



RESEARCH ARTICLE

Risk of adverse pregnancy outcomes in twin- and singleton-born women: An inter-generational cohort study

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Abstract

Objective: To compare the risk of adverse pregnancy outcomes between twin-born and singleton-born women. We also evaluated whether in utero exposure to pre-eclampsia or preterm delivery affected adverse pregnancy outcomes in women's own pregnancies.

Design: Population-based cohort study.

Setting: Medical Birth Registry of Norway 1967–2020.

Population: 9184 twin-born and 492 894 singleton-born women during 1967–2005, with their later pregnancies registered during 1981–2020.

Methods: Data from an individual's birth were linked to their later pregnancies. We used generalised linear models with log link binomial distribution to obtain exponentiated regression coefficients that estimated relative risks (RRs) with 95% confidence intervals (CIs) for associations between twin- or singleton-born women and later adverse pregnancy outcomes.

Main outcome measures: Pre-eclampsia, preterm delivery or perinatal loss in twin-born compared with singleton-born women.

Results: There was no increased risk for adverse outcomes in twin-born compared with singleton-born women: adjusted RRs for pre-eclampsia were 1.00 (95% CI 0.93–1.09), for preterm delivery 0.96 (95% CI 0.90–1.02) and for perinatal loss 1.00 (95% CI 0.84–1.18). Compared with singleton-born women exposed to pre-eclampsia in utero, twin-born women exposed to pre-eclampsia had lower risk of adverse outcomes in their own pregnancies; the aRR for pre-eclampsia was 0.73 (95% CI 0.58–0.91) and for preterm delivery was 0.71 (95% CI 0.56–0.90). Compared with preterm singleton-born women, preterm twin-born women did not differ in terms of risk of pre-eclampsia (aRR 1.05, 95% CI 0.92–1.21) or perinatal loss (aRR 0.99, 95% CI 0.71–1.37) and had reduced risk of preterm delivery (RR 0.83, 95% CI 0.74–0.94).

Conclusions: Twin-born women did not differ from singleton-born women in terms of risk of adverse pregnancy outcomes. Twin-born women exposed to pre-eclampsia in utero, had a lower risk of pre-eclampsia and preterm delivery compared with singleton-born women exposed to pre-eclampsia.

KEY WORDS

cohort study, epidemiology, inter-generational, perinatal loss, pre-eclampsia, preterm birth, twin pregnancy

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1 | INTRODUCTION

Infants born preterm or in pregnancies with pre-eclampsia are disproportionately more likely to have long-term significant sequelae than are infants born without these adverse pregnancy complications.^{1–3} There is accumulating evidence that exposure to complications in utero may influence later health.^{4,5} Pre-eclampsia is a pregnancy-specific condition characterised by elevated blood pressure and proteinuria.⁶ Both preterm delivery and pre-eclampsia are associated with increased risk of later maternal health consequences;^{7,8} however, the exact cause of these complications is not fully understood.

Studies have investigated the inter-generational impact of adverse pregnancy outcomes, such as recurrence of pre-eclampsia or preterm delivery in daughters born preterm or those whose mothers had pre-eclampsia.^{9,10} Twin gestations are associated with higher occurrence of adverse pregnancy outcomes such as pre-eclampsia, preterm delivery and perinatal loss.^{11–13} However, little is known about the inter-generational recurrence of adverse pregnancy outcomes in twin-born women compared with singleton-born women.

Using a national population-based registry containing information on women's own birth and their later pregnancies, the objective in this study was to compare the risk of adverse pregnancy outcomes between twin-born and singleton-born women. We also evaluated whether in utero exposure to pre-eclampsia or preterm delivery were associated with adverse pregnancy outcomes in women's own pregnancies.

2 | METHODS

2.1 | Data source

This study used data from the nationwide population-based Medical Birth Registry of Norway (MBRN). Using unique national identification numbers, we linked birth record information of females born in 1967–2005 to the birth record information of their own offspring born in 1981–2020, providing information on pregnancies across two generations. Information on women's highest attained level of education by 2020 was obtained from the National Education Database at Statistics Norway.

The MBRN is based on mandatory notification of all live births, stillbirths and pregnancy losses from 16 weeks of gestation. The registry includes prospectively collected data on women's health before and during pregnancy, the delivery and the immediate postpartum period, including demographics, complications and treatments during delivery as well as infant outcomes.¹⁴ 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, the registry has undertaken a gradual transition to electronic birth notification (complete in 2014) and the notifications are now

based on prespecified extractions from the medical records at the delivery units. Reporting of pregnancy complications including mild pre-eclampsia has improved over time.¹⁵ The MBRN is routinely matched with the National Population Register and receives all national identification numbers through this linkage. Given that the registry has registered pregnancies for more than 50 years, this enabled us to study pregnancies to women who were themselves registered in the MBRN.

2.2 | Study population

To evaluate inter-generational associations, we studied women born 1967–2005 and registered in the MBRN, whose own singleton pregnancies were registered in the MBRN during 1981–2020. This enabled us to stratify the women by plurality at birth (twin-born or singleton-born) and retrieve information on their own intrauterine exposure to pregnancy complications (pre-eclampsia and/or preterm delivery).

2.3 | Exposure

The exposure variable was the plurality status (twin or singleton) of the women at their birth. We also explored possible modification by in utero exposure to pre-eclampsia or preterm delivery among twin-born versus singleton-born women. All exposures were obtained from the woman's birth record.

2.4 | Outcome

The main outcomes of interest were the risks of pre-eclampsia, preterm delivery or perinatal loss in any pregnancy of twin-born women compared with singleton-born women.

Pre-eclampsia was coded using the clinical definitions in place at the year of birth. The definition has been an increased blood pressure to at least 140 systolic or 90 mmHg diastolic combined with proteinuria (protein excretion of ≥ 0.3 g/24 hours or $\geq 1+$ on dip-stick) after 20 weeks of gestation, the criteria corresponding to the Norwegian Society of Gynaecology and Obstetrics.¹⁶ Preterm delivery was defined as pregnancies < 37 completed weeks of gestations. Perinatal losses included miscarriages (16–21 weeks), stillbirths (≥ 22 weeks) and early neonatal deaths during the first week after delivery.

2.5 | Covariates

Estimates were adjusted for the decade of the twin-born or singleton-born women's birth (categorised as 1967–1969, 1970–1979, 1980–1989, 1990–1999 and 2000–2005) and the

women's mother's educational attainment through 2020 (categorised as <11, 11–13 and ≥ 14 years). In a sensitivity analysis, we also accounted for women's total number of pregnancies categorised as 1, 2, 3+ registered in the MBRN through 2020, and their own educational attainment through 2020 (categorised as <11, 11–13 and ≥ 14 years).

2.6 | Exclusion and inclusion

We excluded women born in higher order pregnancies (>2 fetuses) and women who only had second or later pregnancies registered in the MBRN (such as first births outside Norway). We only included singleton pregnancies to twin-born and singleton-born women for a homogeneous comparison.

2.7 | Statistical analysis

We used generalised linear models with log link binomial distribution to estimate relative risks (RRs) with 95% confidence intervals (CIs) for associations between twin-born women and later adverse pregnancy outcomes relative to singleton-born women. The estimates were adjusted for women's own decade of birth and their mother's educational attainment. We ran separate models for each outcome. Models accounted for correlations between siblings using clustered standard errors. We also ran stratified models based on in utero exposure to pre-eclampsia or preterm delivery with similar outcomes as the main analyses. We used Knol and VanderWeele's recommended¹⁷ methods for presenting RR for these strata. Further, we obtained E-values¹⁸ for estimates with CIs that excluded the null to assess the suggested influence of unmeasured confounding. Statistical analyses were performed using STATA IC statistical software (version 17.0).

2.8 | Ethics approval

The study was approved in Norway by the Regional Ethics Committee REK VEST 13818 on 1 July 2020.

3 | RESULTS

The study population consisted of 9184 twin-born and 492 894 singleton-born women in 1967–2005, with their later births registered in the MBRN during 1981–2020 (Figure 1).

Table 1 shows the birth characteristics of twin-born and singleton-born women. About 40% of both twin-born women and singleton-born women were born during 1970s and 36–40% of twin-born or singleton-born women had their first pregnancies after 2009. Twin-born women were older at their first birth, but there was no difference in educational attainment for twin-born and singleton-born women. Almost 50% of both twin- and singleton-born women had two pregnancies.

Twin-born women were more frequently exposed to in utero pre-eclampsia than were singleton-born women (8% versus 2%) and were more often born preterm (29% versus 4%).

Table 2 shows the risk of pre-eclampsia, preterm delivery and perinatal loss in women's own pregnancies among twin-born versus singleton-born women. There was no increased risk for adverse outcomes in twin-born women compared with singleton-born women: adjusted RR (aRR) for pre-eclampsia 1.00 (95% CI 0.93–1.09), for preterm delivery 0.96 (95% CI 0.90–1.02) and for perinatal loss 1.00 (95% CI 0.84–1.18). Analyses were adjusted for twin-born and singleton-born women's own decade of birth, and their mother's educational attainment.

We further investigated whether the risk of adverse outcomes differed by in utero exposure to pre-eclampsia (Table 3). Compared with singleton-born women with no in utero exposure to pre-eclampsia, singleton-born women exposed to pre-eclampsia had an increased risk of pre-eclampsia (aRR 2.17, 95% CI 2.07–2.28) and preterm delivery (aRR 1.23, 95% CI 1.17–1.30) in their own pregnancies. Twin-born women delivered from a non-pre-eclamptic pregnancy had no increased risk of any adverse pregnancy outcome compared with singleton-born women from non-pre-eclamptic pregnancies. Twin-born women exposed to pre-eclampsia in utero did have an increased risk of pre-eclampsia in their own pregnancies (aRR 1.57, 95% CI 1.26–1.97) compared with singleton-born women with no pre-eclampsia, but it was lower than that experienced by singletons exposed to pre-eclampsia (aRR 0.73, 95% CI 0.58–0.91; Table 3). Twins born with in utero exposure to pre-eclampsia had a possible decrease in the risk of perinatal loss in their own pregnancies compared with those singleton-born without pre-eclampsia (aRR 0.47, 95% CI 0.20–1.14) and with pre-eclampsia (aRR 0.45, 95% CI 0.19–1.10), but the estimates were imprecise due to small numbers. Analyses were adjusted for covariates as in the main analyses.

We also investigated whether the risk of adverse outcomes differed by preterm birth among twin-born versus singleton-born women (Table 4). Compared with singletons born term, singleton women born preterm had an increased risk of pre-eclampsia (aRR 1.18, 95% CI 1.12–1.24), preterm delivery (aRR 1.35, 95% CI 1.30–1.40) and perinatal loss (aRR 1.15, 95% CI 1.03–1.28) in their own pregnancies. Women who were term twins had a slightly decreased risk of pre-eclampsia (aRR 0.90, 95% CI 0.82–1.00) and preterm delivery (aRR 0.91, 95% CI 0.84–0.99) in their own pregnancy compared with women who were term singletons, with no association with perinatal loss (aRR 0.94, 95% CI 0.76–1.17). Women born as a preterm twin had an increased risk of pre-eclampsia in their own pregnancies (aRR 1.26, 95% CI 1.11–1.44) compared with women born as term singletons; however, this risk was not increased compared with singleton women born preterm (aRR 1.05, 95% CI 0.92–1.21). Preterm twin-born women had a slightly increased risk of preterm delivery compared with term singleton-born women (aRR 1.12, 95% CI 1.00–1.26); however, this risk was decreased (aRR 0.83, 95% CI 0.74–0.94) compared with singletons born preterm. Preterm twin-born women had no increased risk of

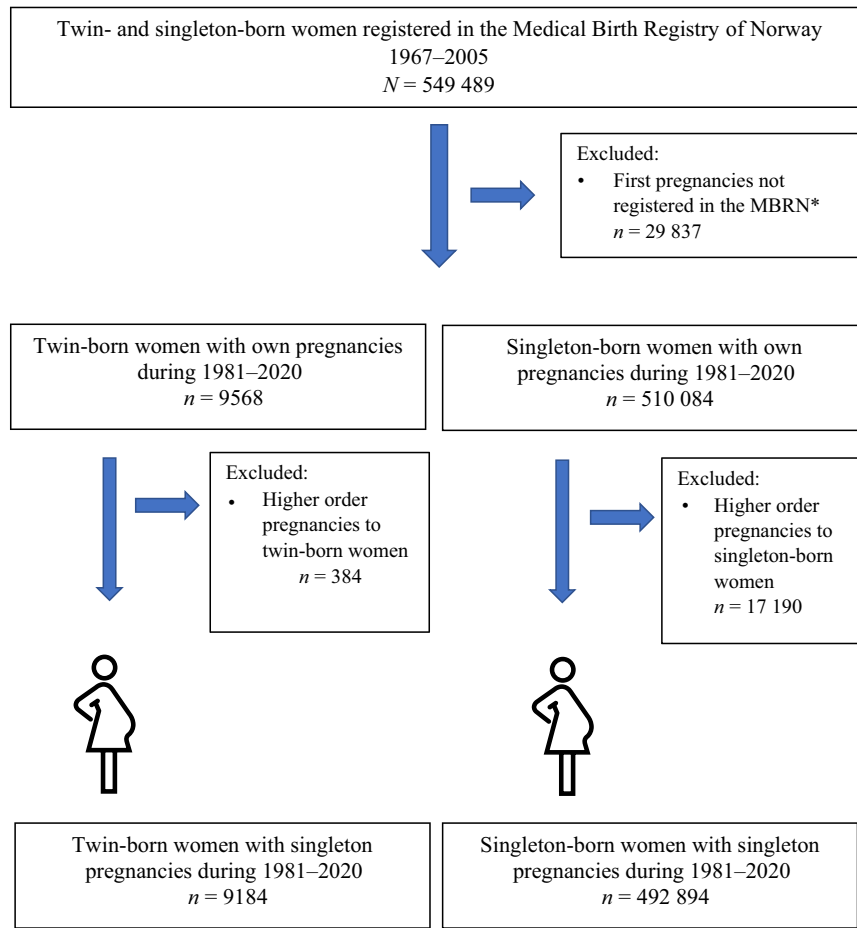


FIGURE 1 Flowchart of the study population. *Women who only had second or later pregnancies registered in the Medical Birth Registry of Norway (MBRN) were excluded (such as first births outside Norway).

perinatal loss in their own pregnancies compared with both term and preterm singleton-born women.

In a sensitivity analysis, we also adjusted our main models for other factors such as women's educational status and total number of pregnancies; the results were essentially the same (Table S1).

4 | DISCUSSION

4.1 | Main findings

We found that, on average, there was no difference in the risk of pre-eclampsia, preterm delivery or perinatal loss in the singleton pregnancies to twin-born women compared with singleton-born women, despite pre-eclampsia and preterm delivery being much more frequent in twin pregnancies. Twin-born women with in utero exposure to pre-eclampsia had a lower risk of pre-eclampsia and preterm delivery in their own pregnancies compared with singleton-born women with in utero exposure to pre-eclampsia. Further, preterm twin-born women did not differ in terms of their risk of pre-eclampsia or perinatal loss compared with preterm singleton-born women, and they had a reduced risk of preterm delivery.

4.2 | Interpretation

Earlier studies have evaluated several risk factors contributing to higher incidences of pregnancy complications in twin versus singleton pregnancies such as obstetric history, age and pre-existing hypertension.^{19–21} In our study, we evaluated whether twin-born women have a higher risk of adverse pregnancy outcomes in their own pregnancies compared with singleton-born women. Our results therefore add to the existing literature by demonstrating that twin-born women, despite more frequently experiencing in utero exposure to pre-eclampsia or being born preterm, generally seem to have no increased risk of adverse outcomes in their own pregnancies compared with singleton-born women. This may be due to the different underlying causes of pregnancy complications in twin compared with singleton pregnancies. Some of the causes of pregnancy complications in twin pregnancies may be less likely to carry an increased inter-generational risk and be related more to the larger intrauterine volume of two growing fetuses.

Recurrence of pre-eclampsia across generations has been well documented in singleton-born women;^{9,22} however, less is known for twin-born women. Although we see evidence for an increased inter-generational recurrence risk

TABLE 1 Pregnancy characteristics of twin-born ($n=9184$) and singleton-born ($n=492\,894$) women, from the Medical Birth Registry of Norway, 1967–2020.

	9184 twin-born women, n (%)	492 894 singleton-born women, n (%)
Decade of women's birth		
1967–1969	1367 (14.9)	74 571 (15.1)
1970–1979	3663 (39.9)	206 067 (41.8)
1980–1989	3073 (33.5)	161 187 (32.7)
1990–1999	1070 (11.7)	50 713 (10.3)
2000–2005	11 (0.1)	356 (0.1)
Characteristics of women's own pregnancy		
Decade of first pregnancy		
1981–1989	296 (3.2)	17 896 (3.6)
1990–1999	2222 (24.2)	131 326 (26.6)
2000–2009	2999 (32.7)	165 430 (33.6)
2010–2020	3667 (39.9)	178 242 (36.2)
Age at first pregnancy, years		
≤19	658 (7.2)	41 357 (8.4)
20–25	3375 (36.7)	189 074 (38.4)
26–30	3406 (37.1)	172 093 (34.9)
31–35	1339 (14.6)	71 402 (14.5)
>35	406 (4.4)	18 968 (3.8)
Years of attained education		
<11	1219 (13.3)	67 868 (13.8)
11–13	2891 (31.5)	149 096 (30.2)
≥14	5046 (54.9)	275 231 (55.8)
Missing	28 (0.3)	699 (0.1)
Number of pregnancies		
1	2456 (26.7)	120 535 (24.5)
2	4401 (47.9)	239 649 (48.6)
3	1908 (20.8)	107 002 (21.7)
4 or more	419 (4.6)	25 708 (5.2)
Characteristics of women's in utero exposures		
Women exposed to in utero pre-eclampsia		
Yes	755 (8.2)	11 507 (2.3)
No	8429 (91.8)	481 387 (97.7)
Women born preterm (<37 weeks)		
Yes	2647 (28.8)	18 527 (3.8)
No	6139 (66.8)	446 260 (90.5)
Missing	398 (4.3)	28 107 (5.7)

of pre-eclampsia in both singleton-born and twin-born women who themselves were exposed to pre-eclampsia compared with those who were not, twin-born women exposed to pre-eclampsia had a lower recurrence of pre-eclampsia compared with singleton-born women exposed to pre-eclampsia. One inter-generational study from Sweden has shown less recurrence of preterm delivery in preterm twin-born women than in preterm singleton-born women.²³

TABLE 2 Relative risks (RRs) with 95% CIs for pre-eclampsia, preterm delivery (<37 weeks) and perinatal loss^a in twin-born women compared with singleton-born women.

Women born	Total N	n (%)	Adverse outcomes in own pregnancy		Reference	Crude RR (95% CI)	aRR ^b (95% CI)	n (%)	Crude RR (95% CI)	aRR ^b (95% CI)
			Pre-eclampsia	Preterm delivery						
Singleton	492 894	32 091 (6.5)	Reference	Reference	Reference	Reference	7290 (1.5)	Reference	Reference	Reference
Twin	9184	597 (6.5)	1.00 (0.92–1.08)	1.00 (0.93–1.09)	0.96 (0.90–1.02)	0.99 (0.84–1.18)	135 (1.5)	0.95 (0.89–1.02)	0.99 (0.84–1.18)	1.00 (0.84–1.18)

Abbreviations: CI, confidence interval; RR, relative risk.

^aMiscarriages, stillbirths and early neonatal deaths <7 days of life.

^baRRs obtained by generalised linear models with log link binomial distribution. Analyses were adjusted for twin-born and singleton-born women's own decade of birth, and their mother's education.

TABLE 3 Relative risks (RRs) with 95% CIs for pre-eclampsia, preterm delivery (<37 weeks) and perinatal loss^a in twin-born women compared with singleton-born women, when the women were themselves exposed to pre-eclampsia.

	Adverse pregnancy outcomes in own pregnancy		RR (95% CI) for twin- versus singleton-born women within strata of in utero exposure to pre-eclampsia
	Singleton-born women	Twin-born women	
Outcome = Pre-eclampsia in own pregnancy	<i>n</i> with/without pre-eclampsia	aRR ^b (95% CI)	aRR ^b (95% CI)
In utero exposure			
Pre-eclampsia = 0	30 549/481 387 (6.3%)	Reference	0.98 (0.90–1.07)
Pre-eclampsia = 1	1542/11 507 (13.4%)	2.17 (2.07–2.28)	0.73 (0.58–0.91) ^c
Outcome = Preterm delivery (<37 weeks) in own pregnancy	<i>n</i> with/without preterm delivery	<i>n</i> with/without preterm delivery	
In utero exposure			
Pre-eclampsia = 0	47 892/481 387 (9.9%)	Reference	0.97 (0.91–1.04)
Pre-eclampsia = 1	1371/11 507 (11.9%)	1.23 (1.17–1.30)	0.88 (0.69–1.11)
Outcome = Perinatal loss ^a in own pregnancy	<i>n</i> with/without perinatal loss ^a	<i>n</i> with/without perinatal loss ^a	
In utero exposure			
Pre-eclampsia = 0	7146/481 387 (1.5%)	Reference	1.04 (0.87–1.24)
Pre-eclampsia = 1	164/11 507 (1.4%)	1.03 (0.88–1.20)	0.47 (0.20–1.14)

Abbreviations: CI, confidence interval; RR: relative risk.

^aMiscarriages, stillbirths and early neonatal deaths <7 days of life.

^baRRs obtained by generalised linear models with log link binomial distribution. Analyses were adjusted for twin-born and singleton-born women's own decade of birth, and their mother's education.

^cE-values for these estimates ranged from 2.1 to 2.2, suggesting that unmeasured confounding of such a strength would be needed to move this point estimate to null.

TABLE 4 Relative risks (RRs) with 95% CIs for pre-eclampsia, preterm delivery (<37 weeks) and perinatal loss^a in twin-born women compared with singleton-born women, when the women themselves were born preterm.

	Adverse pregnancy outcomes in own pregnancy		RR (95% CI) for twin-versus singleton-born women within strata of preterm delivery at birth
	Singleton-born women	Twin-born women	
Outcome = Pre-eclampsia in own pregnancy	n with/without pre-eclampsia	aRR ^b (95% CI)	aRR ^b (95% CI)
In utero exposure			
Preterm delivery = 0	28 906/446 260 (6.5%)	Reference	0.90 (0.82–1.00)
Preterm delivery = 1	1420/18 527 (7.7%)	1.18 (1.12–1.24)	1.05 (0.92–1.21)
Outcome = Preterm delivery (<37 weeks) in own pregnancy	n with/without preterm delivery	n with/without preterm delivery	
In utero exposure			
Preterm delivery = 0	43 953/446 260 (9.9%)	Reference	0.91 (0.84–0.99) ^c
Preterm delivery = 1	2477/18 527 (13.4%)	1.35 (1.30–1.40)	1.12 (1.00–1.26)
Outcome = Perinatal loss in own pregnancy	n with/without perinatal loss ^a	n with/without perinatal loss ^a	
In utero exposure			
Preterm delivery = 0	6586/446 260 (1.5%)	Reference	0.94 (0.76–1.17)
Preterm delivery = 1	318/18 527 (1.7%)	1.15 (1.03–1.28)	1.12 (0.83–1.52)

Abbreviations: CI, confidence interval; RR, relative risk.

^aMiscarriages, stillbirths and early neonatal deaths <7 days of life.

^baRRs obtained by generalised linear models with log link binomial distribution. Analyses were adjusted for twin-born and singleton-born women's own decade of birth, and their mother's education.

^cE-values for these estimates ranged from 1.4 to 1.7, suggesting that unmeasured confounding of such a strength would be needed to move this point estimate to null.

We found similar patterns when looking at later preterm delivery among preterm twin- and singleton-born women. Together with prior literature, this supports the theory that pregnancy complications in twin pregnancies have both similar and distinct origins compared with singleton pregnancies. For instance, studies indicate that the placental size in twin pregnancies may worsen placental perfusion, leading to increased complications such as pre-eclampsia in twin pregnancies.^{24,25} When the complications are due to the physical demands of the twin pregnancies, they may be less likely to be transferred to the next generation.

4.3 | Strengths and limitations

Prospectively collected data provided the opportunity to study pregnancy outcomes across generations. The large sample size and long follow-up allowed us to evaluate associations stratified by in utero exposure to specific pregnancy complications among twin-born and singleton-born women. Changes to the data recording system over the years are unlikely to impact the reporting of singleton or multiple gestations over time. Linked pregnancy complications across a woman's reproductive life are necessary for studies such as this one, but using linked birth registry data does have limitations. Data on covariates relevant to the mother's own birth (i.e. her mother's smoking or BMI, chorionicity of twins) were not collected. Given the analysis of a woman's whole reproductive course, we did not take into account intermediate factors (smoking, inter-pregnancy interval) that may predict specific adverse outcomes, but which will vary for each pregnancy. We did take into account factors that may be associated with the woman's own birth (mother's education, decade of birth). However, in a sensitivity analysis, we also accounted for woman's education along with their total number of pregnancies as a surrogate for the opportunity to experience adverse pregnancy outcomes. We saw very little change in the estimates with these adjustments. Further, there is no large difference in reproduction of twin- or singleton-born women. In our population, 77% of twin-born women had a recorded pregnancy as compared with 84% of singleton-born women. Finally, for the estimates which showed decreased risk of adverse outcomes for twins within strata of their own in utero exposure we have provided E-values. The E-values for these estimates ranged from 2.1 to 2.2 when women were stratified according to in utero exposure to pre-eclampsia and 1.4 to 1.7 when women were stratified according to preterm birth, suggesting that unmeasured confounding of such strength would be needed to move these point estimates to the null.

5 | CONCLUSION

Despite the fact that twin-born women are more often exposed to adverse pregnancy outcomes in utero, the risk of pre-eclampsia, preterm delivery and perinatal loss in

twin-born women is not increased in their own pregnancies compared with singleton-born women. Twin-born women exposed to pre-eclampsia in utero had a reduced risk of pre-eclampsia, preterm delivery or perinatal loss in their own pregnancies compared with singleton-born women exposed to pre-eclampsia in utero. Preterm twin-born women had no increased risk of pre-eclampsia or perinatal loss in their own pregnancies and a reduced risk of preterm delivery compared with preterm singleton-born women.

AUTHOR CONTRIBUTIONS

PB, RS, LGK and QEH contributed to study design. PB performed the data analysis. RS, LGK, QH, LMS, N-HM, AS, KK contributed critical comments to the analysis. RS is guarantor for data quality. PB wrote the first draft of the paper. LGK, QEH, LMS, N-HM, KK, AS contributed to the revision. All authors agree with the final version of the paper.

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CONFLICT OF INTEREST STATEMENT

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 licence for this study. Data are available from <https://www.fhi.no/en/hn/health-regis-tries/medical-birth-registry-of-norway/medical-birth-registry-ofnorway/> with the permission of the Norwegian Institute of Public Health.


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REFERENCES

- Huang C, Li J, Qin G, Liew Z, Hu J, László KD, et al. Maternal hypertensive disorder of pregnancy and offspring early-onset cardiovascular disease in childhood, adolescence, and young adulthood: a national population-based cohort study. *PLoS Med.* 2021;18(9):e1003805.
- Irving RJ, Belton NR, Elton RA, Walker BR. Adult cardiovascular risk factors in premature babies. *Lancet.* 2000;355(9221):2135–6.
- Skilton MR, Viikari JS, Juonala M, Laitinen T, Lehtimäki T, Taittonen L, et al. Fetal growth and preterm birth influence cardiovascular risk factors and arterial health in young adults: the cardiovascular risk in young Finns study. *Arterioscler Thromb Vasc Biol.* 2011;31(12):2975–81.
- Crump C. An overview of adult health outcomes after preterm birth. *Early Hum. Dev.* 2020;150:105187.
- Lu HQ, Hu R. Lasting effects of intrauterine exposure to pre-eclampsia on offspring and the underlying mechanism. *AJP Rep.* 2019;9(3):e275–91.
- Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet.* 2016;387(10022):999–1011.
- Lykke JA, Langhoff-Roos J, Sibai BM, Funai EF, Triche EW, Paidas MJ. Hypertensive pregnancy disorders and subsequent cardiovascular morbidity and type 2 diabetes mellitus in the mother. *Hypertension.* 2009;53(6):944–51.
- Parikh NI, Norberg M, Ingelsson E, Cnattingius S, Vasan RS, Domellof M, et al. Association of Pregnancy Complications and Characteristics with Future Risk of elevated blood pressure: the Vasterbotten intervention program. *Hypertension.* 2017;69(3):475–83.
- Skjaerven R, Vatten LJ, Wilcox AJ, Ronning T, Irgens LM, Lie RT. Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort. *BMJ.* 2005;331(7521):877.
- Swamy GK, Ostbye T, Skjaerven R. Association of preterm birth with long-term survival, reproduction, and next-generation preterm birth. *JAMA.* 2008;299(12):1429–36.
- 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(7):e029908.
- Chauhan SP, Scardo JA, Hayes E, Abuhamad AZ, Berghella V. Twins: prevalence, problems, and preterm births. *Am J Obstet Gynecol.* 2010;203(4):305–15.
- Santana DS, Silveira C, Costa ML, Souza RT, Surita FG, Souza JP, et al. Perinatal outcomes in twin pregnancies complicated by maternal morbidity: evidence from the WHO multicountry survey on maternal and newborn health. *BMC Pregnancy Childbirth.* 2018;18(1):449.
- Irgens LM. The medical birth registry of Norway. Epidemiological research and surveillance throughout 30 years. *Acta Obstet Gynecol Scand.* 2000;79(6):435–9.
- Klungsoyr K, Morken NH, Irgens L, Vollset SE, Skjaerven R. Secular trends in the epidemiology of pre-eclampsia throughout 40 years in Norway: prevalence, risk factors and perinatal survival. *Paediatr Perinat Epidemiol.* 2012;26(3):190–8.
- Thomsen LC, Klungsoyr K, Roten LT, Tappert C, Araya E, Baerheim G, et al. Validity of the diagnosis of pre-eclampsia in the medical birth registry of Norway. *Acta Obstet Gynecol Scand.* 2013;92(8):943–50.
- Knol MJ, VanderWeele TJ. Recommendations for presenting analyses of effect modification and interaction. *Int J Epidemiol.* 2012;41(2):514–20.
- VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med.* 2017;167(4):268–74.
- Sibai BM, Hauth J, Caritis S, Lindheimer MD, MacPherson C, Klebanoff M, et al. Hypertensive disorders in twin versus singleton gestations. National Institute of Child Health and Human Development network of maternal-fetal medicine units. *Am J Obstet Gynecol.* 2000;182(4):938–42.
- Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. *BJOG.* 2014;121(10):1197–208; discussion 209.
- Kalafat E, Abiola A, Thilaganathan B, Bhide A, Khalil A. The association between hypertension in pregnancy and preterm birth with fetal growth restriction in singleton and twin pregnancy: use of twin versus singleton charts. *J Clin Med.* 2020;9(8). 2518.
- Esplin MS, Fausett MB, Fraser A, Kerber R, Mineau G, Carrillo J, et al. Paternal and maternal components of the predisposition to pre-eclampsia. *N Engl J Med.* 2001;344(12):867–72.
- Bladh M, Josefsson A, Carstensen J, Finnström O, Sydsjö G. Inter-generational cohort study of preterm and small-for-gestational-age birth in twins and singletons. *Twin Res Hum Genet.* 2015;18(5):581–90.
- Ros HS, Cnattingius S, Lipworth L. Comparison of risk factors for preeclampsia and gestational hypertension in a population-based cohort study. *Am J Epidemiol.* 1998;147(11):1062–70.
- Roberts JM, Redman CW. Pre-eclampsia: more than pregnancy-induced hypertension. *Lancet.* 1993;341(8858):1447–51.

SUPPORTING INFORMATION

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

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