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HYPERTENSION IN PREGNANCY AND OFFSPRING CARDIOVASCULAR RISK IN YOUNG ADULTHOOD: PROSPECTIVE AND SIBLING STUDIES IN THE HUNT STUDY IN NORWAY.

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Abstract

Women with hypertensive disorders in pregnancy are at increased lifetime risk for cardiovascular disease. We examined the offspring's cardiovascular risk profile in young adulthood, and also their siblings' cardiovascular risk profile.

From the HUNT Study in Norway 15 778 participants (mean age 29 years), including 210 sibling groups, were linked to information from the Medical Birth Registry of Norway. Blood pressure, anthropometry, serum lipids and CRP were assessed.

706 participants were born after exposure to maternal hypertension in pregnancy: 336 mothers had gestational hypertension, 343 had term preeclampsia, and 27 had preterm preeclampsia. Offspring whose mothers had hypertension in pregnancy had 2.7 (95% CI 1.8-3.5) mmHg higher systolic blood pressure, 1.5 (0.9-2.1) mmHg higher diastolic blood pressure, 0.66 (0.31-1.01) kg/m^2 higher BMI, and 1.49 (0.65-2.33) cm wider waist circumference, compared with offspring of normotensive pregnancies. Similar differences were observed for gestational hypertension and term preeclampsia, but term preeclampsia was also associated with higher concentrations of non-HDL cholesterol (0.14 mmol/L, 0.03-0.25) and triglycerides (0.13 mmol/L, 0.06-0.21). Siblings born after a normotensive pregnancy had nearly identical risk factor levels as siblings who were born after maternal hypertension.

Offspring born after maternal hypertension in pregnancy have a more adverse cardiovascular risk profile in young adulthood than offspring of normotensive pregnancies. Their siblings, born after a normotensive pregnancy, have a similar risk profile, suggesting that shared genes or lifestyle may account for the association, rather than an intrauterine effect. All children of mothers who have experienced hypertension in pregnancy may be at increased lifetime risk of cardiovascular disease.

Key words: Hypertensive disorders in pregnancy, preeclampsia, cardiovascular risk factors, cardiovascular disease (CVD), offspring, sibling

Introduction

Hypertensive disorders of pregnancy include gestational hypertension and preeclampsia.[1] In addition to hypertension, preeclampsia is characterized by proteinuria and is a leading cause of maternal and perinatal morbidity.[2-4] It is well established that women with a history of hypertension in pregnancy are at increased risk of cardiovascular disease (CVD) later in life,[5-8] and their offspring may also have an increased lifetime risk of CVD.[9-11] Children and adolescents whose mothers had preeclampsia appear to have higher body mass index (BMI) and blood pressure than others, but it is not entirely clear if other cardiovascular risk factors, such as serum lipids, may also differ.[12] Also, it remains to be determined whether siblings born after a hypertensive pregnancy, differ in their cardiovascular profile, compared to siblings born after a normotensive pregnancy. Such an analysis might help clarify whether the children's risk factors could be attributed to the hypertensive pregnancy, or whether shared genes or shared lifestyle are equally relevant.

Using a prospective cohort design, we investigated whether intrauterine exposure to maternal hypertensive disorders (gestational hypertension, term preeclampsia or preterm preeclampsia) is associated with cardiovascular risk factors in young adulthood. We also compared cardiovascular risk factors between siblings discordant for *in utero* exposure to maternal hypertension.

Materials and methods

Study population

The Nord-Trøndelag Health Study (the HUNT Study) consists of three population-based surveys in Nord-Trøndelag county in Norway: HUNT1 (1984-86), HUNT2 (1995-97) and HUNT3 (2006-08). At each survey, all residents 20 years of age or older were invited to participate. The number of participants was 77 212 (89.4 % of those invited) in HUNT1, 61

215 (69.5 %) in HUNT2, and 50 807 (54.1 %) in HUNT3.[13] The HUNT Study comprises extensive questionnaires, clinical examinations and blood samplings (second and third surveys), and provides information on socioeconomic status, health related behavior, and a broad range of self-reported symptoms and prevalent diseases. More than 97 % of the population is of European ancestry.[14] The study has been described in detail elsewhere.[13, 14]

We used the unique personal identity number of Norwegian citizens to link individual-level HUNT data to information recorded in the Medical Birth Registry of Norway (MBRN). The MBRN has registered information for all births in Norway since 1967, as reported on a standardized form filled in at the birth clinics. The form includes information on demographic variables, maternal health before and during pregnancy, complications and registrations during pregnancy and delivery, and health status of the newborn. The form is typically completed by the responsible midwife and returned within a week of the delivery. In the present study, we included all 15 873 singletons born in 1967 or later who subsequently participated in HUNT2 or HUNT3 as adults and excluded 95 participants without information on cardiovascular risk factors, leaving 15 778 participants (with a total of 19 596 HUNT examinations) for analysis. For 13 127 of them (83%, with 16 584 HUNT examinations), additional maternal information on socioeconomic status and cardiovascular risk factors was available because their mothers had also participated in one or more of the HUNT surveys. For the majority of participants, maternal information from the HUNT surveys was collected after the index pregnancy. The study was approved by the regional committee for medical and health research ethics (REC Central).

Classification of hypertensive disorders in pregnancy

The clinical criteria for hypertensive disorders in pregnancy in the MBRN are in accordance with the recommendations of the American College of Obstetricians and Gynecologists.[15]

Gestational hypertension is defined as sustained increase in blood pressure, ≥140 mmHg systolic and/or 90 mmHg diastolic pressure, with onset after 20 weeks of gestation. The diagnostic criteria for preeclampsia are similar, but in addition, proteinuria (at least 0.3 g/24 hours or ≥1+ on a semiquantitative dipstick) after gestational week 20 is also required. In this study, we defined a hypertensive disorder in pregnancy as the presence of either gestational hypertension, term preeclampsia (preeclampsia with delivery ≥37 weeks of pregnancy), or preterm preeclampsia (preeclampsia with delivery <37 weeks of pregnancy).

Cardiovascular risk factors in the HUNT surveys

Specially trained nurses and technicians conducted the clinical examinations in the HUNT surveys. Blood pressure was measured with the person seated using a sphygmomanometer (HUNT1) or a Dinamap 845 XT (Critikon, Tampa, FL) oscillometer (HUNT2 and 3), and the pressure was measured two (HUNT1) or three (HUNT2 and 3) times with one minute intervals. For HUNT1, we used the mean of the two measurements. For HUNT2 and HUNT3, we used the mean of the second and third measurement, and if a third measurement was not conducted (12 % of measurements in HUNT3), only the second measurement was used. At HUNT2 and HUNT3, cuff size was adjusted to the participant's arm circumference. Weight was recorded to the nearest 0.5 kg wearing light clothes but without shoes, and height was measured to the nearest cm. Body mass index (BMI) was calculated as weight (in kg) divided by the squared value of height (in meters). Waist and hip circumference were measured to the nearest cm, using the level of the umbilicus and at the widest part of the hip. Waist-hip ratio was calculated as the ratio of the two measurements.

Blood samples were collected in a non-fasting state and analyzed at the Central Laboratory, Levanger Hospital, Nord-Trøndelag Hospital Trust, using a Hitachi 911 Autoanalyzer (Mito, Japan) with reagents from Boehringer Mannheim (Mannheim, Germany;

for serum lipids) or Roche (Basel, Switzerland; for C-reactive protein (CRP)) in HUNT2 and an Architect ci8200 with reagents from Abbott (Abbott Ireland, Longford, Ireland; and Abbott Laboratories, Abbott Park, IL) in HUNT3. Serum concentrations of total cholesterol were analyzed by enzymatic cholesterol esterase methodology, HDL cholesterol by enzymatic cholesterol esterase (HUNT2) or accelerator selective detergent methods (HUNT3), triglycerides by enzymatic colorimetric (HUNT2) or glycerol phosphate oxidase methods (HUNT3), and CRP by latex immunoassay methodology. Non-HDL cholesterol was calculated as the difference between total and HDL cholesterol concentrations.

Statistical analyses

Using linear regression analysis, we compared CVD risk factors of adult offspring born after hypertensive pregnancy to those among offspring born after normotensive pregnancy. Thus, we compared means of systolic and diastolic blood pressure, BMI, waist circumference, waist-hip ratio, and serum concentrations of HDL cholesterol, non-HDL cholesterol, triglycerides and CRP. We also examined these factors by subtype of maternal hypertensive disorder: gestational hypertension, term preeclampsia, or preterm preeclampsia. CRP and triglycerides were analyzed log-transformed due to a non-normal distribution. We used a clustered sandwich estimator to account for repeated measurements within each offspring. In the main analyses, we adjusted for age (continuous variable), sex, maternal parity and HUNT survey. In a separate analysis among offspring whose mothers had also participated in the HUNT Study, we examined whether the observed differences in cardiovascular risk factors in young adulthood persisted after adjustment for maternal cardiovascular risk factors recorded in the HUNT Study. For that purpose, we first adjusted for maternal smoking (current smoker versus non-smoker) and education (≤9, 10-12, or >12 years), and then added maternal BMI (continuous) and systolic and diastolic blood pressure (continuous) to the model. We used

maternal information collected at the earliest HUNT examination in which the mother had participated.

Using a fixed-effects linear model, we also compared cardiovascular risk factors within siblings born by the same mother, where at least one was exposed to hypertension in pregnancy and one was not. We adjusted for age, sex, maternal parity and HUNT survey. Finally, we compared cardiovascular risk factors among offspring born after hypertensive pregnancy, and among offspring born after normotensive pregnancy but whose mother had at least one hypertensive pregnancy, to offspring of women with no record of hypertensive pregnancy. We used a mixed-effects linear regression model to account for multiple offspring by the same mother, and we adjusted for age, sex, maternal parity and HUNT survey. In these analyses, we included information from the latest HUNT examination in which the offspring had participated. Stata statistical software version 13.1 (College Station, TX) was used for the statistical analyses.

Results

Characteristics of the participants are described in Table 1. Among 15 778 participants, there were 19 596 examinations: 336 (2%) participants were exposed to gestational hypertension *in utero*, 343 (2%) were exposed to term preeclampsia, 27 (0.2%) to preterm preeclampsia, and 15 072 (96%) were born after a normotensive pregnancy. Mean age at attendance was 28.9 (SD 6.2) years.

Participants whose mothers had any hypertensive disorder in pregnancy had 2.7 (95% CI 1.8-3.5) mmHg higher systolic blood pressure, 1.5 (0.9-2.1) mmHg higher diastolic blood pressure, 0.66 (0.31-1.01) kg/m^2 higher BMI, and 1.49 (0.65-2.33) cm wider waist

circumference, compared with participants born after a normotensive pregnancy, adjusted for age, sex, parity and HUNT survey (Table 2).

Among subtypes of hypertensive pregnancies, gestational hypertension and term preeclampsia were associated with similar increases in blood pressure, BMI and waist circumference in the offspring. Offspring of mothers who had term preeclampsia also had slightly higher serum concentrations of non-HDL cholesterol (0.14 mmol/L, 0.03-0.25) and triglycerides (0.13 mmol/L, 0.06-0.21). In contrast, there was no strong evidence of differences between offspring born after preterm preeclampsia, compared with the normotensive group (Table 2). Offspring in the preterm preeclampsia group had 35% higher CRP than offspring in the normotensive group, but due to small numbers, the precision of the difference was low.

In a sub-group analysis (N=13 127 participants with 16 584 HUNT examinations) we adjusted for maternal blood pressure and BMI to find out whether, or to which degree, the observed differences between offspring could be attributed to maternal characteristics. Differences in BMI and waist circumference between offspring of hypertensive and normotensive pregnancies were attenuated by 80-90% after this adjustment, and most of the attenuation was due to adjustment for maternal BMI. Similarly, associations with blood pressure were attenuated by 60-70%, and most of the attenuation was due to adjustment for maternal blood pressure (Table 3).

To further explore the increased cardiovascular risk factor levels in offspring born after hypertensive conditions in pregnancy, we compared cardiovascular risk factors among siblings discordant for the exposure (N=472 participants within 210 sibships; characteristics given in Table 4). We found no evidence of clear differences in cardiovascular risk factors between siblings born by the same mother, where at least one sibling was born after a hypertensive pregnancy (Table 5). Similarly, there were no clear differences in cardiovascular

risk factors among offspring born after a hypertensive pregnancy (N=706) and offspring born after a normotensive pregnancy but whose mother had at least one hypertensive pregnancy (N=653) (Table 6).

In the main analysis, participants born to mothers with pre-pregnancy hypertension without superimposed preeclampsia (N=27) were included in the normotensive group. In a sensitivity analysis, we excluded these participants, and the results remained essentially unchanged (results not shown).

Discussion

In this prospective study of approximately 16 000 young adults, offspring whose mothers had hypertension in pregnancy had an adverse cardiovascular risk factor profile in young adulthood (mean: 29 years of age), compared to offspring of normotensive pregnancies. Intrauterine exposure to maternal gestational hypertension or term preeclampsia was associated with higher systolic and diastolic blood pressure, BMI and waist circumference, and in the term preeclampsia group, non-HDL cholesterol and triglyceride concentrations were slightly higher. Among siblings, we found a cardiovascular risk factor profile that was nearly identical between those who were exposed to maternal hypertension in pregnancy, and siblings who were born after a normotensive pregnancy.

In this study we were able to follow a large number of offspring from birth until young adulthood. Maternal hypertensive disorders in pregnancy were reported to the MBRN after birth, and therefore, this information could not be influenced by future health of the offspring. Moreover, the positive predictive value of preeclampsia and gestational hypertension diagnoses registered in the MBRN is good, although some cases of preeclampsia may be misclassified as gestational hypertension.[16, 17] The collection of cardiovascular risk factors was

standardized and conducted by trained nurses or health care technicians who were unaware of the pregnancy complications. The attendance at the two surveys was 69.5% and 54.1%; however, attendance was as low as 49% and 32% for the age groups with available perinatal information.[13] Because a selective participation cannot be ruled out, the attendance is a limitation of this study. However, the prevalence of preeclampsia in our study population was similar to nation-wide prevalence data for the same birth cohorts[18], suggesting that participation did not vary by exposure to preeclampsia. Also, selective participation may have influenced our findings only if the associations of hypertensive pregnancy disorders with future cardiovascular risk factors differed between those who participated at the HUNT Study and those who did not. The blood sampling was non-fasting, which could have caused a non-differential misclassification between comparison groups, and typically result in a bias towards the null value. In our study, such a bias could have influenced the results for triglycerides, due to daily fluctuations depending on diet, but less likely for HDL and non-HDL cholesterol, which are more stable.[19] Moreover, the maternal information used in the analysis in Table 3 was partly measured before pregnancy, and partly after the pregnancy, and these measurements were assumed to be equally relevant when maternal cardiovascular risk factors were taken into account. This may be a questionable approach, but the results of another study of mothers with hypertensive pregnancy disorders from this population are reassuring, because differences between the groups were similar for blood pressure measured before and after pregnancy.[20] In that study, post-pregnancy cardiovascular risk factors could largely be attributed to pre-pregnancy risk factors, and not to a direct effect of the hypertensive pregnancy. Although our sibling comparison represents a unique design in adjusting for unmeasured (unknown) confounding factors shared by siblings, it does not exclude the possibility for confounding by un-shared factors or by misclassification of the exposure.[21] Women with hypertensive pregnancy disorders may have higher blood pressure

also in their normotensive pregnancies, compared with normotensive pregnancies of other women. The true difference in *in utero* exposure to hypertension may therefore be less in the sibling comparison.

Several studies suggest that offspring born after hypertensive disorders in pregnancy may have increased blood pressure in childhood compared to other children, but few studies have followed children into adulthood. Nonetheless, the results of others suggest that children and adolescents born after a preeclampsia pregnancy have higher blood pressure, BMI, waist circumference and serum cholesterol compared to offspring of normotensive pregnancies. A large Finnish study suggested that offspring born after preeclampsia may be at higher risk of stroke later in life, but found no association with coronary heart disease.[10-12, 22-26] In a systematic review, including more than 45 000 participants, Davis et al[12] reported positive associations of preeclampsia with offspring blood pressure (systolic and diastolic) and BMI that were similar to ours. It has also been suggested that the higher childhood blood pressure associated with maternal hypertension in pregnancy may persist into adulthood.[27] Hence, Davis et al[11] followed offspring of hypertensive pregnancy disorders into young adulthood, and found that they were 2.5 times more likely to have global lifetime risk factor levels (QRISK, a prediction algorithm for cardiovascular disease) above the 75th percentile. Few studies have examined offspring by subtype of maternal hypertensive disorder. The results of two studies suggest that maternal preeclampsia and gestational hypertension may both be associated with higher blood pressure in adolescence, but their findings suggested no association with fasting insulin, glucose, lipid levels, apolipoproteins or inflammatory markers.[28, 29]

An intriguing question is whether the adverse cardiovascular risk profile can be attributed to genetic or behavioral risk factors common to mothers and their offspring, or to intrauterine vascular damage or altered metabolism caused by fetal exposure to hypertension

or preeclampsia.[30-32] There is evidence that preeclampsia and CVD share similar risk factors[33], and that cardiovascular risk factors prior to pregnancy appear to be positively associated with preeclampsia risk.[34] We found that the positive associations of hypertensive pregnancy disorders with offspring blood pressure and BMI were substantially attenuated after accounting for maternal blood pressure and BMI. Furthermore, we found no differences between siblings born to the same mother where one was born after a hypertensive pregnancy, and the other(s) after a normotensive pregnancy.

If cardiovascular factors could be attributed to maternal characteristics, our interpretation would be in favor of genetic effects or shared lifestyle, and conversely, if the effects could be attributed to characteristics of the pregnancy (hypertensive or not), we would lean to an interpretation where the pregnancy itself could be important for the cardiovascular risk profile later in life. In this study, we found that the differences in cardiovascular risk factors were strongly attenuated after adjustment for maternal factors, suggesting that shared genes or lifestyle may largely explain the differences. Nonetheless, the adjustment did not completely rule out the possibility that the hypertensive pregnancy in itself may cause a lasting effect on the offspring, as a slightly higher blood pressure was observed in the offspring of hypertensive pregnancies also after adjustment. However, the influence from maternal blood pressure may not be fully captured by our adjustment, because of possible measurement error due to variation in blood pressure over time. Also, by comparing siblings who were either born after a hypertensive or a normotensive pregnancy, we found that their risk factor profile did not differ, and that finding supports a hereditary or shared lifestyle interpretation of the main findings.

Thus, it seems plausible that transfer of cardiovascular risk factors from mother to child may be an important explanation for our findings, and also for the higher risk of preeclampsia that has been observed in female offspring whose mothers had preeclampsia. [30,

[35, 36,37] However, it has also been suggested that excess cardiovascular risk in the offspring could be a long-term consequence of fetal exposure to preeclampsia.[30, 31] In support of that possibility, another study using information from differentially exposed siblings, found a marked vascular dysfunction (higher pulmonary artery pressure and smaller flow-mediated dilatation) in offspring of pregnancies with late-onset preeclampsia, but normal vascular function in their siblings born after a normotensive pregnancy.[38] In this study, the birth weight in offspring born after preeclampsia was 400 g lower than the controls, suggesting exposure to a more severe placental disease. Moreover, these differences in vascular function were not accompanied by differences in blood pressure and BMI, and it is unclear how these measures of vascular function correspond to the conventional cardiovascular risk factors that we examined.

Many researchers claim that preterm and term preeclampsia are distinctly different diseases,[39] and that different underlying mechanisms suggest that implications for later cardiovascular risk are likely to differ. Thus, the pathway to increased cardiovascular risk for mothers with a history of mild (term) preeclampsia may differ from that of mothers with a history of severe (preterm) preeclampsia.[40] However, it is not known if similar patterns may be replicated in the offspring.[41 42] Unfortunately, low statistical power in our study precludes any definite answer to these questions. Another interesting aspect of preterm preeclampsia is the time-related improvement in prognosis for children born after these pregnancies. The increasingly better survival of these children may also have implications for their future cardiovascular health.

Perspectives

Our findings confirm that offspring of mothers with hypertensive disorders in pregnancy have a cardiovascular risk profile in young adulthood that indicates increased risk of CVD later in

life. This association was substantially, but not fully, attenuated after accounting for maternal cardiovascular risk factors. Cardiovascular risk factor levels were similar for siblings who were either exposed or unexposed to hypertension *in utero*. Although a long-term effect of the hypertensive pregnancy cannot be ruled out, most of the added risk in the offspring may be attributed to a shared environment or to shared genetic factors with the mother. If that interpretation is correct, all children of a mother who has experienced one or more hypertensive pregnancies may be at increased lifetime risk of cardiovascular disease.

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Novelty and significance:

What is new:

- Cardiovascular risk factors in adults born by a mother with hypertension in pregnancy may be attributed to a shared environment or to shared genetic factors with the mother

What is relevant:

- All children of a mother who has experienced one or more hypertensive pregnancies may be at increased lifetime risk of cardiovascular disease

Summary:

Offspring born after maternal hypertension in pregnancy have a more adverse cardiovascular risk profile in young adulthood than offspring of normotensive pregnancies. Their siblings, born after a normotensive pregnancy, have a similar risk profile, suggesting that shared genetics/lifestyle may account for the added risk.

Table 1. Maternal and offspring characteristics according to hypertension status of the mother's pregnancy, given as mean (SD) unless otherwise noted.

Hypertension status	No HT*	Any HT	Gestational HT	Term PE†	Preterm PE
N (participants)	15 072	706	336	343	27
N (observations)	18 732	864	411	422	31
Maternal characteristics					
Age at delivery, years	25.7 (5.4)	26.7 (6.0)	27.5 (6.3)	26.0 (5.7)	25.4 (5.2)
Parity at delivery, %					
0	37.4	49.6	40.8	57.1	63.0
1	33.1	24.4	26.8	22.4	18.5
≥2	29.6	26.1	32.4	20.4	18.5
Body mass index, kg/m^2 ‡	24.1 (3.9)	26.6 (5.2)	26.9 (5.2)	26.4 (5.2)	25.4 (4.9)
Weight, kg[c]	65.7 (11.2)	72.9 (15.0)	73.9 (14.7)	72.3 (15.4)	68.3 (13.5)
Current daily smokers, %[c]	39.3	22.7	23.6	22.9	9.1
Education, %[c]					
≤9 years	51.4	50.3	54.0	47.5	36.4
10-12 years	36.2	36.9	35.4	37.3	50.0
>12 years	12.3	12.9	10.5	15.1	13.6
Offspring characteristics					
Male attendants, %	44.3	43.3	41.7	45.2	40.7
Female attendants, %	55.7	56.7	58.3	54.8	59.3
Gestational age, %					
<34 weeks	0.9	1.2	0.3	0.0	25.9
34-36 weeks	3.0	4.0	2.1	0.0	74.1
≥37 weeks	96.1	94.8	97.5	100.0	0.0
Infant birth length, cm	50.8 (2.2)	50.6 (2.8)	51.1 (2.3)	50.4 (2.6)	44.9 (3.8)
Birth weight, grams	3535 (529)	3432 (669)	3573 (558)	3399 (651)	2094 (629)
Head circumference at birth, cm	35.2 (1.5)	35.1 (1.8)	35.2 (1.6)	35.2 (1.6)	31.3 (3.4)
Age at follow-up, years	28.9 (6.2)	28.4 (6.1)	28.0 (5.8)	28.8(6.3)	29.1 (6.8)
Current daily smokers , %[c]	21.7	20.9	21.1	20.8	20.0

*HT= hypertension
†PE = preeclampsia
‡As recorded in the Nord-Trøndelag Health (HUNT) Study. Maternal characteristics were collected from the earliest HUNT examination in which the mother participated

Table 2. Cardiovascular risk factors in adult offspring by exposure to any maternal hypertensive disorder, gestational hypertension or preeclampsia, shown as mean differences (95% CI*) compared to offspring born after normotensive pregnancy (adjusted for age, sex, maternal parity and HUNT survey). N=15 778 participants with 19 596 observations†.

	Mean value (95% CI†)	Mean differences (95% CI) from the No HT‡ group			
Hypertension status *in utero*	No HT	Any HT	Gestational HT	Term PE§	Pre-term PE
N (participants)	15 072	706	336	343	27
N (observations)	18 732	864	411	422	31
Systolic blood pressure, mmHg	123.0 (122.8, 123.2)	2.7 (1.8, 3.5)	3.3 (1.9, 4.6)	2.3 (1.1, 3.5)	-0.6 (-4.3, 3.1)
Diastolic blood pressure, mmHg	69.3 (69.1, 69.4)	1.5 (0.9, 2.1)	2.1 (1.2, 3.0)	1.0 (0.1, 1.9)	0.0 (-2.1, 2.2)
Body mass index, kg/m^2	25.63 (25.56, 25.70)	0.66 (0.31, 1.01)	0.48 (0.00, 0.97)	0.93 (0.41, 1.44)	-0.78 (-2.05, 0.49)
Waist circumference, cm	85.81 (85.63, 85.99)	1.49 (0.65, 2.33)	1.25 (0.10, 2.41)	1.86 (0.63, 3.09)	-0.50 (-4.74, 3.75)
Waist-hip ratio	0.840 (0.839, 0.841)	0.003 (-0.002, 0.008)	0.000 (-0.006, 0.006)	0.006 (-0.001, 0.013)	0.007 (-0.018, 0.031)
HDL cholesterol‖, mmol/L	1.33 (1.32, 1.33)	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.01)	-0.01 (-0.05, 0.02)	-0.02 (-0.16, 0.12)
Non-HDL cholesterol, mmol/L	3.56 (3.54, 3.57)	0.09 (0.01, 0.16)	0.03 (-0.07, 0.13)	0.14 (0.03, 0.25)	0.14 (-0.17, 0.44)
Triglycerides, mmol/L	1.21 (1.20, 1.22)	0.05 (0.00, 0.11)	-0.03 (-0.09, 0.05)	0.13 (0.06, 0.21)	0.17 (-0.06, 0.43)
C-reactive protein, mg/L	1.10 (1.06, 1.14)	0.05 (-0.06, 0.18)	0.08 (-0.09, 0.28)	0.01 (-0.14, 0.18)	0.38 (-0.18, 1.28)

*CI = confidence interval

†Number of observations for the different variables: Systolic and diastolic blood pressure n=19 480, Body mass index n=19 526, Waist circumference n=19 234, Waist-hip ratio n=19 232, HDL and non-HDL cholesterol n=19 159, Triglycerides n=19 361, C-reactive protein n=12 229.

‡HT= hypertension

§PE = preeclampsia

‖HDL = high density lipoprotein

Table 3. Cardiovascular risk factors in adult offspring by exposure to any maternal hypertensive disorder, gestational hypertension or preeclampsia, shown as mean differences (95 % CI*) compared to offspring born after a normotensive pregnancy. The analysis includes 13 127 participants (with 16 584 observations) with available data on maternal cardiovascular risk factors in the HUNT Study.

	Model 1[†] (CI)	Model 2[‡] (CI)	Model 3[§] (CI)	Model 4[‖] (CI)
Systolic blood pressure, mmHg	2.6 (1.6, 3.5)	2.7 (1.7, 3.6)	2.2 (1.2, 3.1)	1.0 (0.1,2.0)
Diastolic blood pressure, mmHg	1.5 (0.7, 2.2)	1.5 (0.8, 2.2)	1.3 (0.6, 2.0)	0.5 (-0.2, 1.2)
Body mass index, kg/m^2	0.56 (0.18, 0.93)	0.70 (0.33, 1.08)	0.06 (-0.31, 0.43)	0.11 (-0.26, 0.48)
Waist circumference, cm	1.24 (0.35, 2.14)	1.57 (0.67, 2.47)	0.13 (-0.75, 1.02)	0.13 (-0.76, 1.02)
Waist-hip ratio	0.002 (-0.003, 0.007)	0.004 (-0.001, 0.009)	-0.001 (-0.006, 0.004)	-0.002 (-0.006, 0.003)
HDL cholesterol[¶], mmol/L	-0.02 (-0.04, 0.01)	-0.02 (-0.05, 0.01)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)
Non-HDL cholesterol, mmol/L	0.08 (0.00, 0.16)	0.11 (0.03, 0.19)	0.06 (-0.02, 0.14)	0.05 (-0.03, 0.13)
Triglycerides, mmol/L	0.05 (0.00, 0.11)	0.06 (0.01, 0.12)	0.04 (-0.01, 0.10)	0.03 (-0.03, 0.08)
C-reactive protein, mg/L	0.08 (-0.05, 0.22)	0.10 (-0.03, 0.25)	0.03 (-0.10, 0.16)	0.03 (-0.10, 0.17)

[*] CI = confidence interval
[†] Model 1: adjusted for age, sex, maternal parity and HUNT survey
[‡] Model 2: adjusted for age, sex, maternal parity, HUNT survey, maternal smoking and maternal education
[§] Model 3: adjusted for age, sex, maternal parity, HUNT survey, maternal smoking, maternal education and maternal BMI
[‖] Model 4: adjusted for age, sex, maternal parity, HUNT survey, maternal smoking, maternal education, maternal BMI, maternal systolic blood pressure and maternal diastolic blood pressure
[¶]HDL = high density lipoprotein

Table 4. Characteristics of the 472 offspring included in the sibling analysis, by hypertension status of the mother's pregnancy, given as mean (SD) unless otherwise noted.

Hypertension status	No hypertension (n = 254)	Any hypertension (n = 218)
Male attendants, %	49.6	42.2
Female attendants, %	50.4	57.8
Maternal age at delivery, years	25.1 (4.7)	25.9 (5.3)
Maternal parity at delivery, %		
0	25.6	45.9
1	48.0	24.8
≥2	26.4	29.4
Gestational age, %		
<34 weeks	1.3	1.4
34-36 weeks	1.7	1.9
≥37 weeks	97.1	96.7
Infant birth length, cm	51.1 (2.1)	50.8 (2.4)
Birth weight, grams	3605 (544)	3498 (651)
Head circumference at birth, cm	35.2 (1.3)	35.4 (1.7)
Age at follow-up, years	29.1 (6.2)	29.8 (6.0)
Current daily smokers at follow-up , %	19.4	19.9

Table 5. Sibling analysis: Mean differences in cardiovascular risk factors in adult offspring exposed to maternal hypertensive disorder compared to their unexposed siblings, adjusted for age, sex, maternal parity and HUNT survey. The analysis includes 210 sibling groups where at least one sibling was born after hypertensive pregnancy and at least one sibling was born after normotensive pregnancy (total n = 472).

Risk factors	N (observations)	Mean differences (95% CI*) between siblings exposed to maternal hypertensive disorder of pregnancy and their siblings born after normotensive pregnancy
Systolic blood pressure, mmHg	470	-0.7 (-3.0, 1.5)
Diastolic blood pressure, mmHg	470	-0.8 (-2.6, 0.9)
Body mass index, kg/m^2	470	0.01 (-0.74, 0.75)
Waist circumference, cm	463	-0.09 (-2.09, 1.91)
Waist-hip ratio	463	-0.001 (-0.013, 0.010)
HDL cholesterol†, mmol/L	459	-0.02 (-0.07, 0.04)
Non-HDL cholesterol, mmol/L	459	0.11 (-0.07, 0.29)
Triglycerides, mmol/L	461	-0.01 (-0.13, 0.13)
C-reactive protein, mg/L	267	-0.10 (-0.41, 0.34)

*CI = confidence interval
†HDL = high density lipoprotein

Table 6. Mean differences (95% CI*) in cardiovascular risk factors among offspring born after hypertensive pregnancy (n=706), and offspring born after normotensive pregnancy but whose mother had at least one hypertensive pregnancy (n=653), compared to offspring of women with no record of hypertensive pregnancy (n=14 419) (adjusted for age, sex, maternal parity and HUNT survey).

Risk factors	Born after hypertensive pregnancy	Born after normotensive pregnancy, but with a mother who had at least one hypertensive pregnancy
Systolic blood pressure, mmHg	2.6 (1.7, 3.5)	2.8 (1.9, 3.8)
Diastolic blood pressure, mmHg	1.5 (0.9, 2.2)	1.8 (1.0, 2.5)
Body mass index, kg/m^2	0.52 (0.18, 0.86)	0.49 (0.13, 0.85)
Waist circumference, cm	1.15 (0.26, 2.04)	1.44 (0.50, 2.38)
Waist-hip ratio	0.002 (-0.003, 0.007)	0.006 (0.001, 0.011)
HDL cholesterol† mmol/L	-0.01 (-0.04, 0.01)	-0.01 (-0.02, 0.03)
Non-HDL cholesterol, mmol/L	0.07 (0.00, 0.14)	-0.01 (-0.08, 0.07)
Triglycerides, mmol/L	0.03 (-0.02, 0.08)	0.01 (-0.04, 0.07)
C-reactive protein, mg/L	0.05 (-0.06, 0.18)	0.11 (-0.02, 0.26)

*CI = confidence interval
†HDL = high density lipoprotein