



Markovitz, A. R., Haug, E. B., Horn, J., Fraser, A., Tilling, K. M., Rimm, E. B., Missmer, S. A., Williams, P. L., Romundstad, P. R., Åsvold, B. O., & Rich-Edwards, J. W. (2020). Normotensive preterm delivery and maternal cardiovascular risk factor trajectories across the life course: The HUNT Study, Norway. *Acta Obstetricia et Gynecologica Scandinavica*. <https://doi.org/10.1111/aogs.14016>

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ORIGINAL ARTICLE

Normotensive preterm delivery and maternal cardiovascular risk factor trajectories across the life course: The HUNT Study, Norway

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Funding information

This work was supported by the American Heart Association (grant number 16PRE29690006) to AM and the Research Council of Norway (grant number 231149/F20) to BOÅ, JH, and EBH. AM was additionally supported by Training Grant T32HD060454 in Reproductive, Perinatal and Pediatric Epidemiology from the National Institute of Child Health and Human Development, National Institutes of

Abstract

Introduction: Preterm delivery (<37 weeks) predicts later cardiovascular disease risk in mothers, even among normotensive deliveries. However, development of subclinical cardiovascular risk before and after preterm delivery is not well understood. We sought to investigate differences in life course cardiovascular risk factor trajectories based on preterm delivery history.

Material and methods: The HUNT Study (1984-2008) linked with the Medical Birth Registry of Norway (1967-2012) yielded clinical measurements and pregnancy outcomes for 19 806 parous women with normotensive first deliveries. Women had up to three measurements of body mass index, waist-to-hip ratio, blood pressure, lipids, non-fasting glucose, and C-reactive protein during follow up between 21 years before

Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; HUNT, Nord-Trøndelag Health Study; MBRN, Medical Birth Registry of Norway.

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Health. JH and BOÅ were also supported by the Liaison Committee for education, research, and innovation in Central Norway. BOÅ was additionally supported by St. Olavs Hospital and the Faculty of Medicine and Health Sciences, NTNU; and by the Fulbright Program. EBH and BOÅ work in a research environment supported by Stiftelsen KG Jebsen. AF is supported by a personal fellowship from the UK MRC (grant number MR/M009351/1). AF and KT work in a Unit that receives core funding from UK MRC (grant number MC_UU_12013/5 and MC_UU_12013/9).

to 41 years after first delivery. Using mixed effects models, we compared risk factor trajectories for women with preterm vs term/postterm first deliveries.

Results: Trajectories overlapped for women with preterm compared with term/post-term first deliveries for all cardiovascular risk factors examined. For instance, the mean difference in systolic blood pressure in women with preterm first deliveries compared with those with term deliveries was 0.2 mm Hg (95% CI -1.8 to 2.3) at age 20 and 1.5 mm Hg (95% CI -0.5 to 3.6) at age 60.

Conclusions: A history of preterm delivery was not associated with different life course trajectories of common cardiovascular risk factors in our study population. This suggests that the robust association between preterm delivery and cardiovascular end points in Norway or similar contexts is not explained by one or more commonly measured cardiovascular risk factors. Overall, we did not find evidence for a single cardiovascular disease prevention strategy that would reduce risk among the majority of women who had preterm delivery.

KEYWORDS

anthropometry, blood pressure, C-reactive protein, gestational age, lipids, maternal health, premature birth, women's health

1 | INTRODUCTION

Preterm delivery, <37 weeks gestation, is associated with a two- to three-fold greater risk of maternal cardiovascular disease (CVD).¹ Although this association is likely due to shared etiologic pathways,² which specific biologic pathways might be involved is not well understood. There is some evidence that preterm delivery is associated with subclinical markers of CVD both before³⁻⁵ and after⁵⁻⁸ delivery. However, these associations diminish after taking into account hypertensive disorders of pregnancy,³⁻⁷ a common reason for preterm delivery.⁹ Whether preterm delivery in the absence of hypertension is associated with subclinical markers of CVD risk remains inconclusive.

Characterizing how subclinical CVD risk factors develop across the life course is critical to understanding how CVD risk emerges in women with a history of preterm delivery. To our knowledge, only one study has examined preterm delivery and CVD risk factors measured both pre-pregnancy and postpartum.⁵ Other studies examined only differences in CVD risk factors at a single point in time either pre- or postpartum and were not able to evaluate how risk factor trajectories evolved with time since pregnancy.

We examined differences in CVD risk factor trajectories based on preterm delivery history using the population-based Nord-Trøndelag Health Study (the HUNT Study) linked with the Medical Birth Registry of Norway (MBRN). Our study cohort allowed consideration of measured anthropometric factors and biomarkers from 21 years before to 41 years after first delivery to illustrate differences in risk factor levels across the life course.

Key Message

Women with a normotensive preterm first delivery did not have consistently elevated levels of commonly measured cardiovascular risk factors across their life course.

2 | MATERIAL AND METHODS

2.1 | Study population

The HUNT Study is a population-based, open cohort study in Norway's Nord-Trøndelag county.¹⁰ Every decade, all current residents aged 20 years or older are identified from Statistics Norway's population registry and invited to participate in a health assessment survey. We examined data from the first three surveys: HUNT1 (1984-86), HUNT2 (1995-97), and HUNT3 (2006-08), during which participants provided blood samples, clinical measurements, and completed questionnaires. Using Norway's unique personal identifier, we linked HUNT data to the MBRN, which records all deliveries in Norway. We identified a total of 25 922 female HUNT participants whose first delivery was recorded between the start of the birth registry in 1967 and the end of our data collection in 2012. Our study population included 19 806 women after excluding women with first deliveries complicated by hypertensive disorders of pregnancy, multiple gestation pregnancies, and incomplete records (Figure 1). Hypertensive disorders of pregnancy included a pre-pregnancy diagnosis of hypertension or diagnoses of preeclampsia or gestational hypertension, as identified from the MBRN.

2.2 | Preterm delivery

Using the MBRN, we identified gestation length based on ultrasound dating where available (13% of deliveries) or last menstrual period. Our primary analysis considered preterm delivery as a dichotomous

exposure (<37 vs ≥37 weeks gestation), but in sensitivity analyses, we also considered gestation length in categories of very preterm (20-31 weeks), moderately preterm (32-36 weeks), early term (37-38 weeks), term (39-40), and late term/postterm (41-44 weeks). Gestation length recorded in the MBRN has very good validity.¹¹

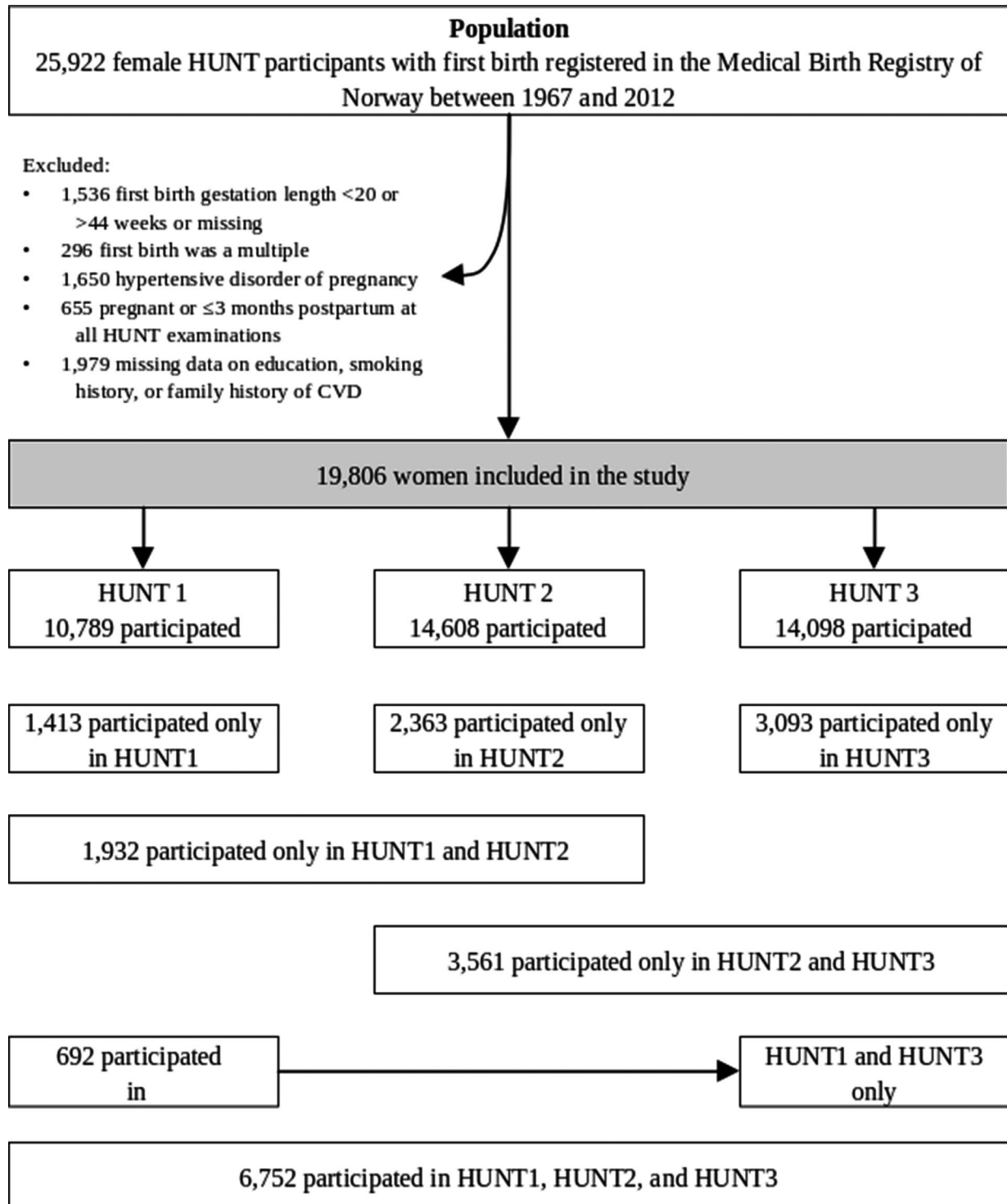


FIGURE 1 | Flow chart of the study population

2.3 | Cardiovascular risk factors

We identified cardiovascular risk factors through clinical measurements and serum samples collected at HUNT examinations by trained staff. At the time of examinations, participants ranged in age from 20 through 77 and examinations occurred between 21 years before to 41 years after participants' first delivery (see Supporting Information Figure S1). Some risk factors were collected only during later HUNT surveys, with a summary of data collection and sample sizes provided in the Supporting Information (Table S1).

All HUNT examinations included clinical measurements of weight and height, from which we calculated body mass index (BMI; kg/m²). HUNT2 and HUNT3 included waist and hip circumference measurements from which we calculated waist-to-hip ratio. All HUNT examinations measured blood pressure and for women who reported taking antihypertensives ($n = 1668$), we used the recommended approach^{12,13} of adding 10 mm Hg to systolic and 5 mm Hg to diastolic blood pressure levels. Staff collected non-fasting serum samples in HUNT2 and HUNT3 from which we measured lipids, glucose, and high-sensitivity C-reactive protein (hs-CRP). Using total cholesterol and high-density lipoprotein cholesterol (HDL-C), we calculated the total cholesterol/HDL-C ratio and non-HDL-C. In HUNT1, staff measured capillary glucose for participants over age 40 years, which we multiplied by 1.11 to approximate serum glucose values.¹⁴ In HUNT2 and HUNT3, technicians directly measured serum glucose for all participants. In HUNT2, collection of hs-CRP was limited to participants from a sample of four out of the 24 included municipalities ($n = 2070$) and expanded to all participants in HUNT3. Supporting Information (Table S2) includes additional details.

2.4 | Covariates

From HUNT questionnaires, we identified use of antihypertensive medication, hours since last meal (<1, 1, 2, 3, 4, 5, or ≥6 hours), family history of CVD (ie, any reported myocardial infarction or angina pectoris in siblings or parents), smoking initiation by age 20 years, highest obtained educational level, and work titles. Education level was omitted from HUNT3 and we instead derived it from work titles for 15% of women based on recommendation from Statistics Norway.¹⁵

2.5 | Statistical analyses

We compared cardiovascular risk factor trajectories as a function of age for women with and without a preterm first delivery using linear mixed effects models. Mixed effects models included a random intercept and slope for each woman to account for repeated measurements at up to three HUNT examinations and enabled estimation of within-woman trajectories.¹⁶ We modeled age using restricted cubic splines with four knots located at ages 23, 34, 44, and 60 years

based on prespecified quantiles of the age distribution, as recommended by Harrell.¹⁷ We log-transformed hs-CRP in all analyses.

Technical details about the models used are available in the Supporting Information (Appendix S1). We accounted for the timing of first delivery in the risk factor trajectories by including both a variable indicating whether the measurement occurred before or after first delivery (covariate I_{ij} in Supporting Information Appendix S1 Equation 1) and a variable for continuous time since first delivery (covariate T_{ij} in Supporting Information Appendix S1 Equation 1), which together modeled both short- and long-term changes in risk factors associated with pregnancy. Using interaction terms, we allowed women with a preterm first delivery to have different age-related changes in risk factors (covariates $P_i A_{ij}$ and $P_i S_{ijk}$ in Supporting Information Appendix S1 Equation 2) as well as different pregnancy-related changes (covariates $P_i T_{ij}$ and $P_i T_{ij}$ in Supporting Information Appendix S1 Equation 2), providing flexibility for trajectories to differ based on preterm delivery history. All models controlled for highest obtained education level, family history of CVD, smoking at age 20 years, HUNT survey, age at first delivery, and time since last meal.

We present figures of estimated risk factor trajectories for women with and without a preterm first delivery. In secondary analyses, we modeled gestation length in categories, keeping the same general model format. We present a comparison of mean risk factor levels by category of gestation length at 40, the study median age. A comparison of trajectories by categorized gestation length across the full age range is available in the Supporting Information. All analyses were performed using STATA IC 13 and MLwiN¹⁸ version 2.34.

2.6 | Sensitivity analyses

We conducted sensitivity analyses among women with two or more measurements of each risk factor, for all risk factors but hs-CRP, to examine the impact of including single measures in trajectory models. We also examined clinical definitions rather than continuous risk factor levels where appropriate, for example, defining hypertension as systolic blood pressure ≥140, diastolic blood pressure ≥90, or a self-reported use of antihypertensives. Our main analyses focused on gestation lengths of first deliveries only, which enabled us to explicitly model the timing of the delivery without the complexity required to incorporate full delivery history. In sensitivity analyses, we instead modeled a history of any preterm delivery vs no preterm delivery controlling for parity and without explicitly modeling the timing of deliveries. We also conducted sensitivity analyses excluding deliveries that were unusually large for their gestation length, defined as a z-score >4 ($n = 57$) that may have been misclassified as preterm deliveries. Additionally, we performed sensitivity analyses excluding women with large- or small-for-gestational age deliveries and women with pre-existing or gestational diabetes, as well as an analysis where we excluded women with induced labor. Small and large for gestational age were defined as a birthweight in the lowest or highest 10th centile given gestational age and sex, based on a Norwegian reference population.¹⁹

TABLE 1 Description of covariates by preterm status of first delivery among parous HUNT participants with a normotensive first delivery (n = 19 806)

	Gestation length	
	Preterm <37 weeks (n = 1097)	Term/Postterm ≥37 weeks (n = 18 709)
Baseline characteristics		
Maternal birth year, median (IQR)	1958 (1951-1967)	1958 (1951-1967)
Smoking history at age 20, n (%)		
Never smoked daily	472 (43%)	8996 (48%)
Ever smoked daily	625 (57%)	9713 (52%)
Education, n (%)		
Lower Secondary (≤9 years)	213 (19%)	3159 (17%)
Upper Secondary (10-12 years)	535 (49%)	8792 (47%)
Tertiary (>12 years)	349 (32%)	6758 (36%)
Family history of CVD ^a , n (%)	312 (28%)	5642 (30%)
Characteristics of first delivery		
Age at first delivery, median (IQR)	22 (20-27)	23 (20-26)
Maternal pre-existing or gestational diabetes	15 (1%)	66 (0%)
Male gender	605 (55%)	9536 (51%)
Birthweight, n (%)		
Small for gestational age ^b	169 (15%)	2472 (13%)
Normal	735 (67%)	15 173 (81%)
Large for gestational age ^c	187 (17%)	1051 (6%)
Not available	6 (1%)	13 (0%)
Stillbirth, n (%)	112 (10%)	77 (0%)
Very preterm (< 32 weeks)	254 (23%)	NA
Induced labor		
1967-2012	164 (15%)	2890 (15%)
1985-2012 ^d	103 (21%)	1326 (16%)
HUNT exam characteristics		
Age at first HUNT exam, median (IQR)	32 (27-37)	32 (27-37)
No. of HUNT exams, n (%)		
1	387 (35%)	6482 (35%)
2	345 (31%)	5840 (31%)
3	365 (33%)	6387 (34%)
HUNT exams relative to first delivery, n (%)		
Before first delivery only	95 (9%)	1586 (8%)
After first delivery only	899 (82%)	15 521 (83%)
Before and after first delivery	103 (9%)	1593 (9%)

Abbreviations: CVD, cardiovascular disease; exam, examination; IQR, interquartile range.

^aFamily history of CVD includes myocardial infarction or angina pectoris in siblings or parents.

^bDefined as a birthweight in the lowest 10th centile given gestational age and sex, based on a Norwegian reference population.

^cDefined as a birthweight in the highest 10th centile given gestational age and sex, based on a Norwegian reference population.

^dLabor initiation was better tracked for deliveries starting in 1985.

2.7 | Ethical approval

This project was approved by the Central Norway Regional Committee for Medical and Health Research Ethics (reference

number: 2013/647, date of approval: 28 May 2015) and was exempt from IRB review by Harvard T. H. Chan School of Public Health (reference number: IRB 16-1054, date of exemption: 28 June 2016).

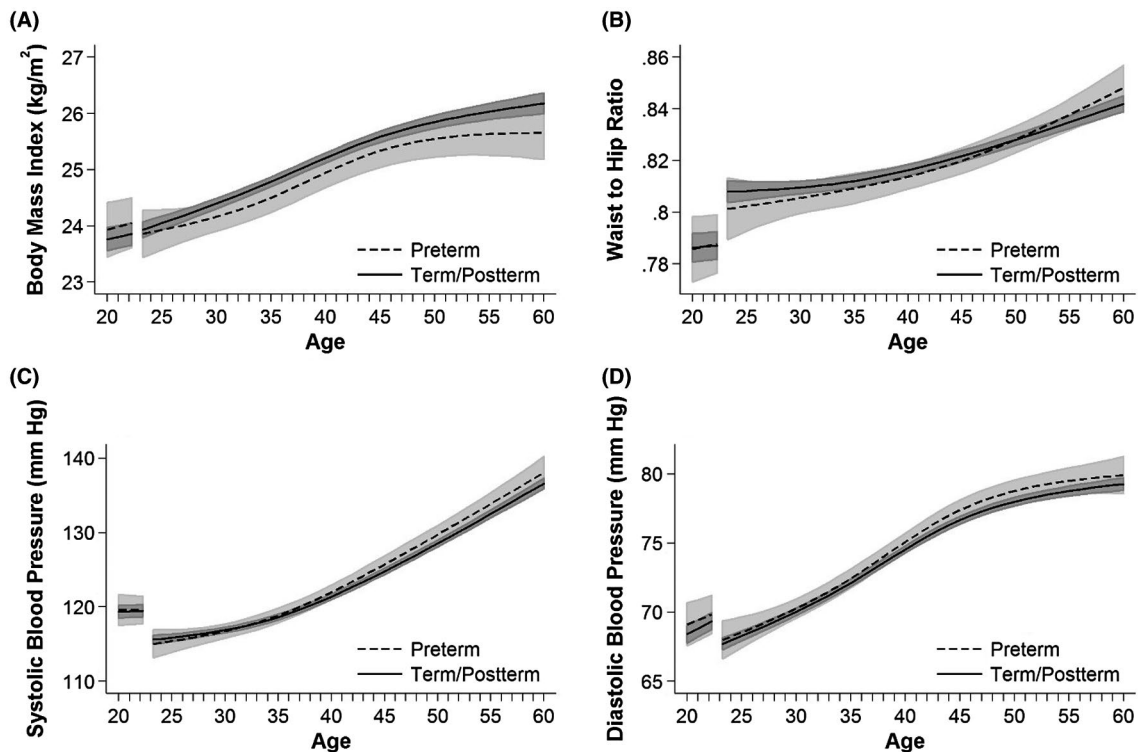


FIGURE 2 Life course trajectories for clinically measured cardiovascular disease (CVD) risk factors among women with preterm and term/postterm normotensive first deliveries. Estimates are adjusted for age, HUNT survey, age at first delivery, highest obtained education level, family history of CVD, smoking at age 20 years, and time since last meal. For the purposes of illustration, we present trajectories in which age at first delivery was set to 23 years, the median age in our study population, and all other covariates were set to their means. As we had insufficient data to model the different risk factor levels typically seen during pregnancy and early postpartum, first pregnancy and 3 months postpartum is depicted as a gap on trajectory graphs. Graphs are shown up to age 60 years, after which data are sparse

3 | RESULTS

After restricting to normotensive first deliveries, 5.5% were preterm. Women with a preterm first delivery were more likely smokers and had lower education. Preterm first deliveries were more likely to be either small or large for their gestation length and much more likely to be stillbirths (Table 1). These differences were more pronounced with lower gestation length (Supporting Information Table S3). Among deliveries from 1985 to 2012 when labor initiation was better tracked,¹¹ 79% of preterm and 84% of term deliveries were spontaneous rather than provider-initiated.

Compared with women with a term first delivery, women with a preterm first delivery had a somewhat lower mean BMI from approximately age 30 years onward, with an estimated -0.5 kg/m^2 difference (95% CI -1.0 to -0.1) at age 60 years (Supporting Information Table S4), but had similar waist-to-hip ratios (Figure 2A,B). Systolic blood pressure was slightly higher for women with a preterm first delivery with a difference of 0.2 mm Hg (95% CI -1.8 to 2.3) at age 20 years and 1.5 mm Hg (95% CI: -0.5 to 3.6) at age 60 years, with similar small differences observed for diastolic blood pressure (Figure 2C,D). Lipid trajectories overlapped (Figure 3A-D), although there was some indication of higher triglycerides before a preterm delivery with an estimated difference of 10.6 mg/dL (95% CI -1.4 to

22.6). Non-fasting glucose before delivery was higher by 5.3 mg/dL in women with a preterm first delivery (95% CI 1.9 to 8.8) and was somewhat higher following preterm delivery (Figure 3E). Women with a preterm first delivery also had slightly higher hs-CRP levels at earlier ages, with a 14% higher hs-CRP at age 20 years (95% CI -34% to 98%).

Gestation length and BMI at age 40 years had a U-shaped relationship, with the lowest mean BMI values observed for women with early term (37-38 weeks) first deliveries and the highest for women with late term/postterm (41-44 weeks) first deliveries (Figure 4A). Women whose first deliveries were after 40 weeks of gestation also had the highest waist-to-hip ratios at age 40 years (Figure 4B). Figure 4C,D suggests a trend toward lower blood pressure values among women with longer gestation lengths, with the lowest mean blood pressure observed for women whose first deliveries were after 41 weeks of gestation. For blood-based measures (Figure 5), no clear trends by gestation length emerged. However, there was some indication that women who had moderate preterm (32-36 weeks) or early term deliveries had less favorable lipid and glucose profiles by age 40 compared with women who had term deliveries (39-40 weeks). The associations seen between gestation length and risk factors at age 40 years were similar across the age range examined (Supporting Information Figures S2 and S3).

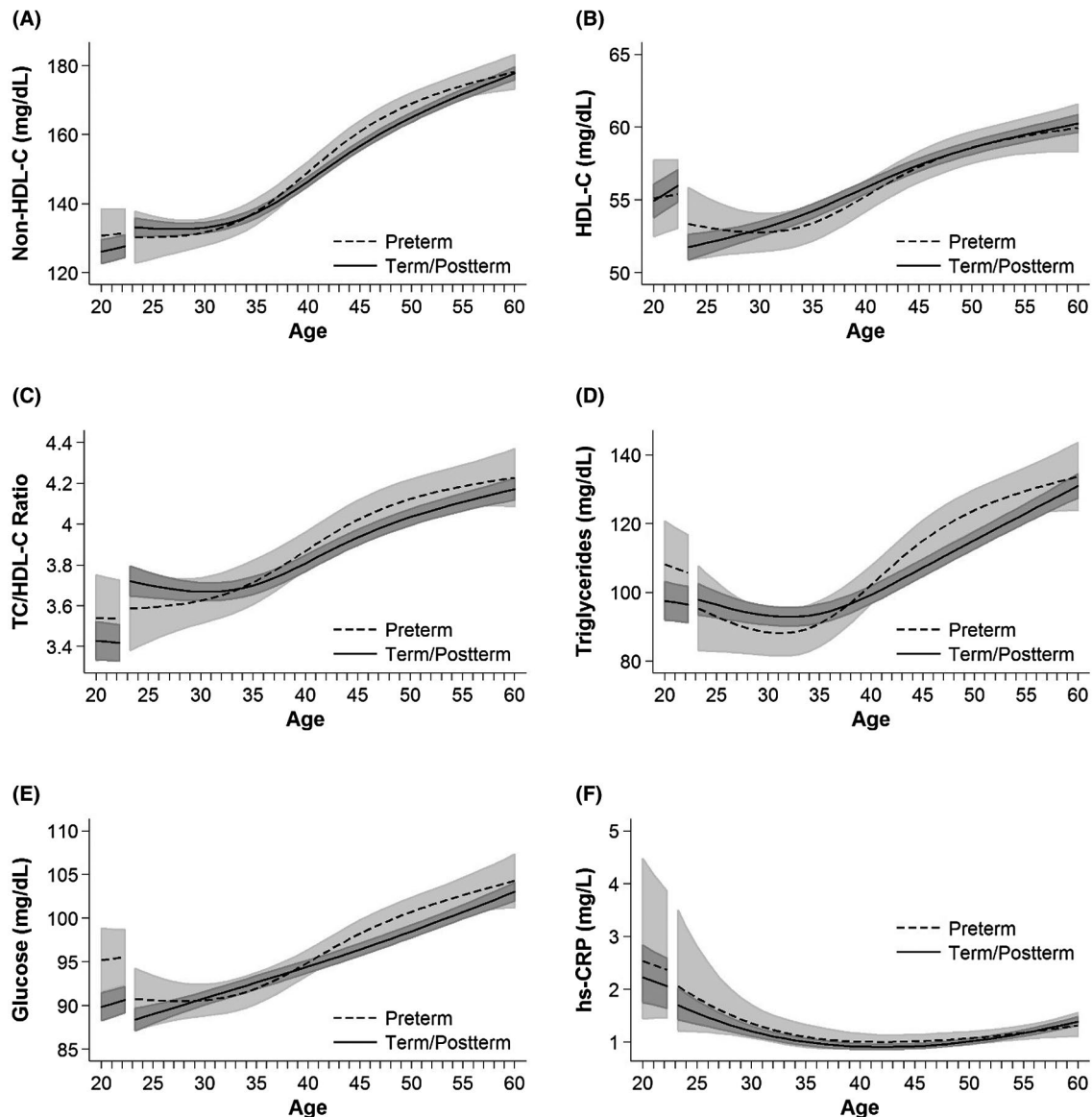


FIGURE 3 Life course trajectories for serum levels of cardiovascular disease (CVD) risk factors among women with preterm and term/postterm normotensive first deliveries. Estimates are adjusted for age, HUNT survey, age at first delivery, highest obtained education level, family history of CVD, smoking at age 20 years, and time since last meal. For the purposes of illustration, we present trajectories in which age at first delivery was set to 23 years, the median age in our study population, and all other covariates were set to their means. As we had insufficient data to model the different risk factor levels typically seen during pregnancy and early postpartum, first pregnancy and 3 months postpartum is depicted as a gap on trajectory graphs. Graphs are shown up to age 60 years, after which data are sparse

The comparison of trajectories based on preterm delivery status was nearly identical when the analysis was restricted to women who contributed two or more measurements (Supporting Information Figures S4 and S5), when using clinical definitions (Supporting Information Figure S6), when examining a history of any preterm delivery (Supporting Information Figures S7 and S8), and when excluding deliveries unusually large for their gestational length (not shown). Excluding women with small or large for gestational age deliveries and pre-existing or gestational diabetes only led to minor changes, as did excluding provider-initiated deliveries (results not shown).

4 | DISCUSSION

We found no evidence of differences in cardiovascular risk factor trajectories based on preterm status in this longitudinal, population-based study of normotensive first deliveries. Pre-pregnancy glucose tended to be higher among women who subsequently had a preterm delivery, but this difference did not appear to persist in the years following pregnancy.

Our findings suggest that most women with a normotensive preterm delivery will have few other strong indicators of an increased risk of CVD, based on commonly measured factors, in the decades

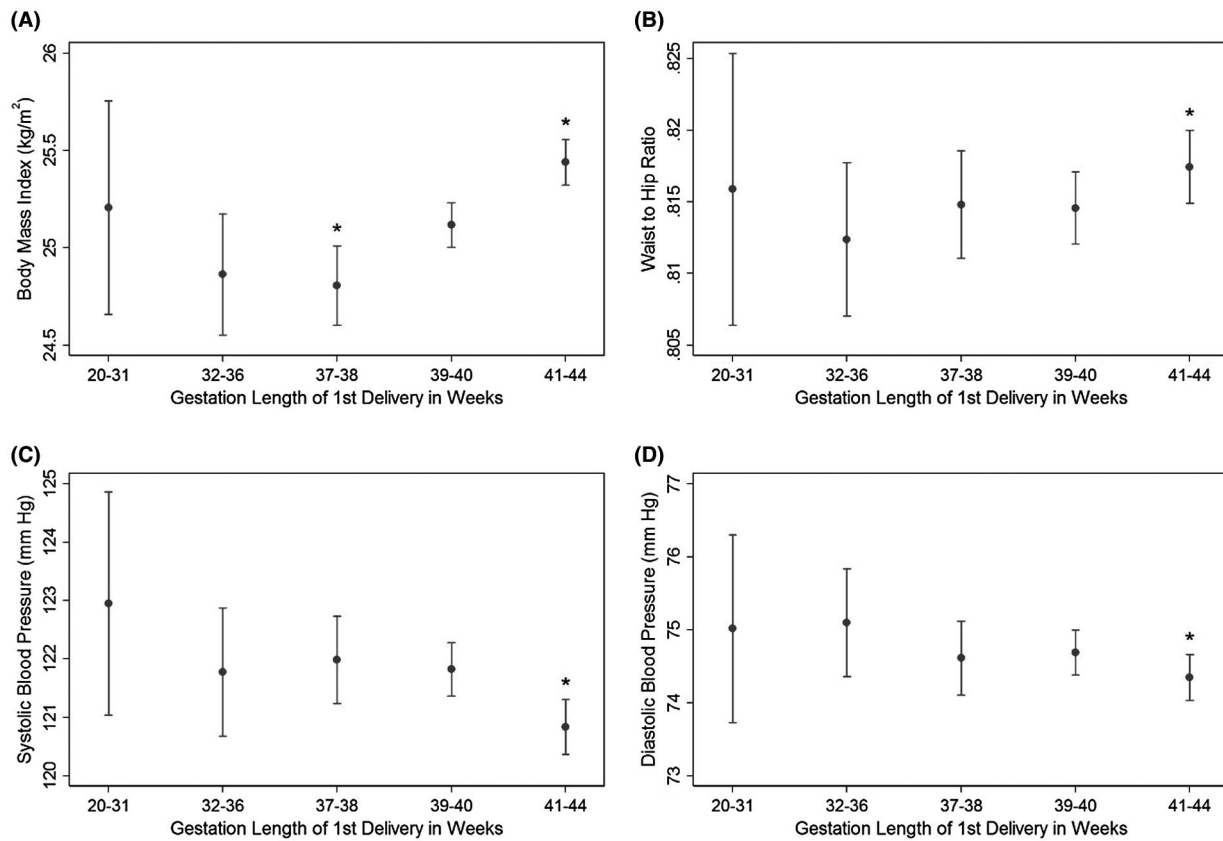


FIGURE 4 Mean clinically measured cardiovascular disease (CVD) risk factors at age 40 years by gestation length of first delivery. Estimates are adjusted for age, HUNT survey, age at first delivery, highest obtained education level, family history of CVD, smoking at age 20 years, and time since last meal. Covariates are fixed at their means

following their first delivery. These null findings are consistent with the Avon Longitudinal Study of Parents and Children, which found similar 10-year Framingham risk scores for women with and without a preterm delivery.⁷ However, previous studies of individual risk factors found conflicting results. After excluding or adjusting for hypertensive disorders of pregnancy, some previous studies found that anthropometric and blood pressure levels did not differ after a preterm delivery,^{6,7} whereas others observed higher BMI and blood pressure^{5,20} or higher rates of hypertension²¹ after a preterm delivery. The CARDIA study found that diastolic blood pressure increased across the childbearing period in women with a history of preterm delivery but decreased in women with term deliveries.²⁰ Our data, in contrast, did not suggest differences in blood pressure changes from before the first pregnancy to after the first pregnancy by preterm delivery status.

Some studies were consistent with our finding of no association between preterm delivery and postpartum lipid levels after accounting for hypertensive disorders,⁵⁻⁷ but two US studies found lower HDL-C levels⁶ and higher rates of hypercholesterolemia among women with a history of preterm delivery.²¹ Except for one study²¹ indicating an increased risk of type 2 diabetes after preterm birth, no previous studies have shown evidence for associations between preterm delivery and postpartum glucose^{6,7} or CRP^{5-7,22} levels when restricting to spontaneous deliveries or accounting for hypertensive disorders.

Although the etiology of preterm delivery is not well understood, there are probably many causes.⁹ The distribution of these causes may differ by study population, which could explain why some previous studies observed associations between preterm delivery and CVD risk factors postpartum. Our study population is fairly representative of Norway²³ with a relatively low preterm delivery rate of 7% (before study-specific exclusions). Studies that found associations between preterm delivery and CVD risk factors, such as the US-based CARDIA and Nurses' Health studies, tended to have higher rates of preterm delivery. The CARDIA study had a preterm delivery rate at 25%.⁵ In the Nurses' Health Study II, the increased risk of hypertension and hypercholesterolemia associated with preterm delivery appeared to be driven by the very preterm group, which in their study population accounted for 2% compared with 1% in our population.²¹ The causes of preterm delivery in these populations may be more strongly associated with metabolic syndrome, leading to the associations they observed.

Our study extends the work of Magnussen et al⁴ who examined cardiovascular risk factors before delivery using only the second HUNT survey. We similarly found that pre-pregnancy non-fasting glucose was associated with shorter gestation length and found some evidence for a less favorable pre-pregnancy lipid profile before preterm delivery. Two previous studies also found higher glucose before preterm delivery^{24,25} and there is some

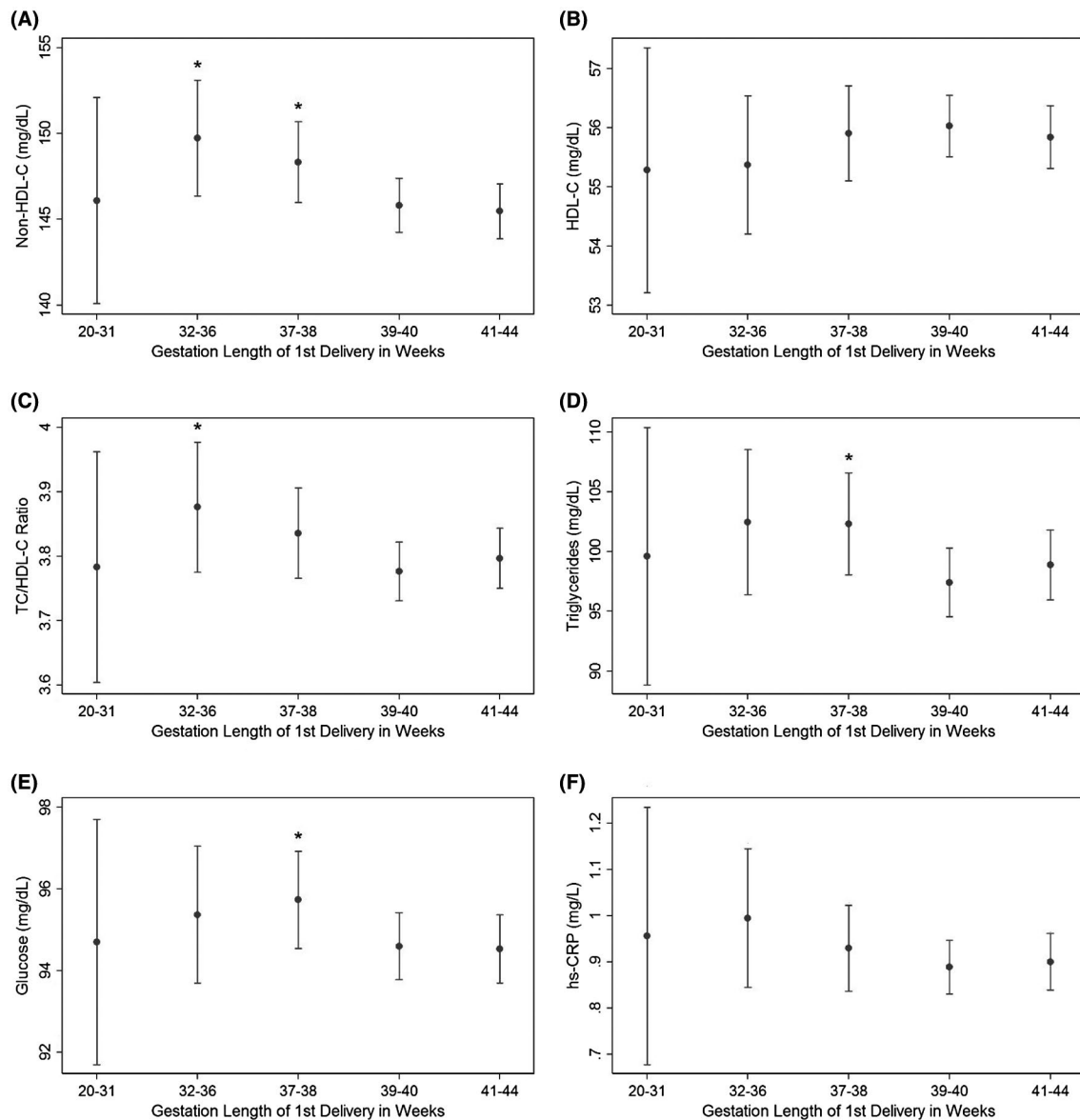


FIGURE 5 Mean serum levels of cardiovascular disease (CVD) risk factors at age 40 years by gestation length of first delivery. Estimates are adjusted for age, HUNT survey, age at first delivery, highest obtained education level, family history of CVD, smoking at age 20 years, and time since last meal. Covariates are fixed at their means

evidence that glucose intolerance is involved in the pathogenesis of spontaneous preterm delivery.²⁶ However, it is unclear why differences in glucose levels based on gestation length do not persist postpartum.

A strength of our study was the use of life course trajectories to provide a more holistic examination of differences in risk factors based on preterm delivery history. With measurements both before and after pregnancy and a wide range of ages, we were able to examine differences in risk factors over a longer period of follow up than previous studies. We were also able to adjust for known predictors of CVD risk including education, smoking, and family history of CVD to ensure that the associations we observed were not just due to these well-established factors, and to adjust for age and HUNT survey occasion to reduce the influence of secular trends on trajectories.²⁷ We controlled for time since last meal to

reduce the potential for error introduced by measuring non-fasting risk factors.

The registry-based definition of gestation length was a strength of our study; however, ultrasound dating was unavailable for the majority of deliveries included in this study. We would expect error introduced by using last menstrual period to bias estimates towards the null, which could explain, in part, our null findings, especially for older women who did not have ultrasound dating as an option for their first pregnancy. As last menstrual period tends to classify more deliveries as preterm,²⁸ we conducted sensitivity analyses excluding deliveries that were unusually large for their gestational age and found no differences in results. Another potential source of misclassification in this study was antihypertensive medication use, which we accounted for using the recommended^{12,13} approach of adding constants to

observed blood pressure measurements for users. Results were not sensitive to the choice of constants added. In addition, antihypertensive use did not differ based on preterm delivery history (8.8% among women with a preterm first delivery vs 8.9% otherwise), making it unlikely that trajectories were differentially affected. We did not have data on statin use, which increased in Norway starting in the late 1990s²⁹ and may have effected lipid measurements taken during HUNT3 (2006-08). If statin use was differential by preterm delivery history then this could have made lipid trajectories appear more similar at later ages when statin use was higher; however, there is no evidence from previous ages that women with a preterm delivery would have been more likely to be prescribed statins given their risk factor levels.

American Heart Association guidelines³⁰ recommend that women with a history of pregnancy complications, including preterm delivery, should have their risk factors carefully monitored and controlled. Our study sought to expand these guidelines by identifying which risk factors to target in this group of women and when this should occur across the life course. However, we did not find evidence that this group of women should be specifically targeted for cardiovascular risk factor control or that interventions should be directed toward any particular risk factor. Our study suggests that women who had a preterm delivery may be too heterogeneous a group to recommend a uniform approach to CVD prevention.

5 | CONCLUSION

Overall, we found that women who experienced a preterm first delivery were on a similar cardiovascular trajectory as those with a first term delivery, based on commonly measured cardiovascular risk factors in early to mid-life. Our findings were unexpected given the consistent evidence that women with a preterm delivery history have a greater risk of CVD,¹ with a two-fold greater risk of CVD death seen even among spontaneous preterm deliveries in Norway.³¹ Although preterm birth is associated with slight increases in cardiovascular risk factors within some populations, the lack of observed differences in risk factor trajectories in our population supports the hypothesis that the association between preterm delivery and CVD is not explained to a large extent by an increase in CVD risk factors postpartum.³² In ours and comparable populations, other factors that could explain the association between preterm delivery and CVD are unknown but may include common genetic factors, low grade inflammation not captured in our measurement of hs-CRP, or the stress of a preterm delivery directly leading to increased CVD events.

ACKNOWLEDGMENTS


The Nord-Trøndelag Health Study (The HUNT Study) is a collaboration between HUNT Research Centre (Faculty of Medicine and Health Sciences, NTNU, Norwegian University of Science and Technology), Nord-Trøndelag County Council, Central Norway

Regional Health Authority, and the Norwegian Institute of Public Health.

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Markovitz AR, Haug EB, Horn J, et al. NORMOTENSIVE preterm delivery and maternal cardiovascular risk factor trajectories across the life course: The HUNT Study, Norway. *Acta Obstet Gynecol Scand*. 2020;00:1–11. <https://doi.org/10.1111/aogs.14016>