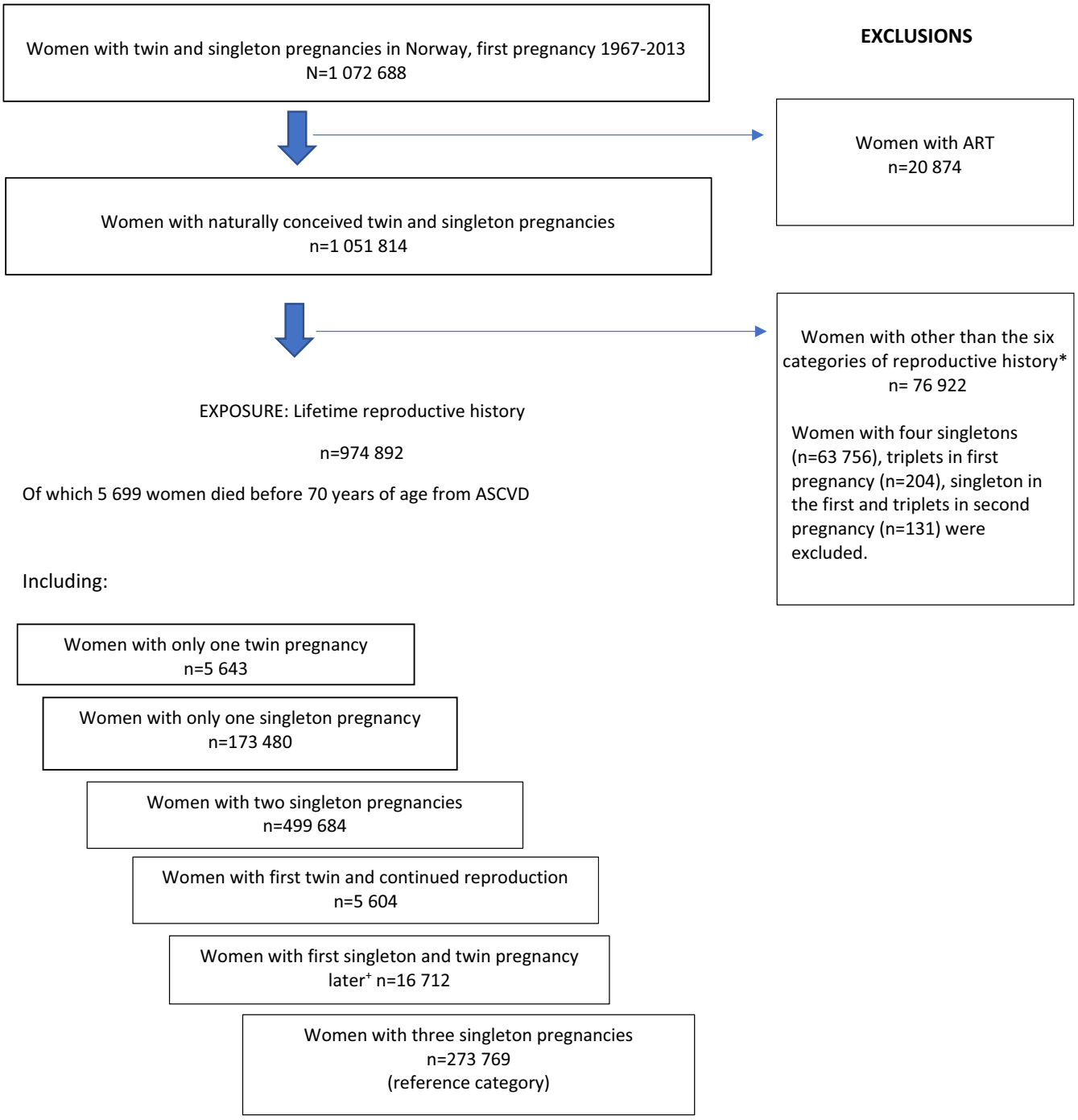

FIGURE 1 Flowchart of study population. ART, assisted reproductive technology; ASCVD, atherosclerotic cardiovascular disease. *Other reproductive history than the six categories presented above were not included in the analysis. For example, mothers with four singletons, triplets in first pregnancy or later etc. were excluded. +Women with twins either in second, third or fourth pregnancy.

the six categories of reproductive history in women, we used Cox proportional hazard regression models with women's age as the underlying time variable. We adjusted for age at first birth, year of first birth, education and chronic medical conditions as potential confounders. Women were considered at risk of death from the age at their last pregnancy. Women were censored at death, age 70 or when follow-up ended in 2020, whichever came first.

2.8 | Missing data

In our study population, missing data on the covariates were rare, we used complete case analysis. Less than 1% of the maternal education and 4.2% of the women's gestational ages were missing. Information on maternal age and year of birth of first child were complete.

2.9 | Sensitivity analysis

To evaluate the robustness of our findings, we conducted multiple sensitivity analyses. We assessed the risk of ASCVD mortality in women who had completed their reproduction (age 40). For this analysis, women who were not 40 years of age by the end of follow-up or women who died before 40 years of age were excluded. We also repeated the main analysis after including women who conceived using ART. We additionally performed the main analysis (ASCVD mortality in the six exposure groups) restricted to gestational age above 22 weeks to evaluate selection bias due to incomplete recording of pregnancies ending before 22 weeks. Finally, we evaluated whether associations by reproductive history changed when the outcome variable was extended to include hypertensive heart disease and cardiomyopathy.

3 | RESULTS

Maternal and pregnancy characteristics of 974,892 women by plurality of first pregnancy (singleton or twin) are shown in Table 1. In total 1.2% of first pregnancies were twins. Women with a first twin pregnancy were older, had higher frequency of university degrees, shorter gestations and more often delivered preterm (48% vs. 6%) compared to women with a first singleton pregnancy. Also, pre-eclampsia (14% vs. 4%) and perinatal loss (6% vs. 1%) were more frequent in women with a first twin pregnancy. In total 42,182 women died before the age of 70 years during 1967–2020, of which 5699 (13.5%) died of cardiovascular causes. ASCVD deaths among women with twins in any pregnancy accounted for 2.8% of all ASCVD deaths.

Table 2 shows the distribution of deaths across the six categories of reproductive history for ASCVD using women with three singleton pregnancies as the referent group. Women with only one lifetime pregnancy had increased risk of ASCVD death, both if their only pregnancy was with twins (adjusted HR (aHR) 1.72, 95% CI 1.21, 2.43) or a singleton (aHR 1.92, 95% CI 1.78, 2.07). The point estimate was slightly higher for women with one lifetime singleton pregnancy than women with one lifetime twin pregnancy. No increased risk was found for women with a first twin pregnancy and continued reproduction (aHR 0.76, 95% CI 0.48, 1.19). Women with a first singleton pregnancy and twins in later reproduction, however, had an increased risk of ASCVD death (aHR: 1.49, 95% CI 1.22, 1.81). A small increase was also found for women with two singletons (aHR 1.08, 95% CI 1.01, 1.15) compared to the referent.

Risk of long-term ASCVD mortality by one or more pregnancy complications (pre-eclampsia, preterm delivery, perinatal loss) is outlined in Table 3. Women with only one lifetime pregnancy had substantially increased risk of dying from ASCVD in the presence of one or more complications. This was true both for women with only one twin (aHR 2.36, 95% CI 1.49, 3.71) or women with only one singleton (aHR 3.56, 95% CI 3.12, 4.06). Women with one lifetime pregnancy without complications also had an elevated risk of ASCVD death if the pregnancy was a singleton (aHR 1.99, 95% CI 1.82, 2.17). The relative risk of dying from ASCVD for women with one lifetime twin pregnancy without complications was aHR 1.57 (95% CI 0.92, 2.66).

TABLE 1 Maternal and pregnancy characteristics of 974,892 women's first pregnancy registered in the Medical Birth Registry of Norway, 1967–2013

	Women with first twin pregnancy	Women with first singleton pregnancy
	N (%)	*N* (%)
Total	11,247	963,645
Maternal age at first birth		
≤19	768 (6.8)	108,321 (11.2)
20–24	3364 (29.9)	359,731 (37.3)
25–29	4006 (35.6)	320,707 (33.3)
30–34	2187 (19.5)	133,135 (13.8)
35–39	761 (6.8)	35,725 (3.7)
40–44	137 (1.2)	5754 (0.6)
≥45	24 (0.2)	272 (0.03)
Maternal education		
Primary school	1899 (16.9)	182,155 (18.9)
High school	4107 (36.5)	377,148 (39.2)
University	5150 (45.8)	395,289 (41.0)
Missing education	91 (0.8)	9053 (0.9)
Gestational age		
<28	578 (5.1)	4877 (0.5)
28–31	768 (6.8)	6353 (0.6)
32–33	987 (8.9)	7458 (0.8)
34–36	3059 (27.2)	38,017 (3.9)
37–38	3101 (27.6)	119,224 (12.4)
39+ weeks	2346 (20.8)	747,552 (77.6)
Missing	408 (3.6)	40,164 (4.2)
Perinatal loss	724 (6.4)	9758 (1.0)
Pre-eclampsia	1588 (14.1)	41,725 (4.3)
Preterm delivery	5392 (47.9)	56,705 (5.9)
Chronic conditions[a]	340 (3.0)	22,488 (2.3)

[a]Includes chronic medical conditions (diabetes, hypertension, kidney disease and rheumatoid arthritis).

When restricting analyses to deaths between 40 and 69 years of age and when including women with IVF, results were essentially the same (Tables S1 and S2). In addition, the results were substantially the same when restricted to gestational age above 22 weeks (Table S3). Additionally, using an extended definition of CVD also yielded similar results (Table S4).

4 | COMMENT

4.1 | Principal findings

Women with only one lifetime twin pregnancy and women with only one lifetime singleton pregnancy had similarly increased risk of ASCVD mortality compared to women with three singleton pregnancies. Although twin pregnancies are more likely to have pregnancy

TABLE 2 Hazard ratios (HRs) with 95% confidence intervals (CI) for atherosclerotic cardiovascular disease (ASCVD) mortality before 70 years of age by various categories of reproductive history in 974,892 women, first pregnancy 1967–2013 and follow-up until 2020. Medical Birth Registry of Norway and Cause of Death Registry

		ASCVD mortality				
Womens' reproductive history	Total women	No. of deaths	Deaths per 1000	Person-years	Unadjusted HR (95% CI)	aHR[a] (95% CI)
Only one twin pregnancy	5643	34	6.0	142,050	2.02 (1.44, 2.84)	1.72 (1.21, 2.43)
Only one singleton pregnancy	173,480	1611	9.3	4,841,214	2.38 (2.22, 2.57)	1.92 (1.78, 2.07)
Two singleton pregnancies	499,684	2607	5.2	12,792,455	1.16 (1.09, 1.24)	1.08 (1.01, 1.15)
First twin pregnancy and continued reproduction	5604	19	3.4	129,221	0.81 (0.51, 1.27)	0.76 (0.48, 1.19)
First singleton pregnancy and twins in later[b] reproduction	16,712	109	6.5	389,105	1.52 (1.25, 1.85)	1.49 (1.22, 1.81)
Three singleton pregnancies	273,769	1319	4.8	6,371,233	1.00 (Reference)	1.00 (Reference)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

[a]Estimates were obtained using Cox regression and adjusted for year of first birth, maternal age at first birth, maternal education and chronic medical conditions (diabetes, hypertension, kidney disease and rheumatoid arthritis).

[b]Women with twins either in second, third or fourth pregnancy.

complications, these complications do not appear to further elevate the risk of ASCVD mortality once total parity is accounted for.

4.2 | Strengths of the study

A major strength of this study was the large population-based longitudinal dataset comprising of successive pregnancies with long follow-up and linked data from the Cause of Death Registry. This rich data source provided unique opportunities to study twin and singleton pregnancies accounting for pregnancy complications and evaluate long-term maternal ASCVD mortality, using lifetime successive pregnancies approach.

4.3 | Limitations of the data

Limitations included lack of information on several potential confounders, such as smoking and body mass index (BMI), that were not registered in the MBRN for most of the study period.

4.4 | Interpretation

Our findings are consistent with previous work in singletons showing that women with one lifetime pregnancy have increased long-term CVD mortality compared to women with more than one pregnancy[1]; however, the underlying mechanisms are uncertain. Several social and biological factors may contribute to the increased CVD mortality in women who stop their reproduction after one pregnancy. Previous research suggests that pregnancy influences endothelial function,[22-25] which may support the hypothesis that repeated pregnancies reduce the risk of CVD mortality.[26] On the other hand, women who stop reproducing may be a selected group of women with pre-existing medical conditions[27] or who suffered severe complications in pregnancy[1,20] or maybe due to changed relationship status. The underlying mechanism may also be related to subfertility issues,[28] which has been shown to be associated with later CVD mortality.[20] We were able to account for some important chronic medical conditions available in the MBRN.

We also examined pregnancy complications in women; pre-eclampsia, preterm delivery, perinatal loss, which are consistently reported to be associated with increased long-term CVD in women.[4–6,28–32] Most studies have focused on singletons and only analysed pregnancy complications in the first pregnancy without considering successive pregnancies and without specific evaluation of twin pregnancies. Twin pregnancies have an increased risk of pre-eclampsia.[33–35] In our study, we found that women with first twin pregnancies had more than three times higher risk of pre-eclampsia than women with singleton first pregnancies (14.1% vs. 4.3%). In our data, preterm delivery was also more common in first twin pregnancies compared to singletons (47.9% vs. 5.9%), as was perinatal loss (6.4% vs. 1.0%).

Although we found that pregnancy complications were more frequent in twin pregnancies, the complications may develop for different reasons[35] and may be viewed as less 'pathological'. Among those with only one pregnancy with complications, the increased relative risk of ASCVD mortality was higher for the

TABLE 3 Hazard ratios (HRs) with 95% confidence intervals (CI) for atherosclerotic cardiovascular disease (ASCVD) mortality before 70 years of age by various categories of reproductive history with and without pregnancy complications (pre-eclampsia, preterm delivery, perinatal loss) at least once in 974,892 women, first pregnancy 1967–2013 and follow-up until 2020. Medical Birth Registry of Norway and Cause of Death Registry

		ASCVD mortality			
Womens' reproductive history	Total women	No. of deaths	Deaths per 1000	Unadjusted HR (95% CI)	aHR[a] (95% CI)
Only one twin pregnancy with one or more complications	3116	19	6.1	2.73 (1.74, 4.31)	2.36 (1.49, 3.71)
Only one twin pregnancy without complication	2527	15	5.9	1.92 (1.15, 3.20)	1.57 (0.92, 2.66)
Only one singleton pregnancy with one or more complications	19,941	320	16.1	5.05 (4.44, 5.74)	3.56 (3.12, 4.06)
Only one singleton pregnancy without complication	153,539	1291	8.4	2.45 (2.25, 2.66)	1.99 (1.82, 2.17)
Two singleton pregnancies with one or more complications	66,143	523	7.9	2.13 (1.92, 2.38)	1.85 (1.66, 2.06)
Two singleton pregnancies without complication	433,541	2084	4.8	1.21 (1.12, 1.30)	1.12 (1.03, 1.21)
First twin pregnancy and continued reproduction with one or more complications	3503	13	3.7	1.04 (0.60, 1.80)	0.95 (0.55, 1.64)
First twin pregnancy and continued reproduction without complication	2101	6	2.9	0.74 (0.33, 1.65)	0.70 (0.31, 1.56)
First singleton pregnancy and twins later[b] with one or more complications	7969	52	6.5	1.87 (1.42, 2.48)	1.78 (1.35, 2.35)
First singleton pregnancy and twins later[b] without complication	8743	57	6.5	1.62 (1.24, 2.12)	1.58 (1.21, 2.07)
Three singleton pregnancies with one or more complications	51,350	384	7.5	1.73 (1.54, 1.95)	1.60 (1.42, 1.80)
Three singleton pregnancies without complication	222,419	935	4.2	1.00 (Reference)	1.00 (Reference)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio.

[a]Estimates were obtained using Cox regression and adjusted for year of first birth, maternal age at first birth, maternal education and chronic medical conditions (diabetes, hypertension, kidney disease and rheumatoid arthritis).

[b]Women with twins either in second, third or fourth pregnancy.

women with a singleton aHR 3.56 (95% CI 3.12, 4.06) rather than a twin pregnancy aHR 2.36 (95% CI 1.49, 3.71) compared to the referent of three singletons with complications. This may support the hypothesis that pregnancy complications in twin pregnancies have important differences. Our finding is similar to an Israelian study that showed that even though women with twin pregnancy had more complications, twin pregnancy was not associated with increased risk of CVD hospitalisation.[34] Consistent to our finding, another recent study reported increased risk of CVD mortality among twin pregnancies complicated by hypertensive disorder compared to uncomplicated twin pregnancies.[36] However, a study from Sweden showed that women who had a multi-foetal pregnancy did not have increased CVD risk even if pre-eclampsia occurred, compared to women without pre-eclampsia in singleton pregnancy.[37] The Swedish study analysed women's first pregnancy only, and in contrast, our study incorporated both pregnancy complications and the number of pregnancies. We could, therefore, separate those with only one lifetime pregnancy, which was important for maternal long-term mortality.

While underlying CVD risk factors might predispose to both pre-eclampsia and later maternal CVD in singleton pregnancies, causes of pre-eclampsia in twin pregnancies may be less linked to long-term CVD.[37] A previous study that examined the association between complications in twin pregnancy and later life CVD, suggested different pathophysiological processes in twin and singleton pregnancies.[34] Likewise, studies have highlighted that there are differences in maternal adaptation during singleton and twin pregnancies; however, they have not found differences in indicators of maternal cardiovascular functions, such as blood pressure in later life.[38] We could not find any studies investigating long-term CVD mortality in mothers with twins who experienced preterm delivery or perinatal loss. As with pre-eclampsia, preterm delivery and perinatal loss, may have different association with maternal mortality in twin and singleton pregnancies.

The higher ASCVD mortality in women with one lifetime pregnancy could have more than one explanation. For women who start with one singleton, stopping reproduction may be due to underlying health concerns, severe pregnancy complications or subfertility,

which prevents further conception. Women with twins may stop reproduction for all the same reasons, however they may also stop due to having achieved their desired family size of two children. The elevated risk of ASCVD mortality in both groups, however, slightly higher for women with one lifetime singleton pregnancy than one lifetime twin pregnancy, suggests multiple pathways through which reproductive patterns can influence later health.

5 | CONCLUSIONS

Women with one pregnancy, twin or singleton, had increased risk of ASCVD mortality, compared to the referent of three singleton pregnancies. However, the relative increase in ASCVD mortality was slightly lower if this was a twin pregnancy. Women with a first twin pregnancy and continued reproduction had similar ASCVD mortality compared to women with three singleton pregnancies. Our findings do not suggest a greater long-term burden on ASCVD mortality in women with twin pregnancies. The heterogeneity in risk found between women with one lifetime pregnancy and women who continue reproduction should be explored in future research. Women who stop reproduction after their first pregnancy, twin or singleton, may benefit from timely follow-up and intervention to mitigate future risk of early deaths.

AUTHOR CONTRIBUTIONS

PB, RS and LGK conceived and designed the study. RS obtained access to the data. PB conducted the data analysis and drafted the initial version of the manuscript. RS is guarantor for data quality. All authors provided important insight during the data analysis and critically revised the manuscript.

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Allen J. Wilcox at the National Institute of Environmental Health Sciences (NIEHS) for providing useful comments on earlier versions of this manuscript.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Norwegian Institute of Public Health. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from https://www.fhi.no/en/hn/health-registries/medical-birth-registry-of-norway/medical-birth-registry-of-norway/ with the permission of Norwegian Institute of Public Health.

ORCID

Prativa Basnet https://orcid.org/0000-0001-9022-9957
Rolv Skjærven https://orcid.org/0000-0002-2983-1233
Linn Marie Sørbye https://orcid.org/0000-0002-3726-5198
Nils-Halvdan Morken https://orcid.org/0000-0002-8256-0778
Kari Klungsøyr https://orcid.org/0000-0003-2482-1690
Aditi Singh https://orcid.org/0000-0002-2302-1723
Janne Mannseth https://orcid.org/0000-0003-1386-5073
Quaker E. Harmon https://orcid.org/0000-0002-5866-848X
Liv Grimstvedt Kvalvik https://orcid.org/0000-0001-6520-9057

REFERENCES

1. Skjaerven R, Wilcox AJ, Klungsoyr K, et al. Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study. *BMJ*. 2012;345:e7677.
2. McDonald SD, Malinowski A, Zhou Q, Yusuf S, Devereaux PJ. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. *Am Heart J*. 2008;156:918-930.
3. Ray JG, Vermeulen MJ, Schull MJ, Redelmeier DA. Cardiovascular health after maternal placental syndromes (CHAMPS): population-based retrospective cohort study. *Lancet*. 2005;366:1797-1803.
4. Neiger R. Long-term effects of pregnancy complications on maternal health: a review. *J Clin Med*. 2017;6:76.
5. Wu P, Gulati M, Kwok CS, et al. Preterm delivery and future risk of maternal cardiovascular disease: a systematic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e007809.
6. Halland F, Morken NH, DeRoo LA, Klungsoyr K, Wilcox AJ, Skjaerven R. Long-term mortality in mothers with perinatal losses and risk modification by surviving children and attained education: a population-based cohort study. *BMJ Open*. 2016;6:e012894.
7. Irgens HU, Reisaeter L, Irgens LM, Lie RT. Long term mortality of mothers and fathers after pre-eclampsia: population based cohort study. *BMJ*. 2001;323:1213-1217.
8. Lykke JA, Langhoff-Roos J, Lockwood CJ, Triche EW, Paidas MJ. Mortality of mothers from cardiovascular and non-cardiovascular causes following pregnancy complications in first delivery. *Paediatr Perinat Epidemiol*. 2010;24:323-330.
9. Laine K, Murzakanova G, Sole KB, Pay AD, Heradstveit S, Raisanen S. Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: a population-based register study. *BMJ Open*. 2019;9:e029908.
10. Heino A, Gissler M, Hindori-Mohangoo AD, et al. Variations in multiple birth rates and impact on perinatal outcomes in Europe. *PLoS One*. 2016;11:e0149252.
11. Tandberg A, Bjorge T, Nygard O, Bordahl PE, Skjaerven R. Trends in incidence and mortality for triplets in Norway 1967-2006: the influence of assisted reproductive technologies. *BJOG*. 2010;117:667-675.
12. Rønsen M. Fertility and family policy in Norway – a reflection on trends and possible connections. *Demogr Res*. 2004;10:265-286.
13. Frejka T. Parity distribution and completed family size in Europe: incipient decline of the two-child family model? *Demogr Res*. 2008;19:47-71.
14. Grundy E, Kravdal O. Reproductive history and mortality in late middle age among Norwegian men and women. *Am J Epidemiol*. 2008;167:271-279.
15. Irgens LM. The Medical Birth Registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand*. 2000;79:435-439.
16. Moth FN, Sebastian TR, Horn J, Rich-Edwards J, Romundstad PR, Åsvold BO. Validity of a selection of pregnancy complications in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand*. 2016;95:519-527.
17. Thomsen LC, Klungsoyr K, Roten LT, et al. Validity of the diagnosis of pre-eclampsia in the Medical Birth Registry of Norway. *Acta Obstet Gynecol Scand*. 2013;92:943-950.
18. Klungsøyr K, Harmon QE, Skard LB, et al. Validity of pre-eclampsia registration in the Medical Birth Registry of Norway for women

participating in the Norwegian mother and child cohort study, 1999-2010. *Paediatr Perinat Epidemiol*. 2014;28:362-371.
19. Skjaerven R. Registry based perinatal epidemiology: the importance of sibling and generation data. *Nor Epidemiol*. 2015;25:53-62.
20. Parikh NI, Cnattingius S, Mittleman MA, Ludvigsson JF, Ingelsson E. Subfertility and risk of later life maternal cardiovascular disease. *Hum Reprod*. 2012;27:568-575.
21. Smith J, Velez MP, Dayan N. Infertility, infertility treatment, and cardiovascular disease: an overview. *Can J Cardiol*. 2021;37:1959-1968.
22. Dorup I, Skajaa K, Sorensen KE. Normal pregnancy is associated with enhanced endothelium-dependent flow-mediated vasodilation. *Am J Physiol*. 1999;276:H821-H825.
23. Faber-Swensson AP, O'Callaghan SP, Walters WA. Endothelial cell function enhancement in a late normal human pregnancy. *Aust N Z J Obstet Gynaecol*. 2004;44:525-529.
24. Saarelainen H, Valtonen P, Punnonen K, et al. Subtle changes in ADMA and l-arginine concentrations in normal pregnancies are unlikely to account for pregnancy-related increased flow-mediated dilatation. *Clin Physiol Funct Imaging*. 2008;28:120-124.
25. Saarelainen H, Valtonen P, Punnonen K, et al. Flow mediated vasodilation and circulating concentrations of high sensitive C-reactive protein, interleukin-6 and tumor necrosis factor-alpha in normal pregnancy – the Cardiovascular Risk in Young Finns Study. *Clin Physiol Funct Imaging*. 2009;29:347-352.
26. Jacobs MB, Kritz-Silverstein D, Wingard DL, Barrett-Connor E. The association of reproductive history with all-cause and cardiovascular mortality in older women: the Rancho Bernardo Study. *Fertil Steril*. 2012;97:118-124.
27. Pirnat A, DeRoo LA, Skjaerven R, Morken NH. Women's prepregnancy lipid levels and number of children: a Norwegian prospective population-based cohort study. *BMJ Open*. 2018;8:e021188.
28. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? *Epidemiol Rev*. 2014;36:57-70.
29. Grandi SM, Filion KB, Yoon S, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. *Circulation*. 2019;139:1069-1079.
30. Bellamy L, Casas JP, Hingorani AD, Williams DJ. Pre-eclampsia and risk of cardiovascular disease and cancer in later life: systematic review and meta-analysis. *BMJ*. 2007;335:974.
31. Wang YX, Arvizu M, Rich-Edwards JW, et al. Hypertensive disorders of pregnancy and subsequent risk of premature mortality. *J Am Coll Cardiol*. 2021;77:1302-1312.
32. Tanz LJ, Stuart JJ, Williams PL, et al. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. *Circulation*. 2017;135:578-589.
33. Trogstad L, Skrondal A, Stoltenberg C, Magnus P, Nesheim BI, Eskild A. Recurrence risk of preeclampsia in twin and singleton pregnancies. *Am J Med Genet A*. 2004;126A:41-45.
34. Okby R, Shoham-Vardi I, Sergienko R, Sheiner E. Twin pregnancy: is it a risk factor for long-term cardiovascular disease? *J Matern Fetal Neonatal Med*. 2016;29:1626-1630.
35. Krotz S, Fajardo J, Ghandi S, Patel A, Keith LG. Hypertensive disease in twin pregnancies: a review. *Twin Res*. 2002;5:8-14.
36. van Baar PM, Welters SM, Ravelli ACJ, de Boer MA, de Groot CJM. Cardiovascular mortality risk a decade after twin and singleton pregnancies complicated by hypertensive disorders of pregnancy. *Pregnancy Hypertens*. 2022;28:9-14.
37. Bergman L, Nordlof-Callbo P, Wikstrom AK, et al. Multi-fetal pregnancy, preeclampsia, and long-term cardiovascular disease. *Hypertension*. 2020;76:167-175.
38. Adank MC, Broere-Brown ZA, Goncalves R, et al. Maternal cardiovascular adaptation to twin pregnancy: a population-based prospective cohort study. *BMC Pregnancy Childbirth*. 2020;20:327.

SUPPORTING INFORMATION

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

How to cite this article: Basnet P, Skjærven R, Sørbye LM, et al. Long-term cardiovascular mortality in women with twin pregnancies by lifetime reproductive history. *Paediatr Perinat Epidemiol*. 2022;00:1-9. doi: 10.1111/ppe.12928