

BMJ Open Maternal reproductive history and premenopausal risk of hypertension and cardiovascular disease: a Danish cohort study

Shannon X Chen,¹ Kathleen M Rasmussen,¹ Julia Finkelstein,¹ H Støvring,² Ellen Aa Nøhr,³ Helene Kirkegaard³

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¹Division of Nutritional Sciences, Cornell University, Ithaca, New York, USA

²Department of Public Health, Section for Biostatistics, Aarhus University, Aarhus, Denmark

³Department of Clinical Research, the Research Unit of Gynecology and Obstetrics, University of Southern Denmark, Odense, Denmark

Correspondence to

Dr Helene Kirkegaard;
hkirkegaard@health.sdu.dk

ABSTRACT

Objectives The metabolic changes of pregnancy resemble a cardiovascular risk profile and may persist postpartum, with body mass index (BMI) as a potential modifier. We examined the association between the number of live-birth pregnancies and maternal premenopausal risks of hypertension and cardiovascular disease (CVD), accounting for pre-pregnancy BMI as well as abortions and stillbirths.

Design A prospective cohort study.

Setting Mothers from the Danish National Birth Cohort (1996 to 2002). For each of these women, registry data on all pregnancies from 1973 to 2011 were obtained, as were self-reported pre-pregnancy weight and height.

Participants A total of 44 552 first-time mothers in the Danish National Birth Cohort.

Outcome measures Risks of hypertension and CVD during and between live-birth pregnancies separately and combined as live-birth cycles.

Results After adjustment for abortions, stillbirths, pre-pregnancy BMI and other covariates, a higher risk of hypertension was observed in the first (HR 1.53, 95% CI: 1.37 to 1.72) and fourth and subsequent live-birth cycles (HR 1.72, 95% CI: 1.15 to 2.58), compared with the second. However, as number of live-birth pregnancies increased, risk of hypertension decreased during live-birth pregnancies and increased between live-birth pregnancies (tests for trend, $p < 0.01$). For CVD, we found an overall J-shaped but non-significant association with number of live-birth pregnancies. No interaction with pre-pregnancy BMI (< 25 versus ≥ 25 kg/m²) was observed.

Conclusions Premenopausal women had the highest risk of hypertension and CVD during their first live-birth pregnancy and after their fourth live-birth pregnancy. All risks were independent of BMI before the first live-birth pregnancy and of number of abortions and stillbirths.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, with obesity and hypertension as important risk factors.¹ Women experience significant metabolic changes during pregnancy, including increased fat mass, blood glucose, triglyceride and low-density lipoprotein cholesterol concentrations.² Although these changes

Strengths and limitations of this study

- The combination of cohort and register data limited risk of confounding by behavioural factors and selection bias due to loss to follow-up.
- An extensive register-based reproductive record was developed for each woman to adjust for pregnancy losses, including induced and spontaneous abortions.
- We studied premenopausal risks of hypertension and cardiovascular disease and differentiated risk during live-birth pregnancies from risk between live-birth pregnancies.
- Maternal body mass index at start of the reproductive period was considered as a potential modifier.
- Although maternal socio-occupational status and lifestyle may change over the reproductive period, it was only available at first live-birth pregnancy.

during pregnancy are largely reversed after delivery, this inflammatory state may still increase the risk of hypertension and CVD later in life.^{3 4} Previous research on the associations between parity and hypertension and CVD has not been consistent. Most researchers have studied postmenopausal women and reported an increased risk of CVD with parity or a J-shaped association with two births as the nadir of risk.^{5–11} Premenopausal risk of CVD and hypertension has only been examined in few studies that show inconclusive findings.^{12 13} None of these studies followed women through their reproductive period, considered the potential different risks during and between pregnancies or accounted for the mother's history of pregnancy loss, even though the metabolic changes that resemble a cardiovascular risk profile occur in all pregnancies, also when the pregnancy does not result in a live birth.

Obesity is a risk factor for hypertension¹⁴ and CVD.¹ During pregnancy, obese women have increased insulin resistance,

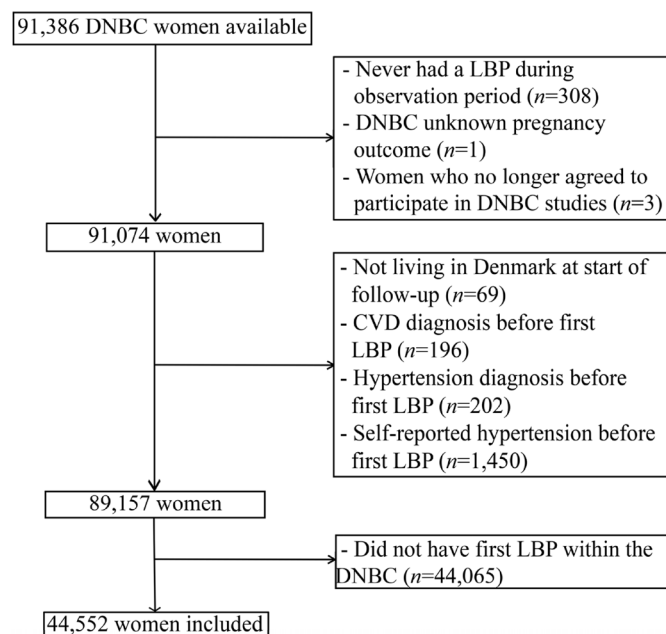


Figure 1 Participant flow chart of women in the Danish National Birth Cohort (DNBC), 1996 to 2002, with inclusion and exclusion criteria for live-birth pregnancies (LBPs) and hypertension and cardiovascular disease (CVD) diagnoses.

inflammatory biomarkers, triglycerides and low-density lipoprotein cholesterol concentrations, compared with normal-weight or underweight women.¹⁵ Therefore, pre-pregnancy obesity may amplify the potential association between pregnancy and risk of hypertension and CVD.

The objective of this study was to examine the associations between the number of live-birth pregnancies (LBPs) and maternal premenopausal risk of hypertension and CVD, while accounting for pregnancy loss. Our first hypothesis was a J-shaped association between the number of LBPs and risk of hypertension and CVD, with the lowest risk with two LBPs. Our second hypothesis was that this association would be stronger among women who were overweight/obese before their first LBP compared with women who were normal-weight/underweight.

METHODS

Study population

This prospective study was conducted among participants in the Danish National Birth Cohort (DNBC), which includes extensive information on 100 418 pregnancies of 91 386 women recruited between 1996 and 2002.¹⁶ Self-reported pregnancy-related information was obtained in four telephone interviews at approximately 16 and 30 weeks of gestation, and at 6 and 18 months postpartum.¹⁶ We excluded women from the analyses for the following reasons: withdrew from the DNBC (n=3), no LBP in the follow-up period (n=308), unknown outcome of a DNBC pregnancy (n=1), emigrated before start of follow-up (n=69), diagnosed with hypertension and/or CVD at the hospital before their first LBP (n=398) (see online supplementary table 1 for the International Classification

of Disease (ICD) codes), and self-reported hypertension before their first LBP (n=1450). Data on self-reported hypertension before the first LBP was obtained from the first pregnancy interview. Finally, inasmuch as women with a prior pregnancy-related CVD diagnosis at the time of DNBC enrolment may be less likely to be pregnant again and therefore not eligible for enrolment in the DNBC, we excluded 44 605 women who were parous at time of DNBC enrolment to prevent potential selection problems and period effects. Our final study population included 44 552 women (figure 1). The Scientific Ethics Committee in Denmark and the Danish Data Protection Agency approved the DNBC and the latter also the present sub-study. All the participants in the DNBC provided written informed consent.

Patient and public involvement

Patients and public were not involved in the present study.

Reproductive history

We established a full reproductive history for each participant (1973 to 2011) by linkage to registry data using the unique identification numbers from the Danish Civil Registration System (see online supplementary figure 1 for timeline). Because we only included women who had their first LBP within the DNBC, all LBPs occurred between 1996 to 2011. Data on births not recorded in the DNBC were extracted from the Medical Birth Registry (MBR).¹⁷ Because of a shift in the definition of a stillbirth recorded in the registers, a stillbirth was defined as fetal demise that occurred at ≥ 28 weeks gestation from 1973 to 2003 and at ≥ 22 weeks gestation after 2003.¹⁸ Data for spontaneous abortions (miscarriages) were obtained from the National Patient Registry (NPR) (1977 to 2011).¹⁹ Induced abortions were recorded in the Registry of Legally Induced Abortions (1974 to 1994)²⁰ and the NPR (1995 to 2011). See online supplementary table 1 for specific codes included. In total, we identified 289 372 pregnancies for our data set.

Our exposure was number of LBPs as we wanted to account for number of complete reproductive cycles, which included a full pregnancy, a potential period of breastfeeding and child-rearing-related behavioural changes. Thus, stillbirths were not included in the exposure, but were adjusted for as done for spontaneous and induced abortions.

Outcomes

Hypertension and CVD diagnostic ICD-8 and ICD-10 codes were extracted from the NPR from January 1977 to February 2016. The NPR contains information on all inpatient contacts since 1977 and also outpatient contacts since 1995.¹⁹ CVD outcomes in this study included incident diagnoses of ischaemic heart disease, stroke, atherosclerosis and thrombosis, and pregnancy-specific diagnoses of thrombosis and stroke. Hypertension outcomes in this study included both chronic hypertension and gestational hypertension (see online supplementary table 1

for specific ICD codes and online supplementary figure 1 for a timeline of the data sources). We did not include preeclampsia as it may have a different origin/aetiology than hypertension and CVD. We also did not adjust for preeclampsia because it is a risk factor for later hypertension and CVD and therefore a potential mediator on the pathway from LBP to hypertension and CVD.

Covariates

In the first DNBC pregnancy interview, women provided information about their weight (kg) and height (m), alcohol intake before pregnancy (0, 1 to <7 or ≥7 units/week) and leisure-time exercise during pregnancy (0, 1 to 180 or >180 min/week). Body mass index (BMI) (kg/m^2) was categorised using WHO criteria (<18.5, 18.5 to <25, 25 to <30, ≥30 kg/m^2). Underweight/normal-weight women included those with BMI <25 kg/m^2 and overweight/obese women included those with BMI ≥25 kg/m^2 . Information on socio-occupational status was also obtained from the first pregnancy interview and categorised based on occupation type and education level (high, middle, low).²¹ Smoking status was obtained from the MBR beginning in 1991 and defined as a fixed dichotomous variable (ever/never smoked during any pregnancy).

Statistical analyses

All statistical analyses were conducted using Stata V.15.1 (StataCorp, College Station, Texas). Pearson χ^2 tests were used to compare maternal characteristics across total number of LBPs during follow-up.

We conducted Cox proportional hazard models to examine premenopausal incident hypertension and CVD during three time periods: (a) live-birth cycles (LBCs), (b) during LBPs and (c) between (inter) LBPs (figure 2). An LBC was defined as the time from one LBP-conception to the next, or to the end of follow-up if there were no subsequent LBPs. Our exposure (LBPs) was time-dependent;

thus, women changed exposure group at the conception of each new LBP. We used maternal age as the underlying time axis and women provided risk time from conception (ie, the first day of the last menstrual period) of their first LBP, which had to be within the DNBC enrolment period (1996 to 2002). Follow-up continued until the time of hypertension or CVD diagnosis, emigration, death or end of follow-up, whichever came first. The end of follow-up for the during-LBP and inter-LBP analyses was July 2011, when our data on reproductive histories ended. The end of follow-up for the LBC analyses was February 2016, with women keeping their 2011 exposure status through the end of follow-up, as most women would not have more births after that time. A diagnosis of hypertension or CVD that occurred within the interval from conception to 42 days postpartum was considered to have occurred during a LBP, in accord with the WHO definition of a maternal death.²² A diagnosis of hypertension or CVD that occurred after 42 days postpartum and before the next conception was considered to have occurred in an inter-LBP interval. In analyses of risk during LBPs, we adjusted for prior hypertension or CVD diagnosis in all past inter-LBP intervals. Likewise, in the analyses of risk in inter-LBP intervals, we adjusted for prior hypertension or CVD diagnosis in all past LBP intervals. We did this to focus on the first occurrence of a diagnosis in the period of interest, but still account for potential confounding by a prior diagnosis in the other period. In the analyses of LBCs, women were only considered at risk until their first diagnosis of hypertension or CVD and then censored. We created graphical evaluations of the assumption of proportional hazards and did not observe any violation.

All models were analysed with maternal age as the underlying time-scale (Model 1). We further adjusted for a priori-selected covariates by including induced abortions, spontaneous abortions and stillbirths as time-dependent

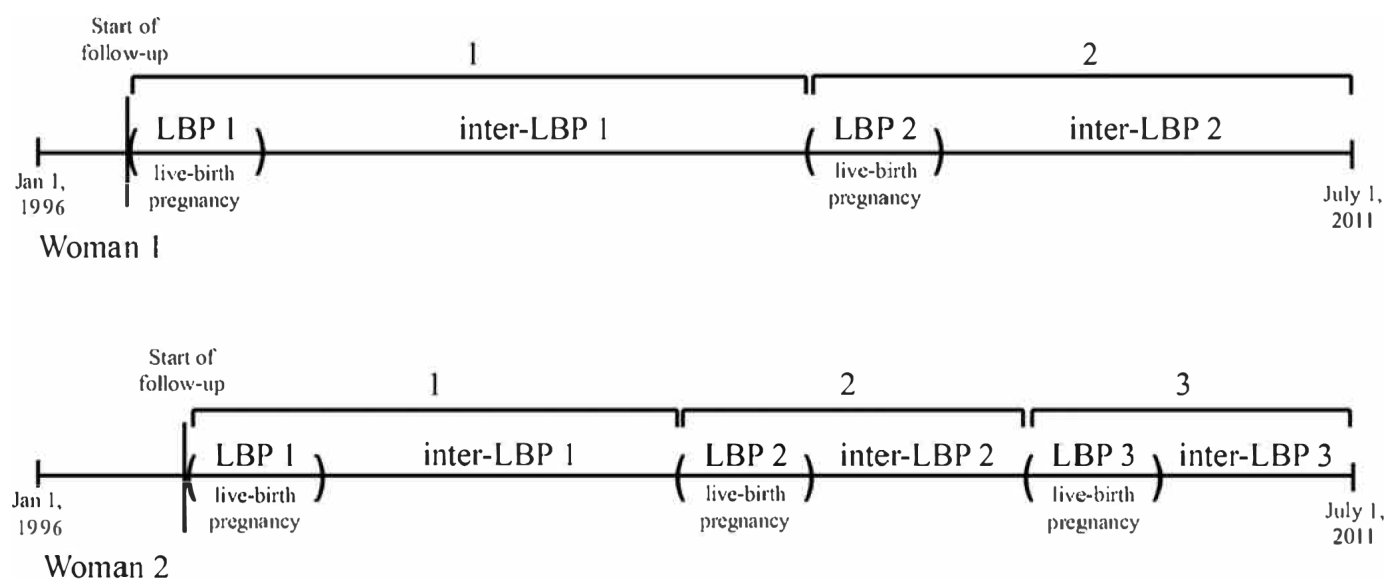


Figure 2 Diagram presenting the follow-up period indicating each live-birth cycle, including live-birth pregnancy (LBP) and inter-live-birth pregnancy (inter-LBP) intervals of two women with two or three LBPs during the follow-up period, respectively.

covariates as they occurred (Model 2), and smoking status, socio-occupational status, leisure-time exercise during pregnancy, alcohol intake before pregnancy and pre-pregnancy BMI category, all as fixed variables (Model 3), thus these were adjusted for throughout the follow-up period. Analyses of Model 1 and Model 2 were based on the whole study population ($n=44\,552$) while the analyses of Model 3 were reduced slightly to 40 177 women due to missing data on covariates.

We considered pre-pregnancy BMI as a potential modifier of the association between the number of LBP and premenopausal risk of hypertension and CVD. We stratified the analyses on pre-pregnancy BMI category and tested for interactions with pre-pregnancy BMI category.

Finally, we conducted sensitivity analyses of the associations between number of LBPs and risk of hypertension and CVD among women who were parous at DNBC enrolment and had been excluded due to potential selection problems. As with the main analysis, follow-up started at conception of their first LBP; however, this means that follow-up may have started before 1996 as these women were parous at enrolment in the DNBC. We also did a sensitivity analysis excluding the 5% of the women who were above 51 years of age at the end of follow-up from the study population because they may be postmenopausal.

RESULTS

Among the study population, 19% had one LBP, 57% two LBPs, 21% three LBPs and 3% four or more LBPs. Compared with women who only had one LBP, women who had more LBPs were younger at birth of their first LBP and had a higher total number of spontaneous abortions. As number of total LBPs increased from one to three, more women had no induced abortions, were of higher socio-occupational status, engaged in leisure-time exercise during pregnancy and were less likely to smoke during pregnancy or be overweight/obese before first LBP (table 1). At the end of follow-up, the median age was 43 years (IQR: 41 to 46). The median follow-up time was 11.3 years (IQR: 10.1 to 12.5) for during-LBP/inter-LBP analyses and 15.8 years (IQR: 14.5 to 17.1) for LBC analyses.

Hypertension

A total of 1731 diagnoses of incident hypertension were recorded during follow-up (table 2). We found a J-shaped association between an increased number of LBCs and risk of hypertension that was similar after adjustment for abortions and stillbirths (Model 2) and in the fully adjusted model (Model 3). Thus, compared with the second LBC, we observed a 53% increased risk of hypertension in the first LBC (HR 1.53, 95% CI: 1.37 to 1.72) and a 72% increased risk in the fourth and subsequent LBC (HR 1.72, 95% CI: 1.15 to 2.58).

A total of 955 and 394 hypertension diagnoses were recorded during LBPs and between LBPs, respectively (table 2). Risk of hypertension during the first LBP was

twice as high as risk during the second LBP (HR 2.10, 95% CI: 1.79 to 2.47) and the risk further decreased as number of LBPs increased (test for trend, $p<0.001$). In contrast, a 24% lower risk of hypertension was observed in the first inter-LBP compared with the second inter-LBP (HR 0.76, 95% CI: 0.60 to 0.97) and the risk of hypertension further increased with greater number of LBPs (test for trend, $p=0.004$). Adjustments only changed these associations slightly.

We observed no interaction ($p=0.18$) by pre-pregnancy BMI in the analyses of LBCs. Both normal/underweight women and overweight/obese women had an increased risk of hypertension in the first LBC (HR 1.63, 95% CI: 1.40 to 1.89 and HR 1.45, 95% CI: 1.23 to 1.71, respectively) compared with the second LBC (table 2). However, only normal/underweight women had an increased risk of hypertension in the fourth and subsequent LBC compared with the second. The risks during pregnancies were modified by pre-pregnancy BMI, with a more clear decreasing trend observed in overweight/obese women than in normal/underweight women ($p=0.04$). No interaction by pre-pregnancy BMI was observed for risk of hypertension between LBPs ($p=0.78$).

Cardiovascular disease

There were 1147 CVD diagnoses reported during follow-up (table 3). We found a tendency towards a J-shaped association with the lowest risk within the third LBC. Compared with the second LBC, a non-significant slightly increased risk of CVD was observed in the first LBC (HR 1.08, 95% CI: 0.94 to 1.24) and fourth and subsequent LBC (HR 1.31, 95% CI: 0.84 to 2.05).

A total of 146 and 537 CVD diagnoses were reported during a LBP and between LBPs, respectively (table 3). The few CVD cases during LBPs made the estimates uncertain, and none was statistically significant. In inter-LBP intervals, the trend in the estimates was similar to that of hypertension, but these were not statistically significant.

We observed no interaction by pre-pregnancy BMI in the analyses of LBCs, the analyses of CVD during LBPs or between LBPs with increasing number of LBPs ($p=0.37$, $p=0.70$ and $p=0.27$, respectively) (table 3).

In sensitivity analyses among parous women at the time of enrolment into the DNBC, we observed a linear association between number of LBCs and risk of hypertension and CVD (online supplementary tables 2 and 3) in contrast to the J-shaped association we observed in our study sample. This suggests that if we had included women who were parous at the time of enrolment into the DNBC, it might have introduced selection bias. Another sensitivity analysis excluding women who were potential postmenopausal during follow-up showed similar results as those presented.

DISCUSSION

In this study, we prospectively examined premenopausal risks of hypertension and CVD throughout a woman's reproductive period and observed an overall J-shaped

Table 1 Characteristics of 44 552 women by total number of live-birth pregnancies during follow-up (1996 to 2011) participating in the Danish National Birth Cohort

Covariates	Number of live-birth pregnancies				P value
	1 (n=8374)	2 (n=25 368)	3 (n=9638)	≥4 (n=1172)	
Age at first live-birth, y (n=44 552)					<0.001
<25 (n=9677)	1133 (14)	5075 (20)	2970 (31)	499 (43)	
25–29 (n=22 350)	2836 (34)	13 542 (54)	5415 (56)	557 (48)	
≥30 (n=12 525)	4405 (53)	6751 (27)	1253 (13)	116 (10)	
Number of induced abortions (n=44 552)					<0.001
0 (n=33 697)	5917 (71)	19 390 (76)	7526 (78)	864 (74)	
≥1 (n=10 855)	2457 (29)	5978 (24)	2112 (22)	308 (26)	
Number of spontaneous abortions (n=44 552)					<0.001
0 (n=34 964)	6802 (81)	20 277 (80)	7085 (74)	800 (68)	
≥1 (n=9588)	1572 (19)	5091 (20)	2553 (26)	372 (32)	
Number of stillbirths (n=44 552)					<0.001
0 (n=44 268)	8315 (99)	25 228 (99)	9562 (99)	1163 (99)	
≥1 (n=284)	59 (1)	140 (1)	76 (1)	9 (1)	
Preterm birth (n=44 552)					<0.001
Ever occurred (n=4436)	962 (11)	2345 (9)	985 (10)	144 (12)	
Never occurred (n=40 116)	7412 (89)	23 023 (91)	8653 (90)	1028 (88)	
Multiple birth (n=44 552)					<0.001
Ever had (n=3664)	758 (9)	1030 (4)	262 (2)	43 (4)	
Never had (n=42 459)	7616 (91)	24 338 (96)	9376 (97)	1129 (96)	
Smoking during pregnancy (n=44 139)					<0.001
Ever smoked (n=2093)	2051 (26)	4799 (19)	1572 (16)	227 (19)	
Never smoked (n=35 490)	5965 (74)	20 517 (81)	8063 (84)	945 (81)	
Missing (n=413)	358	52	3	0	
Socio-occupational status (n=41 733)					<0.001
High (n=23 171)	3881 (50)	13 265 (56)	5426 (59)	599 (55)	
Middle (n=15 154)	2923 (38)	8913 (37)	2973 (33)	345 (32)	
Low (n=3408)	914 (12)	1678 (7)	670 (7)	146 (13)	
Missing (n=2819)	656	1512	569	82	
Leisure-time exercise during pregnancy, min/week (n=41 820)					<0.001
0 (n=24 607)	4821 (62)	13 914 (58)	5193 (57)	679 (62)	
1–180 (n=13 479)	2224 (29)	7898 (33)	3032 (33)	325 (30)	
180+ (n=3734)	697 (9)	2086 (9)	859 (9)	92 (8)	
Missing (n=2732)	632	1470	554	76	
Alcohol intake before pregnancy, units/week (n=44 552)					<0.001
0 (n=42,32)	881 (11)	2301 (9)	898 (9)	152 (13)	
>0–7 (n=32 168)	5607 (67)	18 610 (73)	7121 (74)	830 (71)	
>7 (n=8152)	1886 (23)	4457 (18)	1619 (17)	190 (16)	
Pre-pregnancy BMI before first live-birth (n=40 712)					<0.001
Underweight (n=1827)	384 (5)	970 (4)	397 (5)	66 (6)	
Normal weight (n=28 330)	5017 (66)	16 287 (70)	6300 (71)	726 (70)	
Overweight (n=7478)	1435 (19)	4340 (19)	1523 (17)	180 (17)	
Obese (n=3087)	727 (10)	1680 (7)	608 (7)	72 (7)	
Missing (n=3840)	811	2091	810	128	

Underweight, <18.5 kg/m²; normal weight, 18.5 to <25 kg/m²; overweight, 25 to <30 kg/m²; obese, ≥30 kg/m². Data are *n* women (% of parity group).

BMI, body mass index.

Table 2 Live-birth pregnancies and risk (HRs and 95% CI) of hypertension by reproductive interval for women in the Danish National Birth Cohort

Live-birth cycle	Cases	Person- years	Model 1*	Model 2†	Model 3 ‡	Model 3‡ - stratified by pre-pregnancy BMI	
						UW/normal	OW/OB
Hypertension risk in each live-birth cycle							
Overall	1731	679 354	n=44 552	n=44 552	n=40 177; cases=1547	n=29 762; cases=865	n=10 415; cases=682
LBC 1	857	238 139	1.53 (1.37 to 1.71)	1.54 (1.38 to 1.72)	1.53 (1.37 to 1.72)	1.63 (1.40 to 1.89)	1.45 (1.23 to 1.71)
LBC 2	668	341 266	1 (baseline)	1 (baseline)	1 (reference)	1 (reference)	1 (reference)
LBC 3	179	90 873	1.08 (0.91 to 1.27)	1.07 (0.91 to 1.26)	1.13 (0.95 to 1.34)	1.22 (0.98 to 1.53)	1.02 (0.78 to 1.34)
≥LBC 4	27	9076	1.64 (1.11 to 2.40)	1.63 (1.11 to 2.40)	1.72 (1.15 to 2.58)	2.34 (1.48 to 3.75)	0.91 (0.40 to 2.05)
Hypertension risk during live-birth pregnancies							
Overall	955	80 280	n=44 552	n=44 552	n=40 177; cases=852	n=29 762; cases=469	n=10 415; cases=383
LBP 1	612	38 976	2.12 (1.82 to 2.47)	2.12 (1.82 to 2.47)	2.10 (1.79 to 2.47)	2.37 (1.90 to 2.96)	1.85 (1.47 to 2.31)
LBP 2	261	31 056	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
LBP 3	75	9178	0.85 (0.65 to 1.10)	0.85 (0.65 to 1.10)	0.89 (0.68 to 1.16)	1.23 (0.88 to 1.72)	0.51 (0.32 to 0.84)
≥LBP 4	7	1070	0.63 (0.30 to 1.34)	0.64 (0.30 to 1.36)	0.63 (0.28 to 1.43)	0.80 (0.29 to 2.17)	0.44 (0.11 to 1.79)
Hypertension risk in the inter-live-birth pregnancy intervals							
Overall	394	458 171	n=44 549	n=44 549	n=40 174; cases=339	n=29 760; cases=194	n=10 414; cases=145
Inter-LBP 1	135	198 883	0.80 (0.64 to 1.00)	0.80 (0.64 to 1.00)	0.76 (0.60 to 0.97)	0.75 (0.54 to 1.03)	0.80 (0.55 to 1.15)
Inter-LBP 2	210	214 184	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Inter-LBP 3	43	41 973	1.01 (0.73 to 1.41)	1.01 (0.73 to 1.40)	1.11 (0.79 to 1.56)	0.96 (0.60 to 1.54)	1.35 (0.82 to 2.21)
≥Inter LBP 4	6	3131	1.82 (0.81 to 4.09)	1.81 (0.80 to 4.09)	1.56 (0.64 to 3.83)	1.81 (0.57 to 5.72)	1.23 (0.30 to 5.09)

*Age as underlying time scale, adjusted for previous hypertension diagnosis in an inter-LBP interval for analysis of LBP intervals or previous hypertension diagnosis in a LBP interval for analysis of inter-LBP intervals

†Adjusted for -* and for induced abortions, spontaneous abortions and stillbirths (time-dependent variables)

‡Adjusted for † and for smoking status (ever/never), socio-occupational status, alcohol intake, exercise level and pre-pregnancy body mass index (underweight, normal-weight, overweight and obese)

BMI, body mass index; inter-LBP, inter-live-birth pregnancy; LBC, live-birth cycle; LBP, live-birth pregnancy; OB, obese; OW, overweight; UW, underweight.

association between the number of LBPs and risk of premenopausal hypertension in the entire follow-up period as hypothesised. This may be explained by our observation of increasing risk during LBPs and decreasing risk between LBPs as number of LBPs increased. The association between number of LBPs and risk of premenopausal CVD was similarly J-shaped, but somewhat weaker. Adjustment for pregnancy loss and pre-pregnancy BMI did not alter our findings. In contrast to our second hypothesis, associations among overweight/obese women were not stronger than among normal/underweight women. Thus, our findings suggest that increased number of LBPs may

contribute to risk of premenopausal hypertension and CVD independent of BMI at the start of the reproductive period.

Few investigators have examined the associations between parity and risk of hypertension and CVD in women before menopause. However, parity may be more closely related to premenopausal risk than postmenopausal risk, as hormonal changes, ageing and other factors may become greater contributors to risk after menopause.²³ Further, studies on postmenopausal risk include a study population free of hypertension or CVD at study enrolment in midlife, which limits comparability to our study.^{7 8 10 11}

Table 3 Live-birth pregnancies and risk (HR and 95% CI) of CVD by reproductive interval for women in the Danish National Birth Cohort

Live-birth cycle	Cases	Person- years	Model 1*	Model 2†	Model 3‡	Model 3‡ - stratified by pre-pregnancy BMI	
						UW/normal	OW/OB
CVD risk in each live-birth cycle							
Overall	1147	688 411	n=44 552	n=44 552	n=40 177; cases=1029	n=29 762; cases=705	n=10 415; cases=324
LBC 1	412	240 113	1.13 (0.98 to 1.29)	1.12 (0.98 to 1.28)	1.08 (0.94 to 1.24)	1.14 (0.96 to 1.34)	0.98 (0.77 to 1.25)
LBC 2	580	346 461	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
LBC 3	135	92 628	0.85 (0.70 to 1.03)	0.84 (0.69 to 1.01)	0.85 (0.70 to 1.04)	0.91 (0.72 to 1.14)	0.75 (0.51 to 1.08)
≥LBC 4	20	9209	1.26 (0.81 to 1.97)	1.20 (0.77 to 1.88)	1.31 (0.84 to 2.05)	1.17 (0.65 to 2.07)	1.60 (0.78 to 3.25)
CVD risk during live-birth pregnancies							
Overall	146	81 050	n=44 552	n=44 552	n=40 177; cases=131	n=29 762; cases=97	n=10 415; cases=34
LBP 1	69	39 106	1.20 (0.82 to 1.78)	1.23 (0.83 to 1.82)	1.15 (0.76 to 1.74)	1.26 (0.78 to 2.03)	0.90 (0.42 to 1.90)
LBP 2	51	31 503	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
LBP 3	22	9352	1.21 (0.72 to 2.02)	1.12 (0.72 to 2.01)	1.23 (0.72 to 2.08)	1.40 (0.77 to 2.56)	0.82 (0.27 to 2.50)
≥LBP 4	4	1089	1.60 (0.57 to 4.50)	1.16 (0.36 to 3.81)	1.25 (0.38 to 4.12)	1.67 (0.49 to 5.63)	.
CVD risk in the inter-live-birth pregnancy intervals							
Overall	537	547 365	n=44 549	n=44 549	n=40 174; cases=488	n=29 760; cases=326	n=10 414; cases=162
Inter-LBP 1	213	198 458	0.89 (0.74 to 1.08)	0.89 (0.73 to 1.07)	0.90 (0.74 to 1.10)	0.89 (0.70 to 1.13)	0.95 (0.68 to 1.32)
Inter-LBP 2	270	213 866	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Inter-LBP 3	48	41 927	0.89 (0.65 to 1.21)	0.88 (0.64 to 1.19)	0.90 (0.65 to 1.24)	0.84 (0.56 to 1.25)	1.06 (0.62 to 1.83)
≥Inter LBP 4	6	3115	1.39 (0.62 to 3.12)	1.35 (0.60 to 3.03)	1.47 (0.65 to 3.31)	0.74 (0.18 to 2.97)	2.93 (1.06 to 8.12)

*Age as underlying time scale, adjusted for previous CVD diagnosis in an inter-LBP interval for analysis of LBP intervals or previous CVD diagnosis in a LBP interval for analysis of inter-LBP intervals

†Adjusted for * and for induced abortions, spontaneous abortions and stillbirths (time-dependent variables)

‡Adjusted for † and for smoking status (ever/never), socio-occupational status, alcohol intake, exercise level and pre-pregnancy body mass index (underweight, normal-weight, overweight and obese)

BMI, body mass index; CVD, cardiovascular disease; inter-LBP, inter-live-birth pregnancy; LBC, live-birth cycle; LBP, live-birth pregnancy; OB, obese; OW, overweight; UW, underweight.

Of the studies examining premenopausal risk, the results are generally consistent with our findings. Gold *et al*¹² found that the risk of pregnancy-associated hypertension decreased after the first pregnancy. Given that the first pregnancy is a metabolic stressor, high-risk women are likely to be diagnosed with hypertension during this period. This may explain the increased risk we observed during the first LBP. Gaist *et al*²⁴ found that increasing parity was associated with a reduced risk of subarachnoid haemorrhage from first childbirth in primiparous women until an average age of 38.1 years. We also observed a decreased risk of CVD from the first LBC to the third; however, the risk increased again in the fourth and

subsequent LBCs. This may be because we included a variety of CVD diagnoses in our outcome.

Pregnancy loss may increase women's risk of hypertension and CVD either by pathological processes from the pregnancy loss or by common underlying mechanisms of pregnancy itself.^{25 26} We adjusted for pregnancy loss, but our findings did not change after adjustment, even though women with more LBPs at the end of their reproductive period tended to have more induced and spontaneous abortions.

Obesity may affect a woman's fertility²⁷ and the metabolic changes during pregnancy.^{15 28} However, adjustment for pre-pregnancy BMI category did not alter our results

and we did not find any interactions by pre-pregnancy BMI category, except in risk of hypertension during LBP. Although we had a large sample size, power for these analyses was low, which may have resulted in uncertain estimates. Still, the trend in our estimates did not support our hypothesised stronger association between LBPs and risk of hypertension and CVD in overweight/obese women than normal/underweight. Also, obesity is a strong risk factor for hypertension and CVD in itself; thus, in overweight/obese women it may be difficult to ascertain variances in risks with additional LBPs.

A limitation of the study was that we had to assume that socio-occupational and lifestyle information obtained in the DNBC were constant throughout the reproductive period, as this information was only available for the first LBP. Therefore, we cannot rule out residual confounding due to changes in lifestyle factors related to child-rearing.^{11 29} Nevertheless, we focused on parous women who were all exposed to child-rearing and studied premenopausal risks that may be more likely associated with maternal metabolic changes compared with postmenopausal risks. Further, lifetime duration of breastfeeding may be a modifier of the association between parity and CVD.³⁰ However, we were unable to consider lifetime duration of breastfeeding, as these data were not available. Lifetime breastfeeding duration may also be considered an intermediate factor between LBPs and risks of hypertension and CVD and therefore not a covariate to include in the analyses. In addition, misclassification may have occurred for hypertension disorders of pregnancy, as a previous validation study has observed a positive predictive value (PPV) of 66.7% for gestational hypertension.³¹ However, we assumed such misclassification to be unrelated to the exposure, and therefore non-differential. For diagnoses outside pregnancy, a high validity has been observed with PPVs above 95% for chronic hypertension and myocardial infarction in women.³² Finally, women who participated in the DNBC had a higher socio-occupational status and might be healthier than women in the overall Danish population,³³ which limits the generalisability of our findings.

The primary strength of our study is our use of registry data linked to data from the DNBC. The combination of these data made it possible to develop a comprehensive reproductive record for each woman that eliminated self-reported information on reproductive events and included detailed information on socio-occupational, behavioural and anthropometric information not available in the registers. The reproductive record for each woman enabled us to consider premenopausal risks of hypertension and CVD during and between LBPs beginning from the start of the reproductive period to midlife while considering the women's pregnancy losses. Using register data reduced potential selection biases, as there was minimal loss to follow-up. Further, the large size of the cohort allowed us to restrict our study population to first-time mothers in the cohort and, thus, reduced selection bias. As observed in our sensitivity analysis, women

who were parous at enrolment into DNBC had a different risk of hypertension and CVD during their first LBP than women who were nulliparous at enrolment. We saw this as a selection problem possibly due to fewer complications during the first LBP in parous women, who may also be healthier and more fertile, as they had become pregnant again. Finally, we studied premenopausal risks which may be more likely be related to maternal metabolic changes than postmenopausal risk of hypertension and CVD.

In conclusion, we found a J-shaped association between number of LBPs and risk of hypertension in a large sample of premenopausal women. Our results suggest that as number of LBPs increases, risk of hypertension decreases during pregnancies and increases between pregnancies. Findings did not vary after adjustment for induced abortions, spontaneous abortions and stillbirths, and may not be necessary to control for in future studies on parity. Moreover, adjusting for pre-pregnancy BMI category did not change the findings and women who were overweight/obese women before their first LBP did not have greater risks compared with women who were normal/underweight. In premenopausal women, healthcare providers should consider the number of LBPs and the difference in risks of hypertension and CVD throughout the reproductive period in addition to the traditional risk factors for these diseases. Future work should focus on reproductive and cardiovascular factors during pregnancy that could reveal a biological basis for the observed associations between LBPs and premenopausal risk of hypertension and CVD.

Contributors HK, EAN, KMR and SXC designed research; SXC, HS and HK analysed data; SXC drafted the manuscript; HK, KMR, EAN, JLF and HS interpreted results and revised the manuscript; SXC and HK have primary responsibility for final content. All authors approved the final version for publication.

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Data availability statement The data that provide the findings of this study are available from the Danish National Birth Cohort, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Therefore, data described in the manuscript, code book, and analytic code will not be made available. All requests for data from the Danish National Birth Cohort must include a short protocol with a specific research question and a plan for analysis. More information can be found on www.dnbc.dk

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