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The HUNT study in Norway

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Thesis for the Degree of
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En studie av sammenhengen mellom svangerskap og hjerte- og karsykdom hos kvinner

Bakgrunn: Hjerte- og karsykdom er den vanligste dødsårsaken hos kvinner. Det er forskjeller i utviklingen av hjerte- og karsykdom mellom kvinner og menn. Mange studier tyder på kunnskap om kvinners reproduktive helse kan fortelle oss om deres risiko for hjerte- og karsykdom senere i livet, men vi mangler fortsatt kunnskap om langtidseffektene av svangerskap på tradisjonelle risikofaktorer for hjerte- og karsykdom. Flere studier viser også at kvinner som har hatt forhøyet blodtrykk i svangerskapet eller svangerskapsforgiftning har høyere nivå av tradisjonelle risikofaktorer for hjerte- og karsykdom og økt risiko for å utvikle hjerte- og karsykdom. Det er imidlertid uklart når i livet den ugunstige hjerte- og karrisikoprofilen hos disse kvinnene oppstår og hvordan den utvikler seg gjennom livet. I tillegg er det lite forskning som dokumenterer hvor stor betydning tradisjonelle risikofaktorer for hjerte- og karsykdom har for utvikling av hjerte- og karsykdom hos kvinner som har hatt forhøyet blodtrykk i svangerskapet eller svangerskapsforgiftning.

Metode: Vi har brukt data fra Medisinsk fødselsregister koblet med informasjon fra Helseundersøkelsen i Nord-Trøndelag (HUNT) for å undersøke sammenhengen mellom svangerskap og blodtrykk og mellom forhøyet blodtrykk i svangerskapet, svangerskapsforgiftning og risikofaktorer for hjerte- og karsykdom. I tillegg har vi koblet til data fra Helse Nord-Trøndelag og Dødsårsakregisteret for å studere sammenhengen mellom forhøyet blodtrykk i svangerskapet, svangerskapsforgiftning og hjerte- og karsykdom og hvilken rolle tradisjonelle risikofaktorer for hjerte- og karsykdom spiller for denne sammenhengen.

Artikkel 1: Vi studerte utviklingen av blodtrykk hos 21 513 kvinner med barn og 1925 kvinner uten barn fra 20 til 60 år basert på 1-3 blodtrykksmålinger per kvinne. Før første fødsel hadde kvinner som senere fikk barn samme blodtrykksnivå som kvinner som ikke fikk barn. Hos kvinner som fikk barn gikk det systoliske blodtrykket ned med ≈3 mmHg og det diastoliske blodtrykket gikk ned med ≈2 mmHg fra før til etter første svangerskap. Blodtrykket gikk også noe ned ved senere svangerskap. Blodtrykksnedgangen hos kvinner med barn medførte at de hadde lavere blodtrykk enn kvinner uten barn til de var minst 50 år. Blodtrykksnedgangen hos kvinner med barn kan være med på å forklare forholdet mellom paritet og risiko for hjerte- og karsykdom, samt hvorfor risikoen for svangerskapsforgiftning er høyest i første svangerskap.

Artikkel 2: Vi kartla forløpet av risikofaktorer for hjerte- og karsykdom fra 20 til 60 år hos 22 308 kvinner som hadde normalt blodtrykk i første svangerskap, 1902 kvinner som hadde svangerskapsforgiftning og 478 kvinner med forhøyet blodtrykk i første svangerskap. Allerede før første svangerskap hadde kvinner med svangerskapsforgiftning høyere nivå av fedme, blodtrykk, blodsukker, hvilepuls og lipider sammenlignet med kvinner med normalt blodtrykk i første svangerskap. Etter første svangerskap utviklet risikofaktorene for hjerte- og karsykdom seg parallelt hos kvinner med og uten svangerskapsforgiftning i første svangerskap. For eksempel utviklet høyt blodtrykk seg i gjennomsnitt 10 år tidligere hos kvinner som hadde hatt svangerskapsforgiftning i første svangerskap. Vi fant ingen vesentlige forskjeller mellom hjerte- og karrisikoforløp hos kvinner med svangerskapsforgiftning og kvinner med forhøyet blodtrykk i svangerskapet.

Artikkel 3: Kvinner som hadde hatt svangerskapsforgiftning eller forhøyet blodtrykk i svangerskapet hadde ≈60% økt risiko for hjerte- og karsykdom i aldersgruppen 40-70 år sammenlignet med kvinner som ikke hadde hatt slike svangerskapskomplikasjoner. Høyere nivåer av kroppsmasseindex og blodtrykk forklarte ≈¾ av denne økte risikoen. Våre resultater tyder på at behandling av høyt blodtrykk og fedme vil kunne redusere den økte risikoen for hjerte- og karsykdom blant kvinner som har hatt svangerskapsforgiftning eller forhøyet blodtrykk i svangerskapet.

Kandidat: Eirin Beate Haug

Institutt: Institutt for Samfunnsmedisin og Sykepleie

Veiledere: Bjørn Olav Åsvold, Julie Horn og Pål Richard Romundstad

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Ovennevnte avhandling er funnet verdig til å forsvares offentlig for graden ph.d. i samfunnsmedisin.

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Torsdag 20. desember 2018, kl. 12.15.

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None of this research would have been possible without the Nord-Trøndelag Health Study and its participants, which since the 1980s has provided numerous researchers with high quality population data ready to use for testing a multitude of scientific hypotheses. I am as any researcher working in service to the people who form the source population of such studies and I am grateful for the organized effort by its founders and the thousands of people who have participated.

And last, but not least, I would like to express sincere gratitude to my mother who from an early age laid the foundation for my later academic achievements. It was her love for mathematics and natural science that combined with a very practical and dedicated approach to learning both motivated and disciplined me to pursue an education within science. Nothing was impossible, even for a working class girl if I just worked hard enough. I learned a lot is possible with dedication and hard work, but I also learned that class and gender are still relevant political concepts that affect people's lives in our modern world. We have made progress though, and I am thankful for having stood on the shoulders of the women who came before me and cleared the way.

Eirin Beate Haug

August 2018

List of figures

List of abbreviations

BMI = body mass index

CI = confidence interval

CKD-EPI = Chronic Kidney Disease Epidemiology consortium

CRP = C-reactive protein

CVD = cardiovascular disease

DBP = diastolic blood pressure

DNA = deoxyribonucleic acid

eGFR = estimated glomerular filtration rate

EOP = early onset preeclampsia

ERT = estrogen replacement therapy

FLT1= fms-like tyrosine kinase 1

HDLc = high density lipoprotein cholesterol

HDP = hypertensive disorders of pregnancy

HELLP syndrome = **H**emolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets syndrome

HUNT = Nord-Trøndelag health study

HR = hazard ratio

ICD = international classifications of diseases

IPG-P = P-type inositol phosphoglycans

LOP = late onset preeclampsia

MBRN = Medical Birth Registry of Norway

PCOS = polycystic ovary syndrome

PIGF = placental derived growth factor

PPV = positive predictive value

SBP = systolic blood pressure

sEng = soluble endoglin

sFlt-1 = soluble fms-like tyrosine kinase 1

List of papers

This thesis is based on the three papers listed below. Further reference to them will be made by their Roman numerals.

Paper I

Haug EB, Horn J, Markovitz AR, Fraser A, Macdonald-Wallis C, Tilling K, Romundstad PR, Rich-Edwards JW, Åsvold BO. The impact of parity on life course blood pressure trajectories: the HUNT study in Norway. *European Journal of Epidemiology*. 2018;33(8):751-761

Paper II

Haug EB, Horn J, Markovitz AR, Fraser A, Vatten L, Macdonald-Wallis C, Tilling K, Romundstad PR, Rich-Edwards JW, Åsvold BO. Life course trajectories of cardiovascular risk factors in women with and without hypertensive disorders in first pregnancy: The HUNT study in Norway. *Journal of the American Heart Association.* 2018;7(15).

Paper III

Haug EB, Horn J, Markovitz AR, Fraser A, Vatten L, Klykken B, Dalen H, C, Romundstad PR, Rich-Edwards JW, Åsvold BO. Cardiovascular disease after hypertensive pregnancy disorders: the role of conventional cardiovascular risk factors. The HUNT study in Norway. *Submitted manuscript*.

1. Introduction

Cardiovascular disease (CVD) is the largest cause of death for both men and women, but has traditionally been thought of as a male disease[1,2]. As a result, CVD in women has traditionally, received less attention than it deserves impairing both research and preventive efforts aimed at reducing CVD in women[3,4]. Although progress has been made in recent years to increase the awareness and treatment of CVD in women[3,5], identifying women at increased risk of CVD and implementing effective preventive programs that seek to decrease CVD is still needed. Women's reproductive health has been described[6] as a sentinel of later chronic disease, including cancer and CVD. For example, the risk of CVD varies by parity[7,8], but the reason behind this remains unclear and longitudinal studies examining the long term effect of pregnancy on cardiovascular risk factors may help us answer this question. Previous work[9–14] has also highlighted that women who have a history of hypertensive pregnancy complications are at increased risk of CVD and have higher levels of cardiovascular risk factors[7,15–25] compared to women who had normotensive pregnancies. The substantial cardiometabolic challenges posed by pregnancy[26–28] may function as a window into a woman's later cardiovascular risk. These observations inspired Sattar and Greer[29] to propose the concept of pregnancy as a stress test of cardiometabolic health in women and as an opportunity for early identification of women at increased risk of CVD. However, it remains unclear when in life the adverse cardiovascular risk factor profile in women with a history of hypertensive pregnancy complications is established, and how it evolves during adults life compared to in women without such complications. So far, there is limited evidence[30] for the role of cardiovascular risk factors in explaining the excess CVD risk in women with a history of HDP, and further investigation using a formal mediation analysis approach is needed. These results will help us understand what factors should be targeted to achieve effective CVD prevention in women with history of HDP.

2. Background

2.1 Pregnancy and women's health

2.1.1 Global perspective

Pregnancy is one of the defining features of women and poses large socioeconomic and physiological challenges that can have significant consequences for women's health. In a global perspective, childbirth is associated with a maternal mortality rate of 216 deaths per 100 000 live births, which ranges from 545 deaths in Sub-Saharan Africa to 12 deaths per 100 000 live births in the developed world[31]. Pregnancy has been, and still is for many women, comparable to or more risky than base jumping, which has a fatality rate of 43 per 100 000 jumps[32]. Although 99% of all maternal deaths occur in the developing world, there has been a substantial worldwide decline in maternal mortality of 44% from 1990 to 2015 due to improved access to health care for women in developing countries[1]. There are several causes of maternal mortality with the most common globally being hemorrhage accounting for 27% of maternal deaths and the second most common being hypertensive disorder of pregnancy (HDP), which is responsible for 14% of maternal deaths[33]. Other causes of maternal mortality include sepsis (11%), abortion complications (8%), embolism (3%) and underlying medical conditions (15%) which together account for another 37% of maternal deaths worldwide[31]. There are regional differences in the distribution of causes of maternal mortality where hemorrhage and sepsis are more common in developing countries and embolism is more common in developed regions[33]. Although the worst maternal outcome of birth and pregnancy complications is death, a high and less well-characterized burden of unknown size of maternal acute and chronic morbidity[2] can also follow such complications, potentially leading to infertility, chronic pain and disability[4]. Hypertensive pregnancy complications in the form of preeclampsia or gestational hypertension, the main topic of this thesis, occur in 5-10% of all pregnancies worldwide[35]. If preeclampsia is left untreated, it may progress to eclampsia, a potentially life threatening condition with seizures and organ failures[36]. In developing countries where access to health care is poor, the consequences of preeclampsia are much worse than in the developed world where diagnosis and treatment is usually initiated at earlier stages of the disease[36].

2.1.2 Norwegian perspective

Norway consistently ranks among the top countries on the United Nations Development index[37], offers its citizens good and free access to the public health care and in consequence has a low maternal mortality rate of 8.7 per 100 000 live births[38]. HDP are the most common causes of maternal death in Norway making up 23% of all deaths with thromboembolism coming second accounting for 15% of maternal deaths[38]. Preeclampsia and gestational hypertension complicate 3%[39] and 2%[40] of all pregnancies in Norway, respectively. A slightly increasing trend in the prevalence of preeclampsia from 2% at the inception of the Medical Birth Registry of Norway (MBRN) in 1967 to a peak of 4% in 1999 has been observed in Norway[39]. Possible explanations include changes in risk factors distributions and increasing rates of case ascertainment in addition to changes in notification forms[39].

2.2 Hypertensive disorders of pregnancy

2.2.1 Classification

In Norway, the diagnosis of the HDP follows internationally recommended criteria given by the American College of Obstetricians and Gynecologists[35], which define HDP as follows:

Preeclampsia: *De novo* hypertension with systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg occurring after 20 weeks gestation, accompanied by new onset proteinuria defined as ≥300 mg per 24 hour urine collection or ≥1 on the dipstick test. In 1998, the Norwegian Association for Obstetrics and Gynecology changed the criteria for preeclampsia from one to two separate measurements of hypertension with proteinuria in accordance with international standards[41]. Additionally, in 2013, the American College of Obstetricians and Gynecologists, recommended that the definition of preeclampsia also included cases without evidence of proteinuria, but that had evidence of end-organ dysfunction. This later amendment to the classification of preeclampsia was not operational in the time-period studied in this thesis.

Grade: Preeclampsia can be divided into early onset (EOP: <34 weeks gestation) and late onset (LOP: ≥34 weeks gestation), and by severity (Mild: blood pressure>140 mmHg systolic and/or 90 mmHg diastolic measured at least 3 times 4-6 hours apart, and proteinuria ≥300 mg per 24 hours. Severe: as

for mild preeclampsia, but in addition either blood pressure ≥160 mmHg systolic and/or 110 mmHg diastolic, and/or proteinuria 3 to 5 g/day, and/or end-organ dysfunction), where early and late onset may roughly separate between severe and mild preeclampsia[42].

***H**emolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets (HELLP) syndrome*: A condition associated with severe preeclampsia that is characterized by hemolysis (rupturing of red blood cells), elevated liver enzymes and low platelet count[43].

Eclampsia: Convulsions occurring in women with severe preeclampsia.

Gestational hypertension: *De novo* hypertension with SBP ≥140 mmHg or DBP ≥90 mmHg occurring after 20 weeks gestation without proteinuria.

Chronic (preexisting) hypertension: SBP ≥140 mmHg or DBP ≥90 mmHg, which either predates the pregnancy or occurs before 20 weeks gestation.

Superimposed preeclampsia: Preeclampsia superimposed on maternal chronic hypertension that preceded the pregnancy.

In this thesis, only preeclampsia and gestational hypertension have been included as HDP even though, technically, chronic hypertension and preeclampsia superimposed are also included in the definition of HDP by the American College of Obstetricians and Gynecologists [35]. The reason for this was in order to study cases of hypertensive disorders that were likely related to pathological processes of the pregnancy itself, as opposed to those potentially more related to a pre-existing hypertensive state, and to inform clinical prevention programs targeting women who are not already under clinical supervision due to hypertension.

2.2.2 Clinical manifestation

Mild cases of preeclampsia may not show any other symptoms or signs than high blood pressure readings and positive tests for proteinuria[44]. Women with more severe preeclampsia may start to feel unwell experiencing headaches, edema, upper abdominal pain and vision disturbances[44], which if untreated could result in eclampsia (seizures), elevated liver enzymes, low platelets, hemolysis, coagulation malfunction and organ failures[44,45]. Treatment depends on severity and gestational age and includes close monitoring of blood pressure, urinary protein and platelet count. The main treatment for preeclampsia is delivery, but treatment may include antihypertensive medication to counteract high blood pressure or magnesium sulfate to prevent seizures[35]. Preeclampsia is associated with preterm birth, fetal intrauterine growth restriction, especially the early onset version, and perinatal death[46]. Both maternal and perinatal adverse outcomes correlate with preeclampsia severity[47]. Women initially displaying signs of non-proteinuric hypertension and who receive the diagnosis gestational hypertension are monitored for signs of preeclampsia, as the risk of progressing from gestational hypertension to preeclampsia is 15-46%[48,49]. If severe (SBP ≥160mmHg and/or DBP ≥110mmHg), gestational hypertension may be treated with antihypertensive medication.

2.2.3 History of preeclampsia

Observations of pregnant women displaying signs of preeclampsia in the form of eclampsia (convulsions) can be dated back to as early as Egyptian medical literature 2200 BC[50]. In ancient Greece 440 B.C. aphorism XXXI 507 in the Coan Prognosis stated that "a headache accompanied by heaviness and convulsions during pregnancy is considered bad"[51]. At this time in Greece, the understanding of the condition that caused convulsions in pregnant women was constrained by the theories of the four humors that dominated Greek medicine at the time. Most health problems occurring in women were seen as being caused by a wandering womb[52] and an excess in bodily fluids, leaving women suffering from a pregnancy complicated by preeclampsia with little constructive advice or help to manage her situation[51]. Development and progression in the medical sciences did not pick up speed until the European renaissance when detailed studies of anatomy were conducted providing researchers with detailed descriptions of female physiology. At the beginning of the 17th

century, the first written appearance of the word eclampsia, as a name for the convulsive disease of pregnancy, was mentioned in Varandaeus' treatise on gynecology[51]. Later in the 17th century a Frenchman named Francois Mauriceau established the specialty of obstetrics and, for the first time in history, initiated a systematic observation and description of women with eclampsia. Mauriceau was probably, due to his systematic approach, the first to observe that primigravidas were at greater risk of eclampsia than women who had been pregnant before[51]. In the 18th century the French physician Francois Boissier de Sauvages classified eclampsia as a convulsive condition that was distinctly different from epilepsy by only acutely occurring in pregnancy. Throughout the 18th and early 19th century, further speculation into the causes of eclampsia continued, but progress was slow and the recommended treatments remained misguided and ineffective. In 1843 John Lever discovered albumin in the urine of eclamptic women and throughout the second half of the 19th century the first observations and mention of symptoms preceding eclampsia such as hypertension, headache, temporary loss of vision, stomach pain and edema was made spurring the recognition of pre-eclampsia as a distinct state associated with eclampsia[51].

2.2.5 Pathophysiology

2.2.5.1 Preeclampsia

Abnormal placentation

In 1967 Brosens et al.[53] observed that uterine maternal spiral arteries undergo extensive remodeling during pregnancy to allow for sufficient supply of blood to the growing fetus. A few years later Brosens et al[54] also discovered that spiral arteries failed to convert in preeclamptic pregnancies resulting in an insufficient blood supply to the fetus. Figure 1 illustrates the invasion of fetal cytotrophoblastic cells into the maternal myometrium and spiral arteries in normal and preeclamptic pregnancies. In difference to other mammals, the human placentation process involves a much deeper trophoblastic invasion, a finding which is thought to be due to the comparably large nutrient demands of human brain development[55]. In most mammals trophoblastic invasion lasts 1-2 weeks post conception, whereas in humans it extends for up to 16 weeks gestation. Based on this observation, Pijnenborg et al.[56] proposed the concept of "double wave" implantation in humans where in

preeclampsia the second deeper delayed wave that occurs at the end of the first trimester fails and implantation remains shallow and insufficient for the rest of the pregnancy. Normally, as part of this deeper invasion process, fetal cytotrophoblast cells invade the maternal spiral arteries and convert themselves into endothelial cells that line the newly formed low resistance spiral arteries[57], but they fail to do so in preeclamptic pregnancies[58]. It has been observed[59], in vitro, that low oxygen tension can prevent cytotrophoblasts from invading and maturing into endothelial cells, a finding which suggests that fetal and uteroplacental hypoxia is involved in the pathogenesis of preeclampsia. However, there have also been observations of reduced placental perfusion in pregnancies complicated by growth restricted or preterm birth[60,61] that were unassociated with preeclampsia. Since placental hypoxia has not exclusively been observed together with preeclampsia, speculation arose that an additional maternal predisposition to preeclampsia was necessary for manifestation of the disease.

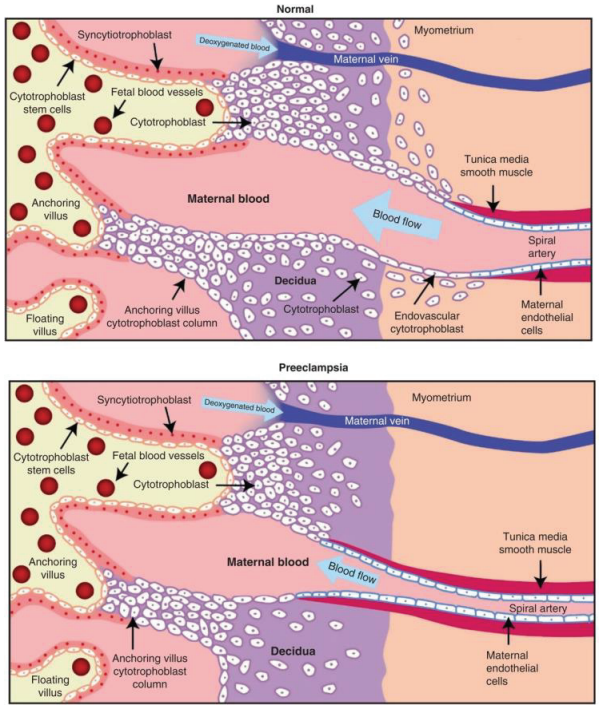

Figure 1. A comparison of normal fetal cytotrophoblastic cell invasion into the maternal myometrium (top) and shallow cytotrophoblastic cell invasion in preeclampsia (bottom). Maternal spiral arteries fail to convert adequately in preeclamptic pregnancies leading to insufficient blood flow to the fetus. Figure is taken from Lam et al.[29] and used with permission.

Endothelial dysfunction

Throughout the 20th century Mayer (1924)[62], Bell (1932)[63] and Spargo et al. (1976)[64] observed that the integrity of the renal glomerular endothelial fenestrae was interrupted and that the cytoplasm of endothelial cells was swollen in women with preeclampsia, a condition Spargo et al.[64] named renal glomerular capillary endotheliosis. Further vascular injury in the form of capillary endotheliosis in women with preeclampsia was also observed in the placenta[65], liver[66] and in the form of systemically circulating endothelial cells[67]. The endothelium controls vascular tone and in preeclampsia, vasoconstriction occurs as levels of the vasodilator prostacyclin decreases and levels of the vasoconstrictor thromboxane increases[68] leading to hypertension. In 1991, Roberts and Taylor et al.[69] proposed the hypothesis that a poorly perfused placenta released vasoactive factors into the maternal circulation causing maternal endothelial dysfunction and leading to hypertension. They later provided support for this hypothesis when they showed that serum from preeclamptic women was cytotoxic to endothelial cells[70]. Further corroboration came from an in vitro study that incubated vessels from normal pregnant women together with plasma from women with preeclampsia, showing a significant reduction in endothelium-dependent relaxation of the vessels [71]. Wimalasundera et al.[72] showed that myometrial and subcutaneous resistance arteries from women with preeclampsia displayed a diminished response to acetylcholine. In these experiments[72], the resistance arteries failed to produce the expected fall in intracellular calcium concentration upon exposure, a finding that could explain the weakening of endothelium-dependent relaxation in women with preeclampsia. The same authors also reported[73] that in response to a vasocontractile trigger, the rate of decline of intracellular calcium concentrations in myometrial and subcutaneous resistance arteries of preeclamptic women was slower, delaying relaxation compared to in normotensive pregnant women. The factors affecting endothelial function in preeclampsia may in fact, as hypothesized, come from the placenta in the form of trophoblastic debris as was shown by a study[74] exposing endothelial cells to trophoblastic debris from molar pregnancies that exhibited symptoms of preeclampsia.

Normal endothelial function in adults is under influence of vascular endothelial growth factors, which promote vasculogenesis (the formation of new blood vessels in embryonic life), angiogenesis (branching of blood vessels to form new vessels) and survival and proliferation of

endothelial cells[75–78]. Vascular endothelial growth factor induces vasodilation in a dose-dependent manner[79] and antagonizing it with anti-angiogenic factors that bind and inactivate vascular endothelial growth factors as part of cancer therapy, induces endotheliosis, hypertension and proteinuria[80,81], the hallmarks of preeclampsia. Elevated levels of the anti-angiogenic protein soluble fms-like tyrosine kinase (sFlt-1) that correlate with disease severity have been observed[82–88] in women with preeclampsia, suggesting it plays a crucial role in the development of the condition. Pregnant rats administered sFlt-1 develop hypertension and proteinuria, but fail to show the signs of liver dysfunction and cerebral changes that are present in women with severe preeclampsia[82]. However, when sFlt-1 was administered together with another anti-angiogenic factor, soluble endoglin (sEng), which also has been found to be elevated in preeclamptic women, all the symptoms of severe preeclampsia occurred in the pregnant rats[89]. In vitro studies[90,91] give evidence that a hypoxic environment triggers the release of sFlt-1 and sEng, suggesting that shallow trophoblast invasion and faulty maternal spiral artery conversion causes the release of factors that disrupt the endothelium leading to preeclampsia. Animal studies[92,93] confirm that uteroplacental ischemia introduces sFlt-1 into the maternal circulation accompanied by symptoms of preeclampsia.

The angiogenic placental derived growth factor (PIGF), which is similar to other vascular endothelial growth factors, is expressed in high amounts in the placenta during pregnancy, but is reduced in women with preeclampsia[86,94]. The ratio of sFlt-1 to PIGF is a better predictor of preeclampsia than either measure alone, a finding indicating that it is the balance between angiogenic and anti-angiogenic factors that is important for the development of preeclampsia[86,95,96]. Delivery of the placenta resolves the symptoms of preeclampsia[50], and consistent with sFlt-1 being one of the causative agents, serum sFlt-1 levels fall significantly after removal of the placenta[97].

Recently, it has also been observed that P-type inositol phosphoglycans (IPG-P) are elevated in the serum of women with preeclampsia[98,99]. IPG-P is a transmembranous second messenger involved in carbohydrate metabolism that due to its hydrophobic nature coagulates when erroneously released into the blood stream mimicking an endotoxin[100]. Circulating endotoxin is capable of causing inflammation, endothelial dysfunction and preeclampsia[101].

Renin-angiontensin aldosterone pathway

In normal pregnancy renin, angiotensin and aldosterone are elevated, but their vasoconstrictive effects are compensated by a reduced sensitivity to angiotensin II[102], and vascular resistance is normally lower than before pregnancy[103]. Women with preeclampsia fail to reduce their sensitivity to angiotensin[102] and may instead develop agonistic autoantibodies to the angiotensin receptor[104], which would increase their sensitivity to angiotensin. Injecting these agonistic angiotensin receptor autoantibodies into pregnant mice produces hypertension, proteinuria, endothelial damage and elevated levels of sFlt-1 and sEng[105], providing evidence that they could be involved in causing preeclampsia. These agonistic angiotensin autoantibodies also remain elevated in women who had preeclampsia after the pregnancy[106], suggesting they could be involved in influencing long-term cardiovascular health in women with a history of preeclampsia.

Immunological model

The comparably deep trophoblastic invasion of fetal cells in humans poses immunological challenges to the mother who during pregnancy has to down-regulate her natural defensive mechanisms that otherwise would have rejected cells of a different genetic origin than herself. As a suggested evolutionary compensatory mechanism, humans have the lowest fertility rate of all mammals allowing for extended pre-pregnancy maternal exposure to paternal antigens, which in theory could facilitate immune-adaptation and tolerance[107]. Consistent with this idea is the finding that women infected with the human immune deficiency virus have lower rates of preeclampsia that are brought back up to normal levels with the administration of anti-retroviral therapy[108]. In support of this, epidemiological studies have also showed that the risk of preeclampsia is higher in first pregnancies[109]. Additionally, length of sexual cohabituation is inversely proportional to the risk of preeclampsia in both primi- and multigravidae women[110], while barrier contraceptives increase the risk[111]. Studies also found that change of partner increased the risk of preeclampsia in multigravidae women[112,113], and that the protective effects of abortions disappeared after partner change[114]. Such observations has led to the "primipaternity model" or "immunological model" [115] which describes preeclampsia as an immune maladaptation disorder that occurs due to insufficient exposure to paternal antigens. However,

adjusting for interpregnancy interval removed the increased risk of preeclampsia that was associated with change of partner[116], suggesting changing partners in reality is a proxy for increasing time since previous pregnancy, and that other factors increasing with age influence the risk of preeclampsia.

Vascular versus immunological model

Iacobelli et al. observed that EOP is more frequent than LOP in developing countries (30%) compared to in developed countries (10%). Based on these geographical differences and the observations that sexual cohabitation is generally much longer in developed countries, Robillard et al.[117] suggested that EOP was placental in origin and caused by immune maladaptation and that LOP was caused by a maternal vascular predisposition that rendered women who developed preeclampsia more vulnerable to endothelial dysfunction and hypertension. Robillard and colleagues[118] have also previously proposed a model for the risk of preeclampsia where age-dependent relative contributions of immunology and maternal vascular predisposition together explained the risk of preeclampsia. In this model, immunology played the most important role in younger women, and as the age increased her vascular predisposition would increase and the importance of immunology for developing preeclampsia was reduced (Figure 2). Since the age at first pregnancy is lower in developing countries, immunology would play a relatively larger role for the development of preeclampsia in these countries, resulting in a higher percentage of EOP (Figure 2). However, research on the potential differences between EOP and LOP does not seem able to decide if the two types are fundamentally different or just part of the same continuum, with LOP being a weaker and milder version of EOP[47].

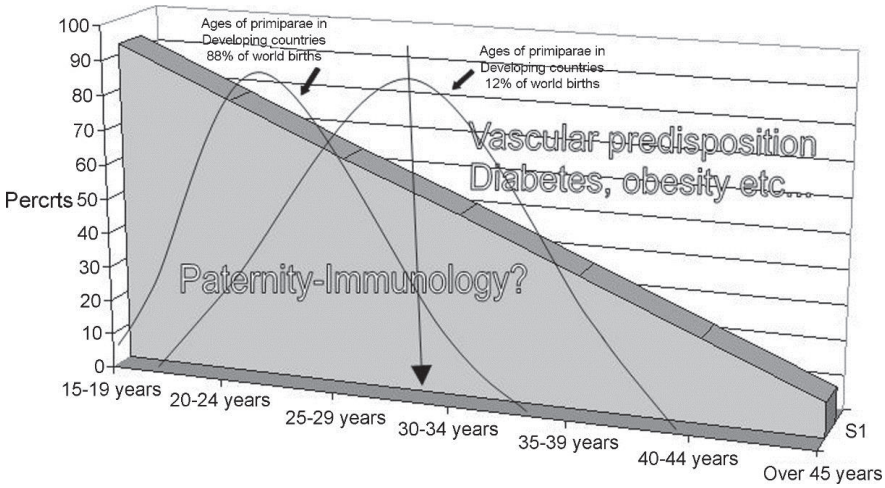

Figure 2. The graph displays the proposed relative contributions of immunology and maternal vascular predisposition to the etiology of preeclampsia. In younger women, immunology predominates as a cause of preeclampsia, but as the vascular predisposition increases with increasing age, the relative contribution of immunology to the etiology of preeclampsia decreases. Figure is taken from Robillard et al.[118] and used with permission.

2.2.5.2 Gestational hypertension

Two studies[119,120] have compared placental pathology in women with gestational hypertension and preeclampsia both indicating that gestational hypertension represented similar, albeit milder, pathological placental changes compared to preeclampsia, suggesting the two conditions do not represent two fundamentally different placental conditions. However, studies[121,122] indicate that the anti-angiogenic factors sFlt-1 and sEng are elevated in women with preeclampsia, but not in women with gestational hypertension. According to Noori et al.[121] the increase in anti-angiogenic factors during a preeclamptic pregnancy is mostly driven by the increase in women with EOP and not those with LOP. Circulating endothelial cell residues indicating endothelial damage were also only found in women with preeclampsia and not in those with gestational hypertension[123]. Some[124] interpret these observations to imply that preeclampsia and gestational hypertension are two distinct entities, but an estimated 15%-46% of women who initially present with gestational hypertension go on to develop preeclampsia indicating that the conditions share some common etiology[48,49].

2.2.6 Risk factors

2.2.6.1 Risk factors for preeclampsia

Age

Increasing maternal age has been associated with development of preeclampsia in several studies, which when combined into a meta-analysis[125] gives a dose response trend for every five year increase after age 35. Maternal age below 35 does not appear to be associated with preeclampsia[126]. A time trend graph from a Norwegian cohort[50] gives a visual display of the association between age and preeclampsia (Figure 3). Figure 3 shows a nearly linear association between age and preeclampsia that starts from age 35 in nulliparous women and from 25 years in multiparous women.

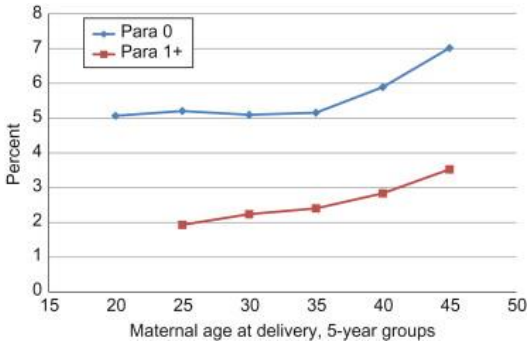

Figure 3. Graphical display of the association between age and preeclampsia in nulliparous (blue line) and multiparous (red line) women. Figure is from personal communication with Dr. Kari Klungsøyr and used with permission.

Socioeconomic status

Robillard et al.[115] argued that preeclampsia was one of the few conditions where socioeconomic status had no influence, except for in cases where reproductive patterns substantially differed between social groups as would be predicted by the immunological model of preeclampsia. Some more recent studies[127,128] than what Robillard et al.[115] based their inferences on have clearly indicated that low socioeconomic status does confer a higher risk of preeclampsia, while others[129–131] have provided weaker or more limited evidence for the same. Variations in results may have been caused by studies using different proxies for socioeconomic status and because they adjusted for different variables.

Body mass index

Higher maternal body mass index (BMI) has consistently been shown to be associated with development of preeclampsia in many studies, which when combined in a meta-analysis[132] comprising nearly 1.4 million women gave a dose-response trend where the risk of preeclampsia increased by 0.54% (95% confidence interval (CI), 0.27–0.80) for each 1-kg/m^2 increase in BMI (Figure 4). The mechanism by which higher BMI may contribute to preeclampsia is not known, but O'Brien et al. speculated that the hypertriglyceridemia that is associated with obesity could contribute to preeclampsia by impairing endothelial-dependent vasodilation[133]. Another explanation could be that BMI is a proxy for other risk factors for preeclampsia that are associated with BMI such as diabetes mellitus or chronic hypertension.

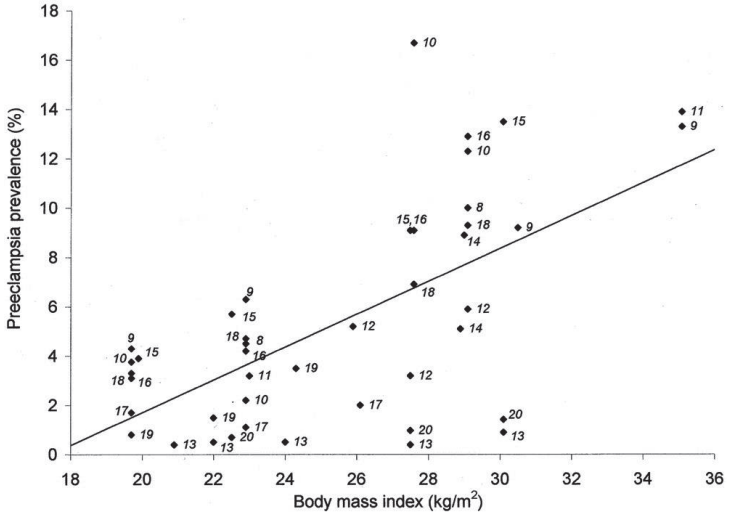

Figure 4. The association between maternal body mass index and preeclampsia based on 13 cohort studies represented by the italicized numbers. Figure is taken from O'Brien et al.[132] and used with permission.

Multiple pregnancy

Multiple pregnancy has been associated with preeclampsia in several studies[128,134–137], which show that the risk of preeclampsia typically more than doubles in pregnancies with more than one fetus.

Parity

Studies have consistently given evidence that nulliparity (no previous births) increases the risk of preeclampsia, which when combined into a meta-analysis give and estimated summary odds ratio of 2.61 (95% CI, 1.78 – 3.82)[109]. Robillard et al.[115] have argued that the increased risk of preeclampsia in nulliparous women is due to immunological maladaptation that is attenuated in the second pregnancy due to previous exposure to paternal antigens. There has, however, according to Luo et al.[109] been limited biochemical evidence for an abnormal immune response in nulliparous compared to multiparous women: Two studies have indicated that nulliparous women experience immune-maladaptation by having higher levels of antilymphocyte antibodies[138] and higher white blood cell counts[139] than multiparous women. There is evidence[140,141] that nulliparous compared to multiparous women have higher levels of circulating anti-angiogenic factors such as sFlt-1 that cause endothelial dysfunction, but it is not known if sFlt-1 is raised due to immune-maladaptation or other causes.

Previous preeclamptic pregnancy

A history of preeclampsia is strongly and consistently associated with developing preeclampsia in subsequent pregnancies increasing the risk several fold[135,137,142–147].

Pre-existing medical conditions

- *Pre-existing chronic hypertension*

  According to a meta-analysis[148] based on 55 studies and 795 221 pregnancies, women with pre-existing hypertension have a 7.7 (95% CI, 5.7 – 10.1) times higher risk of developing superimposed preeclampsia than women without pre-existing hypertension.

- *Diabetes mellitus*

Studies[143,149–152] indicate that the presence of pre-pregnancy diabetes mellitus increases the risk of preeclampsia substantially with an average around five-fold[152]. There is limited knowledge about what mechanisms underlie the increased risk in diabetic women, but a systematic review reported[152] that duration of diabetes, poor glycaemic control, retinopathy, high blood pressure, diabetic vasculopathy and diabetic nephropathy are all risk factors for developing preeclampsia in diabetic women.

- *Other conditions*

Renal disease[153], chronic autoimmune disease[126] and antiphospholipid syndrome[126], which includes systemic lupus erythematosus, all increase the risk of preeclampsia.

Time between pregnancies

The risk of preeclampsia is at least twice as high in first pregnancies as in second or subsequent pregnancies[109]. It was initially suggested that the risk of preeclampsia only decreased from first to second pregnancy if the mother's partner was the same as in the first pregnancy[112,113]. This was in line with the immunological model of preeclampsia where previous exposure to paternal antigens protected against preeclampsia[154]. Since the change of partner was associated with time between pregnancies, it was later suggested that the increased risk seen with partner change was in reality explained by the birth time interval. In 2002 Skjærven et al.[155] confirmed this in a Norwegian cohort showing that there was no increased risk of preeclampsia with change of partners after adjusting for the interbirth time interval, a finding that contested the primipaternity hypothesis. Robillard et al.[154] later defended the primipaternity hypothesis by suggesting the MBRN did not assign paternity correctly in 1-30% of cases and/or that the ascertainment of the preeclampsia diagnosis in the MBRN was inadequate for a substantial number of women.

Genetics

It has been observed since the 19th century that preeclampsia cluster within families[50]. Leon Chesley formalized observations of familial clustering of preeclampsia later in the 1980s laying the groundwork and inspiration for what became genetic research into preeclampsia[50]. Since then, it has been documented that heritability plays an important role in preeclampsia [156], and that the recurrence risk for preeclampsia in daughters of either eclamptic or preeclamptic mothers was in the 20–40% range and in the 11-37% range for sisters[157]. Familial clustering of preeclampsia does not distinguish between genetic and environmental causes, as members of the same family are likely to have similar dietary patterns, life style and socioeconomic status, which are factors that could all plausibly influence the risk of preeclampsia. In order to address this issue of genes versus environment, twin studies estimating the difference in concordance of preeclampsia cases within monozygotic and dizygotic twins have been performed. One twin study showed that 22%[158] of preeclampsia risk was due to heritable factors as opposed to environmental ones, while another reported an estimate of 54%[159], but due to limited sample sizes in these twin studies, the confidence intervals around these estimates were wide making interpretation difficult.

A study by Lie et al.[160] showed that a woman who becomes pregnant by a man who has already fathered a preeclamptic pregnancy in a different woman has an 80% (95% CI, 20 – 60) higher risk of developing preeclampsia than a woman who falls pregnant with a man who fathered a normotensive previous pregnancy. This result suggests that also paternal genes expressed in the fetus affect the risk of preeclampsia, but like other studies reporting familial clustering of preeclampsia, the increased risk could also be due to shared lifestyle and socioeconomic factors of the two women chosen by the father, which the study failed to adjust for.

Recently, in 2017, a genome wide association study[161] identified a susceptibility locus near the fms-like tyrosine kinase 1 (FLT1) gene in the offspring of preeclamptic mothers. They[161] suggested that different genotypes of fetal FLT1, expressed in the form of sFLT1, increased susceptibility to preeclampsia, potentially by contributing to the increased levels of SFLT1 that have been observed in preeclampsia.

Smoking

Smoking during pregnancy is associated with several adverse pregnancy and perinatal outcomes including placental hypoxia, preterm birth, spontaneous abortion, still birth, sudden infant death syndrome, reduced birth weight and long-term neurobehavioral deficits[162–166]. Since smoking during pregnancy is associated with abnormal placental development and hypoxia[163,164], one would think that smoking during pregnancy would increase the risk of preeclampsia, but the opposite is actually what studies have found. The earliest study on the relationship between smoking in pregnancy and preeclampsia was performed by Duffus et al.[167] in 1968 and reported that "the incidence of albuminuric preeclamptic toxæmia is lower in women who smoke cigarettes than in non-smokers". Numerous later studies have also found that smoking during pregnancy is associated with a lower risk of preeclampsia, which a recent meta-analysis[168] have combined into a relative risk of 0.67 (95% CI, 0.60 – 0.75) for preeclampsia in women who smoke during pregnancy compared to non-smokers. A study by Wikström et al.[169] found that the risk of preeclampsia was only reduced for smoking mothers if they continued to smoke into the second half of pregnancy, suggesting that smoking prior to or in the first half of pregnancy does not provide a protective effect. A systematic review[170] corroborates these findings, but also reports that smoking cessation in early pregnancy was associated with a slightly reduced risk of preeclampsia.

In general, smoking has previously been associated with lower SBP and DBP and a reduced risk of hypertension[171], but a recent Mendelian Randomization analysis found no evidence for a causal role for smoking with regards to blood pressure[171]. This suggests that direct influences of smoking on blood pressure are not responsible for lowering the risk of preeclampsia in smoking mothers. Some[172] have found that smoking during pregnancy is associated with lower circulating levels of anti-angiogenic factors and higher levels of the pro-angiogenic protein placental growth factor, effects that both would be protective against endothelial dysfunction and reduce the risk of preeclampsia. Others have suggested that smoking reduces the proposed exaggerated immune response of preeclampsia[170], or that it reduces plasma volume (and hence blood pressure) via nicotine exposure[168]. However, Wikström et al.[169] reported that tobacco combustion products rather than nicotine were responsible for

the reduced risk of preeclampsia in smokers, suggesting that the effect of nicotine on plasma volume was not important. Smoking has been found to cause a multitude of maternal endothelial and metabolic alterations, which Salfia and Shiverik[173] noted were very similar to those observed in preeclampsia. These observations spurred Salfia and Shiverik[173] to speculate that chronic smoking could cause a desensitization of the responsivity of the maternal endothelium to acute perturbations that occurred in preeclampsia. In their view[173], the protective effect of smoking could then in theory for instance be caused by an absent or diminished endothelial response to circulating anti-angiogenic factors. Finally, a simulation based study by Lisonkova and Joseph[174], provided evidence that loss of pregnancies among smokers before 20 weeks gestation may explain why smoking appears protective; pregnancies that were destined to develop preeclampsia had been lost before they could be diagnosed with preeclampsia.

Specific dietary factors

Circulating levels of the active form of vitamin D and its binding protein increase during normal pregnancy, and around 50% of this increase comes from the placenta and decidual tissues[175]. Cells within the interface between the maternal uterine myometrium and the fetus (decidua) mediate immune tolerance during pregnancy, and vitamin D may play an important immunoregulatory role at this interface[176]. Studies[177,178] have found that women with preeclampsia have lower levels of vitamin D, and that the rates of preeclampsia are higher in winter months[179], when sunlight-dependent vitamin D production is reduced and vitamin D levels in pregnant women are lower[180]. Further, a recent meta-analysis[181] based on 27 randomized controlled trials comprising 28 000 women, showed that supplementation with vitamin D, calcium and the combination of vitamin D and calcium lowered the risk of preeclampsia with pooled risk ratios of 0.47 (95% CI, 0.24, 0.89), 0.54 (95% CI, 0.41, 0.70) and 0.50 (95% CI, 0.32, 0.78), respectively.

Folate is a B vitamin that is essential for nucleic acid synthesis, cell division and DNA methylation and repair, making it a vital component of rapidly dividing cells like those of embryogenesis[182]. The protective effect of folate on neural tube defects is substantial and well established[183,184], but a recent meta-analysis[185] also showed that folate moderately lowers the risk of

preeclampsia reporting an odds ratio of 0.78 (95% CI 0.63-0.98) for developing preeclampsia among women who took a folate supplement compared to women who did not supplement folate.

2.2.6.2 Risk factors for gestational hypertension

Studies[150,186–188] comparing risk factors for preeclampsia and gestational hypertension have shown that the two conditions share most of the risk factors studied such as multiple pregnancy, nulliparity, preeclampsia in previous pregnancy, obesity, smoking during pregnancy, season, diabetes mellitus, renal disease and age, but that often the association is slightly weaker for gestational hypertension.

2.3 Cardiovascular health in women

2.3.1 Cardiovascular disease and risk factors

CVD constitutes the leading cause of death worldwide and is comprised of conditions that involve the heart or vascular system, with the most common being ischemic heart disease, heart failure, cerebrovascular disease and disease of the aorta and arteries[1]. Risk factors for CVD have been thoroughly examined and include both modifiable ones such as hypertension, smoking, obesity, type 2 diabetes mellitus, abnormal lipids, unhealthy diet, and physical inactivity, and less or non-modifiable ones such as low socioeconomic status, type 1 diabetes mellitus, advancing age, race, gender, and genetic disposition[1]. Mortality rates from the most frequent CVDs have decreased steadily in the past decades in the developed world as both prevention and treatment have improved[1,189]. Alongside this decline in CVD mortality, there has been a reduction in some cardiovascular risk factors such as hypercholesterolemia, hypertension and smoking and an increase in others including obesity and diabetes[190].

2.3.2 Gender difference in cardiovascular health

CVD is the leading cause of death in both men and women, but women tend to have lower risk than men at younger ages as they develop CVD 7-10 years later and hence lose less years of life due to CVD[1,2]. In spite of CVD being equally common in women as in men, it has traditionally been viewed as a male disease and largely been understudied, underdiagnosed and undertreated in women[3,4]. There are gender differences in the types of CVD that are most common with coronary heart disease being more common in men and women suffering more frequently from stroke and heart failure[191]. Most cardiovascular risk factors are, however, similar in both sexes[1,2], but lower levels of these risk factors at younger ages in women largely account for the differences in cardiovascular risk between men and women[2,192]. One recent mediation analysis[193] found that the combination of higher levels of blood pressure, cholesterol, glucose and a larger degree of smoking in men explained 41% of the CVD risk differences between men and women below the age of 50 years.

Before menopause CVD rates in women remain relatively low compared to men, but they start rising more abruptly after menopause[194]. This observation lead to the hypothesis that female ovarian steroid hormones conferred protection against CVD, a speculation that gained support from several observational studies reporting that estrogen replacement therapy (ERT) was beneficial in post-menopausal women[195]. Subsequent randomized controlled trials[196,197] refuted this hypothesis showing that no beneficial effect of ERT was present, and that there instead rather was an increase in adverse events associated with the treatment. It was pointed out that the average ages at enrolment for these randomized controlled trials[196,197] were 63 and 67 years, i.e. approximately a decade later than the age when women would usually start ERT. A meta-analysis[198] based on 23 randomized controlled trials examining the effect of ERT by age found that ERT protected against CVD in women up to10 years past their menopause, but that this protective effect was absent in women who were older than 10 years past their menopause. Research[199] has shown that estrogen exerts its cardio-protective effect by inducing vasodilation and inhibiting the response of blood vessels to injury and the development of atherosclerosis, but it remains unclear why this effect diminishes with advancing age.

2.3.4 Pregnancy and cardiovascular disease

2.3.4.1 Cardiometabolic changes in pregnancy

Pregnancy poses substantial physiological challenges to the maternal cardiovascular system as blood volume increases by ≈ 35-45%[26,27] and cardiac output increases by ≈40%[27] to supply the growing fetus with enough oxygen and nutrients. To accommodate the increased demand for oxygen, maternal tidal volume increases causing an increase in the partial pressure of oxygen and a concurrent state of alkalosis[26]. The expecting mother produces new red blood cells, but plasma volume rises faster and to a larger extent resulting in a state of reduced hematocrit and red blood cell concentration[27]. The large increase in blood volume is accompanied by a fall of 15-30% in vascular systemic resistance[26,27], which is caused by gestational hormones, circulating prostaglandins, heat produced by the fetus and newly formed blood vessels in the placenta[27]. In the first half of pregnancy, maternal blood pressure falls somewhat, before it around gestational week 20 starts rising towards term[103,200,201]. The decrease in maternal blood pressure during pregnancy activates the arterial baroreceptors, the renin-angiotensin-system, hypothalamic release of antidiuretic hormone and the sympathetic nervous system, which combined action seeks to increase blood pressure. A reduced maternal sensitivity to angiotensin 2 during pregnancy compensates for some of the vasoconstrictive effects of angiotensin 2[26], but higher levels of antidiuretic hormone induces a hypoosmolar and hypervolaemic state that lasts throughout pregnancy[26]. Pregnancy also causes an increase in clotting factors that prevent hemorrhage during delivery, but which also increase the risk of thrombosis[26,27].

To provide glucose for the developing fetus, a diabetogenic state characterized by insulin resistance is induced by human placental lactogen, growth hormone, progesterone, cortisol and prolactin. These diabetogenic hormones decrease insulin sensitivity in the maternal adipose tissues and skeletal muscle by disrupting the insulin receptor signalling[26]. This triggers lipolysis that releases fat from adipose tissues, which the mother can use as an energy source while preserving glucose for the fetus[26]. In general, all lipids are elevated during pregnancy inducing what some have called an atherogenic state[202], not only to provide energy for the mother or to be building blocks for the fetus,

but also to serve as substrates for the large rise in steroid hormones such as progesterone and estrogen that occurs during pregnancy[203].

2.3.4.2 Parity and cardiovascular risk

Several studies have been conducted that investigated the association between parity and CVD, but results vary somewhat. Some studies have reported a positive association between CVD and increasing number of births[204–208], while others have reported similar but insignificant associations or associations that were only significant for women with ≥5 births[209–212]. A large cohort study of >1.3 million women from Sweden by Parikh et al. together with another study from the UK by Lawlor et al.[8,213] found J-shaped associations between parity and CVD with the nadir of risk being for women with 2 births (Figure 5). Several studies have investigated the levels of cardiovascular risk factors by parity status, especially blood pressure, which many[214–219] have reported to be lower in parous compared to nulliparous women. A few other studies[220–222] reported insignificant associations between blood pressure and parity. Age is potentially an effect modifier of the association between parity and blood pressure as Hardy et al.[219] and Dratva et al.[214] reported that the blood pressure difference was present at younger ages for then to disappear by 53-60 years. Hardy et al.[219] also found that an increasing number of births compared to only one birth was associated with higher BMI and lower high-density lipoprotein cholesterol (HDLc) at age 53, but that this association was attenuated when adjusting for socioeconomic status, smoking and physical activity. A more recent study by Shen et al.[208] conducted in Chinese women also found that women with more than one birth had higher levels of BMI, SBP, glucose, had lower HDLc and more frequently had diabetes and hypertension, indicating that increased levels of cardiovascular risk factors could explain the positive association between parity and coronary heart disease among women with higher parity. Women with polycystic ovary syndrome (PCOS) are more likely to be infertile[223,224] and also to have higher levels of cardiovascular risk factors[225–228], which have been found to translate into a higher risk of CVD[226,228,229]. Since women with PCOS are likely to have lower parity and a higher risk of CVD, they may contribute to the increased risk of CVD observed among women with 0 or 1 births compared to 2 births.

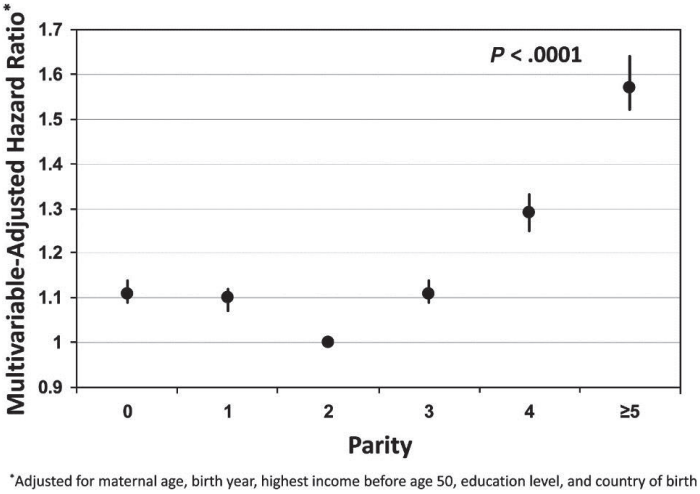

Figure 5. The J-shaped association between parity and incidence of CVD. Figure is taken from Parikh et al.[213] and used with permission.

2.3.4.3 Pregnancy complications and cardiovascular risk

Accumulating evidence[9–13,230,231] has shown that women who experience hypertensive disorders in pregnancy, preterm birth, gestational diabetes mellitus or give birth to a child with fetal growth restriction have higher risk of developing CVD. Women who either had preterm delivery or gave birth to a child who was small for gestational age have a 1.9 (95% CI, 1.5 – 2.4)[9] and 1.43 (95% CI, 1.38 – 1.60)[230] times higher risk than women with uncomplicated pregnancies of developing CVD, respectively. Women whose pregnancies were complicated by either preeclampsia or gestational hypertension have an approximately doubled risk of developing CVD[10–14] compared to women without hypertensive pregnancy disorders. The risk of CVD associated with history of preeclampsia increases by preeclampsia severity to 5 times that of women with normotensive pregnancies for the most severe form[13]. Studies[7,15–25] have shown that women with hypertensive pregnancy complications have higher levels of well-known cardiovascular risk factors such as BMI, blood pressure, lipids and glucose both before and after their first pregnancy. These observations have led to the hypothesis that higher levels of cardiovascular risk factors in women with history of hypertensive pregnancy complications mediate part of the increased CVD risk in these women. The same observations have also inspired the theory that pregnancy serves as a stress test of cardio-metabolic function, and that it provides an early window into a woman's cardiovascular risk profile potentially revealing a phenotype more prone to

CVD[29]. As described in section 2.3.4.1, pregnancy poses substantial challenges to the maternal cardiovascular system, and so the presence of an already adverse cardiovascular profile may contribute to the development of preeclampsia as was also proposed by Robillard et al.[118] (see section 2.2.5.1 *vascular versus immunological model)*. Being born from a pregnancy complicated by a hypertensive disorder is also associated with adverse effects on cardiac function[232,233] and adverse cardiovascular risk factors in young adulthood, although the latter seems to be due to shared genes or environment rather than due to intrauterine exposure to maternal hypertension[234].

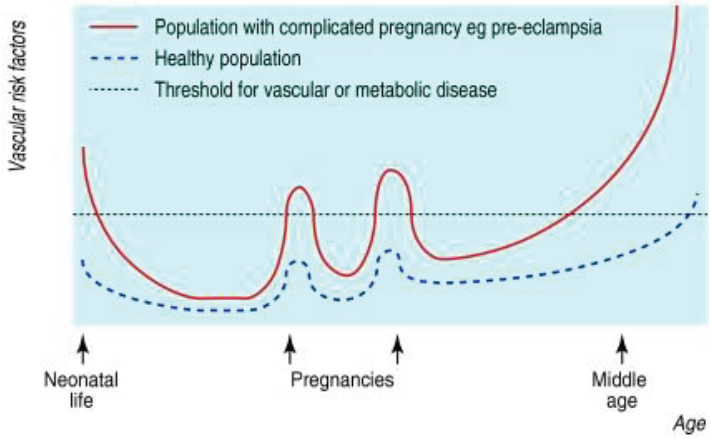

Figure 6. Cardiovascular risk factor profile trajectories for healthy women (blue dashed line) and for women with an elevated cardiovascular risk factor profile (red line). A preeclamptic pregnancy reveals women with an adverse cardiovascular risk factor profile (illustrated by the red tops reaching passed the threshold line for vascular or metabolic disease). Figure is taken from Sattar et al.[29] and used with permission.

2.3.4.4 Prevention of CVD in women

General

During recent decades, there has been a growing awareness of and a substantial progress in treatment and prevention of CVD in women. Since the 1980s, CVD mortality in women has been reduced by two thirds, half of which has been due to treatment improvements and half of which has been due to reducing levels of major cardiovascular risk factors[235]. In a public health perspective, the potential for

further CVD mortality reduction through affecting modifiable risk factors is substantial given that the population attributable risk that is accounted for by modifiable risk factors is over 80%[2,236–238], for both men and women. Guidelines for how to effectively reduce the risk of CVD in women have now been published in both the USA[235] and Europe[238], and in general the advice for women is similar to that for men. Both the European and American CVD prevention guidelines advice using 10-year CVD risk scores based on information about age, smoking habits, family history of CVD and clinical measurements of BMI, waist circumference, blood pressure, serum lipids as a help in assessing a woman's risk of CVD. No threshold for the various CVD risk scores have been proposed as firm cut-offs for warranting intervention and/or treatment, and instead health care practitioners are advised that "the intensity of advice should increase with increasing risk"[238]. According to these guidelines[235,238], women can reduce their risk of CVD by ceasing to smoke, by increasing their physical activity level and by reducing their blood pressure. Women are also advised according to these guidelines[235,238] to increase their consumption of fruits and vegetables, fiber and fish and to limit their intake of salt and saturated fats.

Women with history of HDP

The concept of pregnancy as a stress test of cardio-metabolic function and as a window into a woman's cardiovascular risk profile provides an opportunity for early identification of a group of women that have an increased risk of CVD. A history of hypertensive pregnancy disorders has now been included as a cardiovascular risk factor in both the European and American CVD prevention guidelines[235,238] and both guidelines recommend periodic screening of women with history of hypertensive pregnancy complications. However, there is little knowledge and consensus on how to design and implement prevention efforts in this group of women.

3. Aims of the study

The principal aims of this thesis were:

1) To examine the impact of parity on life course blood pressure trajectories and to compare blood pressure trajectories between parous and nulliparous women (paper I).

2) To compare life course trajectories of cardiovascular risk factors in women with and without hypertensive pregnancy complications in their first pregnancy (paper II).

3) To quantify the associations between hypertensive pregnancy complications and CVD and to examine to what extent these associations are explained by cardiovascular risk factors such as BMI, blood pressure, lipids and glucose (paper III).

4. Materials and methods

4.1 Data sources

4.1.1. The HUNT study

The Nord-Trøndelag Health Study (HUNT) is a longitudinal population-based study that has invited all residents of Nord-Trøndelag county (Figure 7), Norway, from the age of 20 to take part in health surveys. The surveys included written questionnaires and oral interviews about health related topics, blood sampling and clinical measurements. So far, three surveys have been conducted: HUNT1 (1984-86)[239], HUNT2 (1995-97)[240], HUNT3 (2006-08)[241] and with HUNT4 (2017-19) on the way. Participation rates for women were 89.9% in HUNT1[239], 75.5% in HUNT2[240] and 58.7% in HUNT3[241]. The population in Nord-Trøndelag was 135 142 in 2014 and is ethnically homogenous, predominantly White Caucasian, has low and stable immigration and emigration rates and is considered representative of Norway as a whole[240]. Data from HUNT1, HUNT2 and HUNT3 form the basis for this thesis.

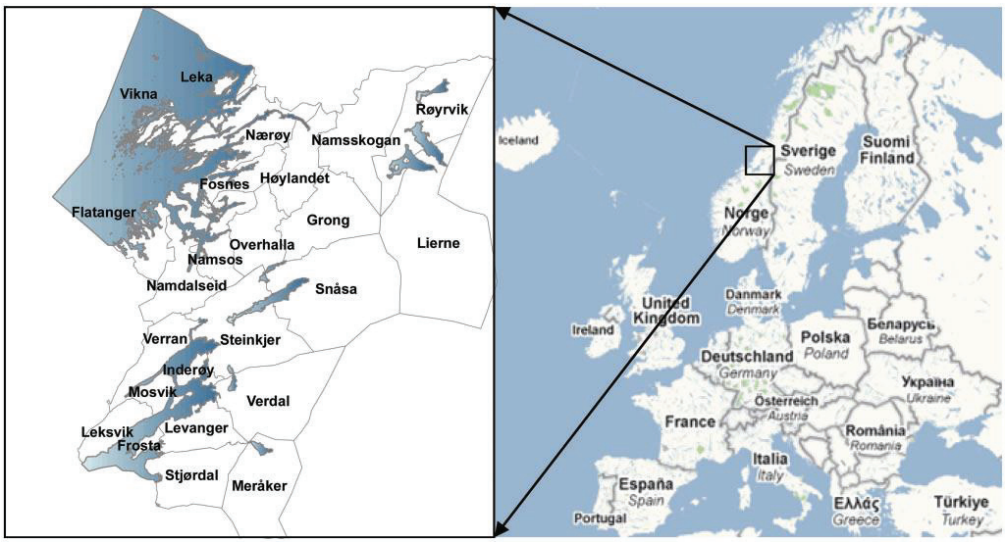

Figure 7. Nord-Trøndelag county with its 24 smaller municipalities. Figure taken from Krokstad et al.[242] and used with permission.

4.1.2 The Medical Birth Registry of Norway

The Medical Birth Registry of Norway was established just after the thalidomide crisis had caused over 10 000 limb reduction deformities[243] and was tasked with keeping epidemiological surveillance of birth defects and perinatal health problems as well as quality assure delivery health services. The MBRN has recorded all births occurring from 16 weeks gestation and onwards in Norway since 1967 along with detailed information on maternal and child characteristics[244,245]. At every birth midwives or physicians fill in a standardized form that collects information on the newborn child together with information on maternal health before and during pregnancy. This form remained unchanged until 1998, at which point it changed structure from free text to check boxes and expanded to include ultrasound based estimates of gestational length and information on maternal smoking and preconceptual vitamin intake. Today, the MBRN is part of the Norwegian Institute of Public Health.

The validity of the preeclampsia diagnosis in the MBRN was examined by Klungsøyr et al[39] and Thomsen et al[41], which found positive predictive values (PPV) of 83.9% (95% CI, 82.7 – 85.1) and 88.3%, respectively. Another study by Moth et al[246] examined the PPV of gestational hypertension in the MRBN reporting it to be 68% (95 CI, 59 – 76). Although the PPV was lower for gestational hypertension, most (88%) women with a diagnosis of gestational hypertension had evidence of either gestational hypertension of preeclampsia in their hospital records[246]. Both the validation study by Thomsen et al.[41] and Moth et al.[246] selected study populations that intersected with parts of the study populations that formed the basis for the investigations undertaken in this thesis.

4.2 Study populations

In Norway, all citizens are given a unique 11-digit personal identification number that can be used to link information on individuals between different data sources. In paper I, II and III we linked records of birth histories from the MBRN together with information from HUNT1, HUNT2 and HUNT3. In paper III, we additionally obtained records of CVD events from to the two local hospitals, Levanger and Namsos, that serve Nord-Trøndelag county and death records labeled as caused by CVD from the Norwegian Cause of Death Registry[247]. The HUNT study regularly receives updated information about the HUNT participants' residency status and deaths from the National Registry[248], which we utilized to censor participants in the analyses in paper III.

Paper I

In paper I, starting with 55 084 women who had taken part in at least one HUNT survey, we excluded women (n=26 246) who were born outside the period 1940-1974, since their complete reproductive histories may then not have been captured by the MBRN. A further 5400 women were excluded for one or more of the following reasons; first birth not recorded in the MBRN, first pregnancy shorter than 20 weeks, all blood pressure measurements taken during pregnancy/3 month postpartum period or incomplete information on blood pressure, smoking or education. After exclusions, 23 438 women remained for analysis.

Paper II

There were 25 932 women who had their first delivery recorded in the MBRN and who had also taken part in at least one HUNT survey. From these, we excluded 314 women whose first birth was a multiple, and since preeclampsia and gestational hypertension cannot be diagnosed before 20 weeks of gestation, we further excluded 56 women with either gestational length <20 weeks, offspring birth weight <350 g or missing information on both gestational length and offspring birth weight. Additionally, we excluded 88 with a pre-first pregnancy diagnosis of hypertension, 357 women who were pregnant or less than 3 months postpartum at all their HUNT examinations and 1239 women who

had incomplete information on smoking, education or cardiovascular risk factors, leaving 23 878 women for analysis.

Paper III

In total, 31 364 women had taken part in at least one HUNT survey and given birth to a child registered in the MBRN between the start (1967) and end of the MBRN follow-up (2012). In order to capture women's reproductive history up until age 40, we excluded 454 women who had their first birth after age 40 and 3901 women who turned 40 after 31st December 2012. A further 227 women were excluded because their births were a combination of multiples, resulted from pregnancies shorter than 20 weeks, were preceded by maternal chronic hypertension, produced offspring <350 grams or because they lacked information on birth weight and gestational length. Additionally, 1593 women were excluded due to incomplete information on smoking, education or history of coronary heart disease in siblings or parents. Lastly, we excluded 292 women with CVD events before the start of follow-up and 1012 women who moved out of Nord-Trøndelag county before the start of follow-up, leaving 23 885 women for our study. See Figure 8 for an overview of the study timeline and associated data sources.

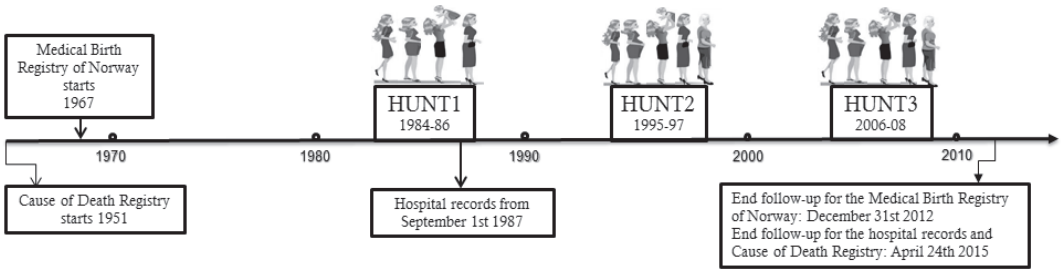

Figure 8. Timeline of follow-up with data sources.

4.3 Ethics and study approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Everyone taking part in HUNT surveys have provided informed consent, and all the studies forming part of this thesis were approved by the Regional Committee for Medical and Health Research Ethics (2013/647/REK midt).

4.4 Exposure and covariates

In all papers information on reproductive histories and details on maternal and perinatal health was obtained from the MBRN. From the HUNT questionnaires and interviews we obtained information on use of antihypertensive medication, diabetes mellitus diagnosis, ever daily smoking, hours since last meal, highest obtained educational level, work titles, family history of coronary heart disease (in sibling or parents), use of oral contraceptives and breastfeeding duration. In HUNT3 education level was not available, and we then derived educational level from work titles based on recommendations from Statistics Norway[249] instead.

4.5 Cardiovascular risk factors

Clinical measurements and blood sampling were carried out by qualified staff at the HUNT examination stations. Height and weight were measured with the person wearing light clothes and no shoes and were rounded to the nearest cm (height) and half kilo (weight). BMI was calculated as weight (in kg) divided by the squared value of height (in m), and obesity was defined as BMI $\geq$30 kg/m^2. In HUNT3, we also calculated BMI at age 18 using self-reported height and weight at age 18 years. In HUNT1, blood pressure was measured manually two times at 1-minute intervals using a sphygmomanometer after the person had come to rest, and we used the mean value of these two measurements in our analysis. In HUNT2 and HUNT3, blood pressure was measured three times at 1-minute intervals using an automatic oscillometric method (Dinamap, Critikon, Florida) after the person had come to rest, with cuff size adjusted to arm circumference. We used the mean of the second and third measurement, except for those women in HUNT3 who lacked the third measurement

due to sick leave amongst staff, for whom we used the second measurement only. In paper I and II, we added 10 mmHg to systolic and 5 mmHg to DBP levels for women who reported taking antihypertensive medication based on recommendations by Cui et al.[250] and Tobin et al.[251]. We classified women as having hypertension if they reported taking antihypertensive medication, or if blood pressure was either ≥140 mmHg systolic or ≥90 mmHg diastolic. Resting heart rate in beats/min was measured one time in HUNT1 and three times in HUNT2 and HUNT3 using the same devices as for blood pressure described above. For HUNT2 and HUNT3 we used the mean of the second and third measurements. Waist and hip circumference (available in HUNT2 and HUNT3) were measured to the nearest cm while the person was standing with arms hanging down at the height of the umbilicus (waist circumference) or at the thickest part of the hip (hip circumference). All serum analyses were performed in non-fasting samples at the Central Laboratory, Levanger Hospital, Nord-Trøndelag Hospital Trust using a Hitachi 911 Autoanalyzer in HUNT2 and Architect cSystems ci8200 in HUNT3. All analyses were performed in fresh serum samples, except C-reactive protein (CRP) in HUNT2, which was measured after 2 years of serum storage at -80 °C. Serum total and HDL cholesterol and triglycerides were analyzed using enzymatic colorimetric methods (Boeheringer Mannheim, Germany) in HUNT2. In HUNT3 HDL cholesterol was measured with an accelerator selective detergent methodology, total cholesterol was analyzed by a cholesterol esterase methodology and triglycerides were measured by a glycerol phosphate oxidase methodology, all by equipment from Abbott, Clinical Chemistry, USA. Non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. High-sensitive CRP was measured in participants from 4 out of 24 municipalities (n=2766) in HUNT2 using a C-reactive protein ultra-sensitive assay (Tina-quant(R), Roche, Basel, Switzerland). In HUNT3 CRP was measured in everyone using a latex immunoassay (Abbott, Clinical Chemistry, USA). In HUNT2 and HUNT3 serum glucose was measured for all persons using an enzymatic hexokinase method. In HUNT1 capillary glucose was measured at the examination stations in participants above 40 years (Reflocheck-Glucose, Boehringer Mannheim, Germany), and for the analysis of mean glucose levels, we transformed capillary levels to equate serum values (in mmol/L) by multiplying with 1.11[252]. In HUNT1, fasting capillary glucose was measured in persons with capillary glucose ≥8.0 mmol/L at the initial examination, and a 2-hour oral

glucose tolerance test was given if fasting capillary glucose was <7.0 mmol/L. If capillary glucose concentrations indicated diabetes (≥7.0 mmol/L fasting or ≥11.1 mmol/L after 2 hours), the corresponding serum glucose concentrations were measured. We defined diabetes by self-report (all HUNT surveys), non-fasting serum glucose ≥11.1 mmol/L (HUNT2 or HUNT3), or fasting serum glucose ≥7.0 mmol/L or 2-hour post-load serum glucose ≥11.1 mmol/L (HUNT1). Serum creatinine was measured with the Jaffe method in HUNT2 (Roche Diagnostics, Mannheim, Germany) and with an alkaline picrate methodology in HUNT3 (Abbott, Clinical Chemistry, USA), and calibrated to isotope-dilution mass-spectroscopy (IDMS) level using an enzymatic method (Roche)[253]. Estimated glomerular filtration rate (eGFR) in ml/min/1.73m^2 was calculated using the Chronic Kidney Disease Epidemiology consortium (CKD-EPI) formula[254] which takes account of creatinine, age and gender.

4.6 Cardiovascular endpoints

For paper III, we obtained records of CVD events based on ICD codes from the two local hospitals, Namsos and Levanger, serving Nord-Trøndelag county. Two cardiologists, Håvard Dalen and Bjørnar Klykken, reviewed all hospital records and confirmed any valid cardiovascular diagnoses according to established criteria, as described in detail in the supplemental material of paper III. We also retrieved death records from the Cause of Death Registry identifying CVD deaths by ICD codes for the underlying cause of death. Table 1 details the ICD codes used to classify deaths due to CVD from the Cause of Death Registry.

Table 1. ICD codes for fatal cardiovascular events in the Cause of Death Registry

	ICD-9 codes (1986-95)	**ICD-10 codes (from 1996)**
All cardiovascular events	401-414 and 424-445	G45, I10-I25, I34-I37, I42-I51, and I60-I77
Myocardial infarction	410 and 412	I21, I22 and I25.2
Heart failure	425 and 428	I42 and I50
Cerebrovascular disease	430, 431 and 433-435	G45, I60, I61, I63, I64, and I69.0, .1, .3, and .4.

4.6 Statistical analyses

Paper I and II

In paper I and II we compared life course blood pressure trajectories between parous and nulliparous women (paper I), and life course trajectories of cardiovascular risk factors among women with and without HDP (paper II). We constructed life course cardiovascular risk factor trajectories using linear spline mixed effects models[255], which included subject specific (random) intercepts and slopes in order to account for up to three repeated measurements (4 for BMI) per woman. Age was modelled using linear splines in order to facilitate non-linear change in cardiovascular risk factors with age. The length of the linear splines (age intervals) was defined by comparing model performance for models with 2, 4, 5, 6, 8, and 10 year age intervals using the Bayesian Information Criterion. Based on these comparisons, models with 10 year age intervals were chosen. All models included a variable indicating pre- or post-first pregnancy and a variable indicating time since pregnancy, which together enabled us to estimate the immediate change in cardiovascular risk factor pre- to post-first pregnancy and also the change in slope after pregnancy. We adjusted for ever having smoked daily, highest obtained educational level, HUNT survey and age at first birth in paper II and in selected models in paper I. Interaction terms were included between the age-dependent change in cardiovascular risk factors (linear splines) and covariates and between pregnancy and covariates in order to allow the age-dependent change in cardiovascular risk factor (linear splines) and effect of pregnancy to vary by the covariates (see Equation 1 for model specification). These linear spline mixed effects models enabled us to estimate differences in cardiovascular risk factor by age between parous and nulliparous women and between women with and without history of HDP. Additionally, these models allowed us to assess potential changes in cardiovascular risk factors associated with pregnancy. All analyses in paper I and II were performed using Stata IC 14[256] and MLwiN version 2.34[257] via the runmlwin command[258] in Stata.

$$Y_{ij} = \beta_0 + \beta_1(HDP)_j + \beta_2(age1stbirth)_j + \beta_3(HUNT)_{ij} + \beta_4(Education)_j + \beta_5(smoke)_j + (postpregind)_{ij}\big(\beta_{6.1} + \beta_{6.2}(HDP)_j + \beta_{6.3}(age1stbirth)_j + \beta_{6.4}(Education)_j + \beta_{6.5}(smoke)_j\big) + (postpregtime)_{ij}\big(\beta_{7.1} + \beta_{7.2}(HDP)_j + \beta_{7.3}(age1stbirth)_j + \beta_{7.4}(Education)_j + \beta_{7.5}(smoke)_j\big) + \mu_{0j} + \sum_{k=1}^{c+1}(\beta_{8.1.k} + \beta_{8.2.k}(HDP)_j + \beta_{8.3.k}(age1stbirth)_j + \beta_{8.4.k}(Education)_j + \beta_{8.5.k}(smoke)_j + \mu_{1j})s_{ijk} + e_{ij}$$

where $e_{ij} \sim N(0,\ {\sigma_e}^2)$, $(\mu_{0j}, \mu_{1j}) = \boldsymbol{\mu} \sim \boldsymbol{N}(0,\ \sum_{\mu})$ and $\sum_{\mu} = \begin{pmatrix} {\sigma_{\mu 0}}^2 & \\ {\sigma_{\mu 01}}^2 & {\sigma_{\mu 1}}^2 \end{pmatrix}$.

Equation 1. Y_{ij} is the mean level of a cardiovascular risk factor for individual j at measurement occasion i. Y_{ij} is modelled to depend on the independent variables hypertensive disorders of pregnancy (HDP), HUNT survey occasion (HUNT), mother's age at first birth (age1stbirth), highest obtained educational level (education), ever daily smoking (smoke), before or after first pregnancy (postpregind; 0 before and 1 after pregnancy), time since first pregnancy (postpregtime; 0 before and continuous after pregnancy) and age interval (s_{ijk}). μ_{0j} and μ_{1j} are random effects for the intercept and slope, respectively and e_{ij} is the random effect for sampling error. This model was used to model the relationship between hypertensive disorders of pregnancy and cardiovascular risk factors in paper II, but is very similar to the model used in paper I.

The spline terms s_{ijk} are defined by constructing c knot points along the age axis at ages $age_k$where $k = 1, \ldots, c$, $age_0 = 20$ and $age_{c+1} = age_{max}$. For person j with cardiovascular risk factor Y_{ij} observed at age age_{ij} we created $c + 1$ splines s_{ijk} (age intervals) such that

for $k = 1, \ldots, c + 1$:

$$S_{ijk} = age_{ij} - age_{k-1}\ if\ age_{ij} \leq age_k$$

$$S_{ijk} = age_k - age_{k-1}\ if\ age_{ij} > age_k$$

$$S_{ijk} = 0\ if\ age_{ij} \leq age_{k-1}$$

Paper III

We used Cox proportional hazards models to estimate the associations between CVD, myocardial infarction, heart failure and cerebrovascular events comparing women with and without a history of HDP. Age was the time scale and women entered the study on September 1st 1987, their first HUNT exam or upon turning 40 years, whichever came last. We followed women up until the CVD event of interest, emigration out of Nord-Trøndelag county, death or April 24th 2015, whichever came first. We presented associations between HDP and CVD that were only adjusted for age and associations that were adjusted for age, maternal birth year, highest obtained educational level, ever daily smoking, family history of coronary heart disease (in sibling or parents), age at first birth and parity before age 40. The Cox proportional hazards assumption was investigated by including interactions between independent variables and time. Violations of the Cox proportional hazards assumption were handled by estimating HRs within separate age-intervals where the assumption was met.

In order to estimate the proportion of excess risk of CVD in women with HDP that was explained by adverse levels of BMI, blood pressure, glucose and lipids, we used an inverse odds ratio weighting approach developed for mediation analysis by Tchetgen Tchetgen.[259]. Only the most recently measured cardiovascular risk factors prior to the cardiovascular event or censoring was included in the mediation analysis. See Figure 9 for a more graphic and detailed explanation of what the natural and indirect effects measure in this analysis. In this mediation analysis, we were able to adjust for the same variables as for the associations between HDP and CVD, and additionally also to adjust for age at measurement of the cardiovascular risk factors ("mediators"). All analyses in paper III were performed using Stata IC 14[256].

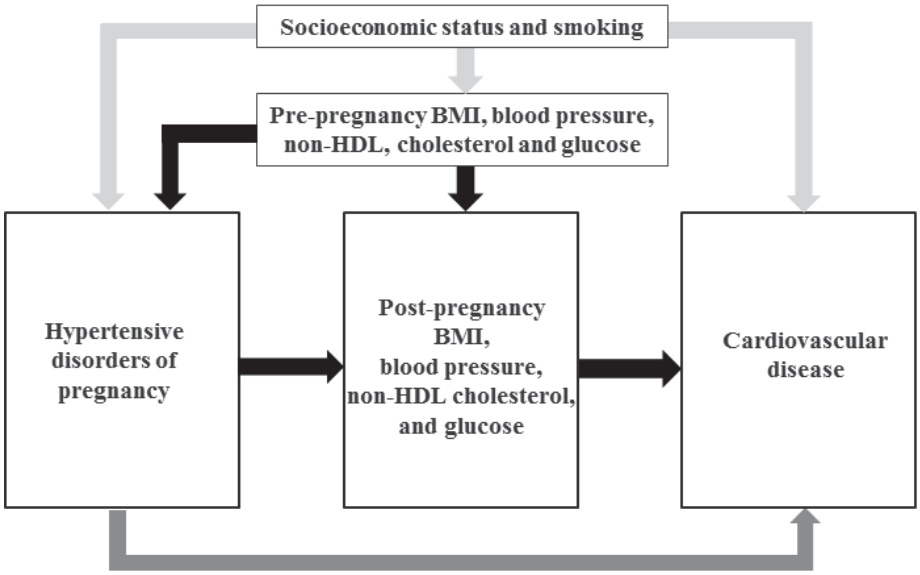

Figure 9. Diagram of relationships between hypertensive disorders of pregnancy (HDP), cardiovascular risk factors in the form of BMI, blood pressure, glucose and non-HDL cholesterol and cardiovascular disease (CVD). The black arrows represent pathways leading to CVD in women with history of HDP that involve these cardiovascular risk factors. In our mediation analysis, we estimate the natural indirect effect (the sum of all the black arrows), interpreting it as the proportion of excess CVD risk in women with history of HDP that is explained by higher BMI, blood pressure, glucose and non-HDL cholesterol. The dark grey arrow represents the possible direct effect of HDP on CVD, and the total effect of HDP on CVD is the sum of the natural direct (dark grey arrows) and indirect effects (black arrows). The light grey arrows represent confounding by socioeconomic status and smoking of the relationship between HDP and CVD and that between cardiovascular risk factors and CVD.

5. Main results

5.1 Paper I: The impact of parity on life course blood pressure trajectories: the HUNT study in Norway

Based on examining the life course blood pressure trajectories (Figure 10) among 21 513 parous and 1925 nulliparous women we found that parous and nulliparous women had indistinguishable mean blood pressure at age 20 when they were both nulliparous. We then observed that from before to after first pregnancy in parous women, blood pressure fell by -3.32 mmHg (95% CI, -3.93, -2.71) systolic and -1.98 mmHg (95% CI, -2.43, -1.53) diastolic. Subsequent pregnancies were associated with smaller reductions in blood pressure. It took parous women roughly a decade to reach their mean pre first-pregnancy levels of blood pressure, but there was a rebound effect between 30-40 years where parous women had a faster rise in blood pressure compared to nulliparous women. By age 50, parous women had a -1.93 mmHg (95% CI, -3.33, -0.53) lower systolic and -1.36 mmHg (95% CI, -2.26, -0.46) lower diastolic blood pressure compared to nulliparous women. Although blood pressure was still lower in parous compared to nulliparous women at age 60, the differences were no longer statistically significant. We concluded that a woman's first pregnancy, and to a lesser extent subsequent ones, are associated with lasting reductions in blood pressure that persist until at least age 50, and that this may protect parous women against CVD.

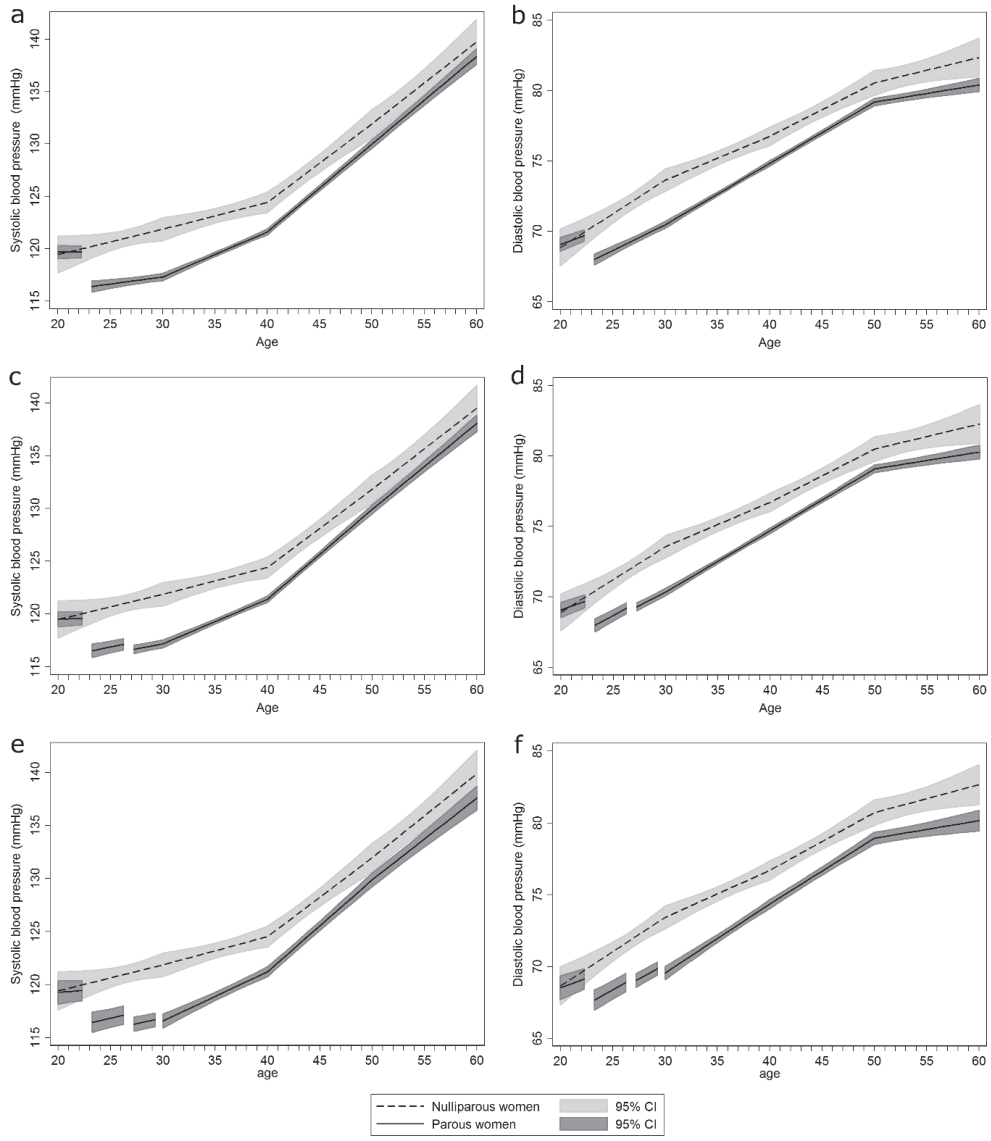

Figure 10. Mean systolic and diastolic blood pressure life course trajectories for nulliparous and parous women with one or more births (a and b), two or more births (c and d) and three or more births (e and f). Trajectories are drawn for women with covariates fixed at their means and with gaps in the graph of parous women corresponding to pregnancy and 3-month postpartum periods with the 1st birth at age 23, 2nd at 27 and 3rd at 30 years. Estimates are adjusted for age, HUNT survey, education and ever daily smoking. Figure is from Haug et al.[260].

5.2 Paper II: Life course trajectories of cardiovascular risk factors in women with and without hypertensive disorders in first pregnancy: The HUNT study in Norway

In this paper we examined life course trajectories of the cardiovascular risk factors blood pressure, adiposity, heart rate and serum lipids and glucose among 22 308 women with normotensive first pregnancies, 1092 women with preeclampsia in their first pregnancy and 478 women with gestational hypertension in their first pregnancy (Figure 11 and 12). Already, before first pregnancy women with a history of preeclampsia in their first pregnancy had higher levels of adiposity, blood pressure, heart rate and serum lipids and glucose compared to women with normotensive first pregnancy. Changes in cardiovascular risk factors associated with first pregnancy were largely similar between women with and without preeclampsia, but in contrast to women with normotensive first pregnancy, women with preeclampsia had a smaller drop in DBP and a larger increase in BMI after their first pregnancy. After first pregnancy, cardiovascular risk factors developed in parallel between women with and without preeclampsia in their first pregnancy, but in terms of cardiovascular risk factor levels, women with preeclampsia in their first pregnancy were approximately 10 years ahead of women with normotensive first pregnancy. The adverse cardiovascular risk factor profile established early in life of women with HDP in their first pregnancy persisted beyond 50 years of age. The higher levels of blood pressure, BMI and glucose observed in women with preeclampsia in their first pregnancy resulted in a higher risk of hypertension, obesity and diabetes than in women with normotensive first pregnancy (Figure 13). We also observed that the cardiovascular risk factor trajectories for women with preeclampsia and gestational hypertension in their first pregnancy were practically indistinguishable from each other.

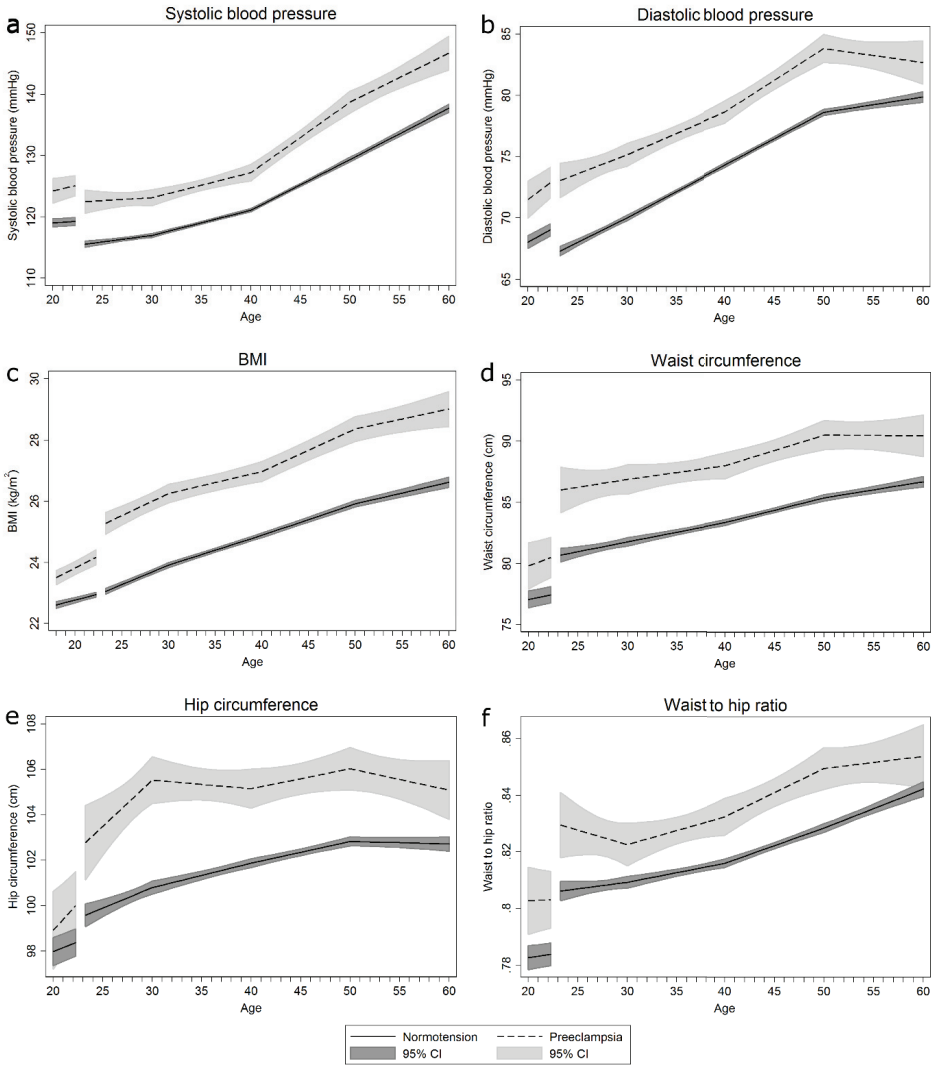

Figure 11. Life course trajectories of mean systolic blood pressure (a), diastolic blood pressure (b), BMI (c), waist circumference (d) hip circumference (e) and waist to hip ratio (f) for women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first birth and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three months postpartum period. Figure is from Haug et al.[261].

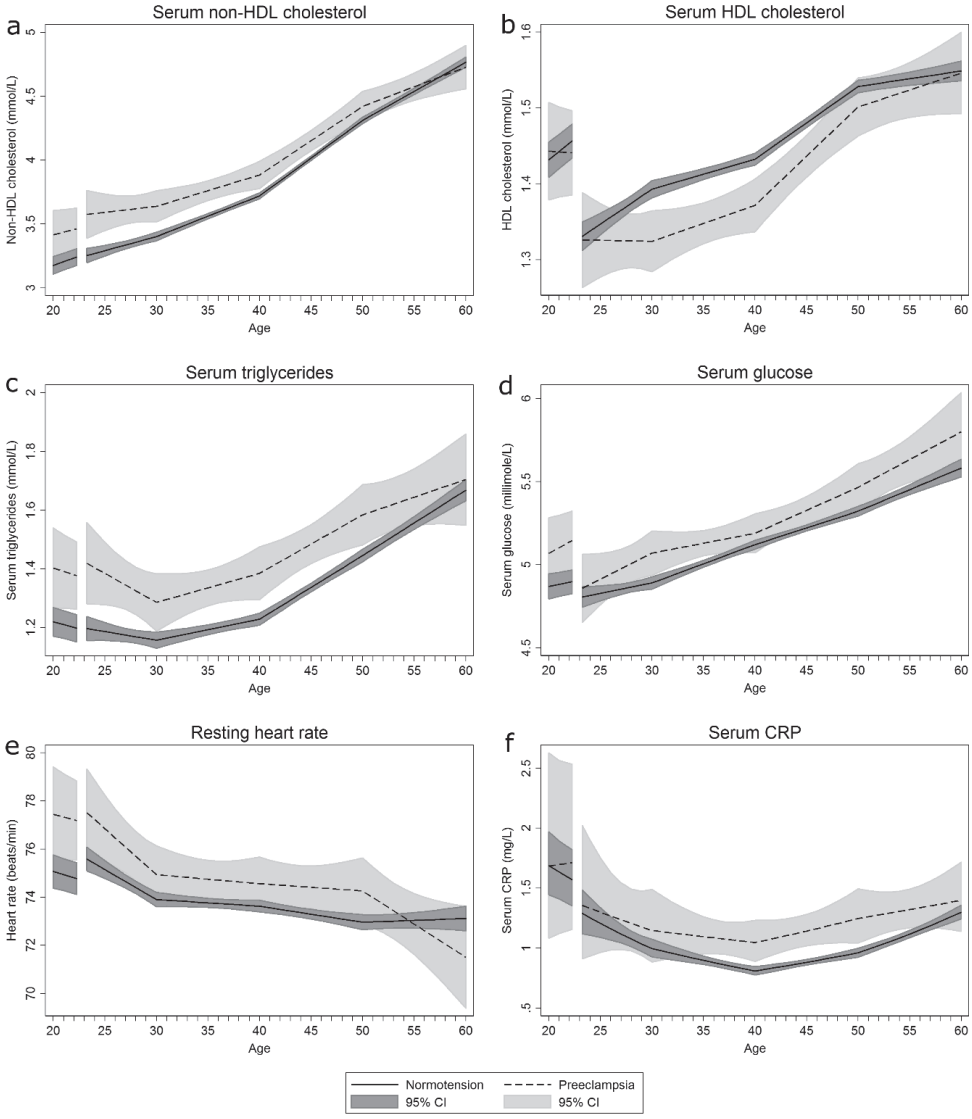

Figure 12. Life course trajectories of mean non-fasting serum non-HDL (a) and HDL (b) cholesterol, triglycerides (c) and glucose (d), resting heart rate (e), and serum CRP (f) for women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey highest obtained education level, age at first birth and ever daily smoking. Analyses of glucose and triglycerides were additionally adjusted for time since last meal. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three month postpartum period. CRP is given as geometric mean. Figure is from Haug et al.[261].

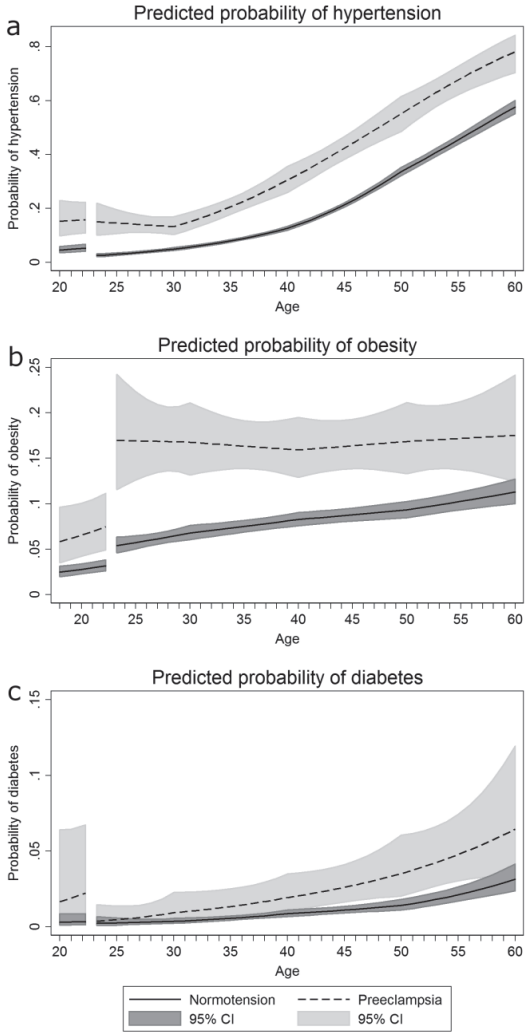

Figure 13. Population average predicted probabilities of hypertension (defined as current antihypertensive medication and/or blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) (a), obesity (defined as a BMI ≥30 kg/m^2) (b) and diabetes (defined as self-reported diabetes, non-fasting serum glucose ≥11.1 mmol/L, fasting serum glucose ≥7.0 mmol/L and/or 2-hour post-load serum glucose ≥11.1 mmol/L) (c) by age in women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first birth and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three month postpartum period. Figure is from Haug et al.[261].

5.3 Paper III: Cardiovascular disease after hypertensive pregnancy disorders: the role of conventional cardiovascular risk factors. The HUNT study in Norway

In this last paper, we examined the associations between HDP and CVD, myocardial infarction, heart failure and cerebrovascular disease among 21 766 women with normotensive pregnancies and 2199 women with history of HDP. From age 40-70, we found that women with a history of HDP had an approximately 60% higher risk (HR=1.57; 95% CI, 1.32 – 1.87) of developing CVD compared to women with only normotensive pregnancies. At older age this increased risk was no longer present (p for interaction by age=0.015), but sparse data prevented conclusive inferences from being made in the age group over 70 years. Associations (HRs) between history of HDP and myocardial infarction, heart failure and cerebrovascular disease were 1.85 (95% CI, 1.39 – 2.47), 1.60 (95% CI, 0.93 – 2.75) and 1.49 (95% CI, 1.17 – 1.90), respectively. Sensitivity analyses of validated cardiovascular events gave almost identical results as the main analysis. When examining the contribution of BMI, blood pressure and serum lipids and glucose to the excess risk of CVD in women with history of HDP, we found that the combination of blood pressure and BMI accounted for up to 77%, while lipids and glucose both accounted for 22% of the excess risk in women with HDP. Separate mediation analyses for history of preeclampsia and gestational hypertension gave evidence for that blood pressure was more important for explaining the excess cardiovascular risk in women with gestational hypertension where it accounted for all excess risk than in women with preeclampsia where mediators maximally accounted for 74% of the excess risk. Among the ≈18 000 women who had their cardiovascular risk factors measured after age 40, the proportions of excess CVD risk in women with a history of HDP that was explained by the cardiovascular risk factors was moderately reduced compared to the overall study population and maximally accounted for 48% of the excess risk

6. Discussion

6.1 Summary of main findings

The research described in this thesis has provided evidence that pregnancy is associated with clinically meaningful reductions in blood pressure, and that these reductions in blood pressure set parous women off on a divergent life course blood pressure trajectory compared to nulliparous women. We have also modelled and drawn life course cardiovascular risk factor trajectories contrasting women with and without a history of HDP in their first pregnancy, and showed that women with history of HDP in their first pregnancy establish an adverse cardiovascular risk factor profile early in life, which lasts beyond menopause. In our third and final study we showed that the modifiable cardiovascular risk factors BMI and blood pressure explained ≈ ¾ of the 60% higher risk of CVD in women with a history of HDP as compared to women with only normotensive pregnancies. The proportion of excess CVD risk explained by these risk factors was moderately lower among women who had their cardiovascular risk factors measured after age 40, suggesting that earlier measurements of cardiovascular risk factors may be more informative about later CVD risk in women with a history of HDP.

6.2 Consistency and novelty

The drop in blood pressure after pregnancy found in paper I was supported by previous longitudinal studies examining changes in blood pressure from pre to post-first pregnancy[103,215,216]. Other cross-sectional studies comparing blood pressure in parous and nulliparous women either reported no association[103,215,216] or lower blood pressure among parous women[217,218], which was more pronounced at younger ages. Compared to previous studies though, we had the advantage of being able to follow women up until older age.

To our knowledge, the studies in paper I and II were the first to compare within-woman life course blood pressure trajectories from before first pregnancy until age 60 between women with and without history of HDP in their first pregnancy. Our observations were largely[196,197196,197] similar to previous cross-sectional studies[7,15–25] comparing levels of cardiovascular risk factors in women with and without history of HDP, but added more evidence to the limited documentation beyond age 50.

Our results also gave credence to the theoretical model for cardiovascular risk factor trajectories in women with history of HDP and the concept of pregnancy as a stress test of cardiometabolic function proposed by Sattar and Greer[29] (Figure 6).

Our finding that women with history of HDP have approximately a 60% increased risk of CVD compared to women with normotensive pregnancies was a bit lower than the doubled risk reported in meta-analyses[10–13]. However, our result was relatively similar to other Norwegian studies, which reported HRs of ≈1.6[262,263] for the association between preeclampsia and CVD mortality. Our third and final paper is to our knowledge the second study to examine the contribution of cardiovascular risk factors to the excess risk of CVD in women with history of HDP. Our results showed that BMI and blood pressure explained a large proportion (77%) of the excess risk of CVD in women with a history of HDP, which is consistent with a previous study published as abstract in 2017[30] reporting that cardiovascular risk factors explained 71% of the excess CVD risk. Our study has added valuable evidence for the central role of BMI and blood pressure in driving the excess CVD risk in women with history of HDP.

6.3 Precision and validity

Throughout our studies, we had the privilege of using high quality and accurate measurements of cardiovascular risk factors that were collected at HUNT examination stations by trained staff. The considerable size of HUNT and longitudinal nature allowed for high precision and estimation of within-woman change over time, which was especially important in paper I and II where we drew life course trajectories of cardiovascular risk factors. In paper I we were additionally dependent on having measurements of blood pressure in women both before and after their first pregnancy in order to estimate the within-woman change associated with pregnancy, a task only made possible by the longitudinal nature of HUNT. In order to account for correlated repeated measures and model within-woman change with time, we used a mixed effects linear spline model[255], which also provided a large amount of flexibility in terms of describing the change with time while also (in paper I) taking account of the timing of pregnancies. The large number of women included in each of our studies ≈ 24 000

gave us high statistical power and enabled us to detect with high precision most of the associations that we were examining in our studies.

In our analyses, we were, with the help of HUNT, able to adjust for relevant confounders such as smoking and highest obtained educational level (proxy for socioeconomic status) while also, where appropriate, able to adjust for family history of coronary heart disease (in sibling or parents) or oral contraceptive use. In our study in paper III, the HUNT data allowed us to link to information about conventional cardiovascular risk factors and relevant confounders, enabling an adjusted "mediation" analysis of the influence of these cardiovascular risk factors on the excess cardiovascular risk in women with history of HDP.

Additionally, HUNT provided information on use of antihypertensive mediation, enabling us to follow recommendations by Cui et al.[250] and Tobin et al.[251] and reduce bias in paper I and II by adding 10 mmHg and 5 mmHg to the measured systolic and diastolic blood pressure, respectively. Although we did add constants to the measured blood pressure values of individuals treated for hypertension, as recommended[250,251], the slope in blood pressure with age may have beeen underestimated. However, we have no reason to believe that this underestimate would differ by parity or HDP status and bias our main results in paper I and II. Similarly in paper II, the use of statin treatment could have lowered non-HDL cholesterol levels in women attending HUNT3 (2006-08) and the use of beta-blockers could have lowered the resting heart rate of women with HDP to a larger extent than for women without HDP. This may have contributed to the smaller differences in non-HDL cholesterol levels and resting heart rate between women with and without HDP that were present after 50 years of age, when statin and beta-blocker use is more frequent.

The female participation rates in the HUNT surveys were fairly high (59%-90%). Those choosing not to participate in HUNT tended to have lower socioeconomic status, lower BMI and more frequently reported to have health problems and/or chronic diseases, but there was no difference in the use of antihypertensive medication between participants and non-participants[264]. Since non-participation was relatively moderate, not related to hypertension and most likely not dependent on HDP status, we do not expect missing observations to have substantially biased our results. The

population in Nord-Trøndelag county is generally considered to be representative of the population within Norway[240], and so our results are likely generalizable to the larger population within Norway. Wider generalization to populations outside Norway is likely possible, but may depend on factors such as race/ethnic composition and quality of and access to health care.

The MBRN provided accurate information on the reproductive histories, and the validity of the preeclampsia diagnosis within this population was generally good with a PPV of 88%[246]. For gestational hypertension the PPV was 68%, but most women with an MBRN diagnosis of gestational hypertension had evidence of either gestational hypertension or preeclampsia in medical records[246]. Compared to most other studies, our study in paper III assessing the association between HDP and CVD had the advantage of having validated 93% of cardiovascular events.

Secular trends in blood pressure[265], BMI[266], waist circumference[267] and cholesterol[268] could potentially have affected our cardiovascular risk factor trajectories in paper I and II. We accounted for age, period and cohort effects by adjusting for HUNT survey occasion and age to reduce the impact of secular trends, but although secular trends may still have influenced the trajectories, we do not expect them to have substantially biased the difference between parous and nulliparous women or between women with and without history of HDP.

6.4 HDP in context

Our finding in paper I that pregnancy and birth are associated with a reduction in blood pressure is interesting in the context of the relationship between parity and CVD, parity as a risk factor for preeclampsia and with regards to the discussion about the vascular versus immunological model of preeclampsia. It is unfortunately difficult to explain the J-shaped relationship between parity and CVD by reductions in blood pressure as a result of pregnancy. The increased risk of preeclampsia that is associated with nulliparity (i.e. first pregnancy)[109] compared to subsequent pregnancies, could partly be explained by the reduction in blood pressure occurring after first pregnancy, which we observed in paper I. As mentioned in section 2.2.5.1, the increased risk of preeclampsia that is associated with changing partners disappeared upon adjusting for inter-pregnancy interval[155], a finding which would also be consistent with our observation from paper I of a temporary lower blood pressure following,

especially, first pregnancy. Our research gives support to an important role for the vascular component in modifying the risk of preeclampsia that depends on parity and change of partners.

In paper II, we observed that BMI increased more in women who had a preeclamptic first pregnancy compared to women who had a normotensive first pregnancy. Additionally, where we observed that diastolic blood pressure decreased from pre- to post-first pregnancy in women with a normotensive first pregnancy, we observed that diastolic blood pressure increased from pre- to post-first pregnancy in women with a pregnancy complicated by preeclampsia. All the other cardiovascular risk factors we examined in paper II displayed similar changes from pre- to post-first pregnancy in women with and without preeclampsia. This indicates that a preeclamptic pregnancy itself is not associated with a more adverse change in cardiovascular risk factors, except for BMI and diastolic blood pressure which did show a more adverse change in women with preeclamptic first pregnancy. Although we have no way of saying if preeclampsia itself caused the increases in BMI and diastolic blood pressure, we found no evidence for preeclampsia in first pregnancy modifying the other cardiovascular risk factors that we examined. From our paper III, we found little evidence for any direct effects of HDP on CVD when taking blood pressure and BMI into account, but we observed that while blood pressure and BMI explained almost all the excess risk of CVD in women with gestational hypertension, the proportion explained was lower for women with history of preeclampsia. This may either indicate that preeclampsia exerts a direct effect on CVD, or that other factors associated with preeclampsia, but not gestational hypertension, cause CVD in these women.

As suggested in section 2.2.5.2, preeclampsia and gestational hypertension seem to share some common etiology, with gestational hypertension potentially representing a milder variant of the HDP disease spectrum. This idea is to some extent consistent with our findings in paper II where we showed that there were no noticeable differences between the cardiovascular risk factor trajectories of women with preeclampsia and women with gestational hypertension in their first pregnancies. However, given that gestational hypertension may be considered a milder variant of HDP, we would perhaps expect that women with gestational hypertension in their first pregnancy had somewhat lower levels of cardiovascular risk factors. In our third paper we observed that the associations between gestational

hypertension and CVD was lower than that between preeclampsia and CVD, and that blood pressure seemed to explain most of the excess risk in women with history of gestational hypertension. Perhaps this could imply that the vascular component is more important for developing gestational hypertension, and that other additional factors are needed to produce preeclampsia.

Unfortunately, we were unable to separately analyze EOP and LOP due to limited number of women with EOP (0.6%). As mentioned previously in section 2.2.5.1, EOP is more frequent in developing countries where the immunological component of preeclampsia is hypothesized to be more important than in developed countries. While we cannot make a comparison of cardiovascular risk profiles between women with EOP and LOP, our results lend support to the central role of cardiovascular risk factors in explaining excess cardiovascular risk and potentially also in explaining preeclampsia risk in women with LOP.

6.4 Clinical implications and future perspectives

In paper I we were unable to investigate the reason why pregnancy is associated with a lowering of blood pressure. In our paper we suggested that the drop in blood pressure pre- to post-pregnancy may be a result of the decrease in vascular resistance[26–28] that take place during pregnancy. Alternatively, lifestyle modifications associated with pregnancy and child rearing could explain the reduction in blood pressure. Another possible explanation is that breastfeeding contributes to the lower blood pressure post-pregnancy, a hypothesis that is consistent with findings from two cross sectional studies[269,270] indicating that longer duration of breastfeeding is associated with lower blood pressure. We examined the influence of breastfeeding on changes in blood pressure pre- to post-first pregnancy in a longitudinal subsample in paper I, and although our sample was too small to make conclusive inferences, we did not observe that the blood pressure reduction was associated with breastfeeding length. Future larger longitudinal studies may be able to examine the effect of breastfeeding on the change in blood pressure pre- to post-pregnancy.

Already, HDP has been classified as a risk factor for CVD in women in both the European[238] and American[235] guidelines for CVD prevention in women. The Norwegian Clinical guidelines[271] for

preventing CVD recommend using the NORRISK 2 calculator[272] for estimating women's 10 year risk of CVD based on sex, age, blood pressure, smoking, serum total and HDL cholesterol, and family history of CVD. Clinicians may additionally incorporate information about certain medical conditions and ethnic origin and multiply the estimate obtained from NORRISK 2[272] to get a modified risk[271] score that is more personalized. History of preeclampsia is listed in the Norwegian clinical guidelines[271] for preventing CVD as an additional condition that confers increased risk of CVD, but there is no information on how this information modifies the risk score and no specific instructions on how to tailor screening and preventive efforts in women with history of preeclampsia, let alone gestational hypertension. Our research has shown that compared to women with normotensive first pregnancy, women with history of HDP in their first pregnancy establish an adverse cardiovascular risk factors profile early in life, which lasts until beyond menopause. We further showed that blood pressure and BMI explain most of the excess risk of CVD in women with history of HDP as compared to women with only normotensive pregnancies. Research suggests that a reduction of 2 mmHg in diastolic blood pressure could reduce the risk of coronary heart disease by 6% and the risk of stroke and transient ischemic attacks by 15%[273]. This implies that women with history of HDP could potentially benefit from an earlier, and closer clinical follow-up of cardiovascular risk factors together with lifestyle modification programs that seek to reduce their cardiovascular risk factors, especially blood pressure and BMI.

What still remains to be examined is if cardiovascular risk factor trajectories and the contribution of cardiovascular risk factors to CVD risk in women with preeclampsia differ by severity of preeclampsia. As we had insufficient power and limited information on preeclampsia severity we were unable to investigate this, and future studies may hopefully be able to examine mild and severe preeclampsia separately.

There is also limited evidence from intervention studies examining the effect of diet modification and lifestyle interventions that aim to alter cardiovascular risk factors in women with a history of HDP. One abstract[274] published in 2012 examining the effect of lifestyle intervention in women with a history of preeclampsia, gestational diabetes mellitus and intrauterine growth restriction

found that measures of adiposity and systolic blood were significantly improved postpartum in women who took part in the active arm of a life style intervention study. Another study[275] investigating the effect of a web-based lifestyle intervention program for women who had gestational diabetes mellitus also found that the intervention had a positive effect on postpartum weight retention. In order to develop effective preventive measures that reduce the increased risk of CVD in women with a history of HDP, more studies that look specifically at HDP are needed. The postpartum period may be well suited for intervention in women with HDP as studies[276,277] have shown that women who recently experienced a complicated pregnancy and find themselves in charge of the health and wellbeing of a newborn child are particularly motivated to engage in lifestyle modification programs that aim to improve their health.

7. Conclusions

Paper I

A woman's first pregnancy, and to a lesser extent her subsequent pregnancies, are associated with clinically relevant reductions in blood pressure that separate and lower the life course blood pressure trajectory of parous women compared to that in nulliparous women. These findings may help explain CVD risk differences defined by parity and why the risk of preeclampsia is highest in first pregnancies compared with later pregnancies.

Paper II

Women with HDP in first pregnancy establish and adverse cardiovascular risk factor profile early in life compared to women with normotensive first pregnancy. Throughout adult life cardiovascular risk factor progression occurs mostly in parallel for women with and without a history of HDP in first pregnancy. Women with HDP in first pregnancy may display CVD risk profiles that warrant clinical follow-up 10 years earlier than women with normotensive first pregnancy. Women with HDP in first pregnancy may benefit from early screening and targeted preventive programs that seek to reduce their cardiovascular risk factor levels.

Paper III

Women with a history of HDP have an increased risk of CVD compared to women without a history of HDP, which is largely explained by higher levels of cardiovascular risk factors such as blood pressure and BMI. Our findings indicate that lifestyle modification programs that seek to reduce blood pressure and BMI in women with history of HDP may reduce their cardiovascular risk.

8. References

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DEVELOPMENTAL EPIDEMIOLOGY

The impact of parity on life course blood pressure trajectories: the HUNT study in Norway

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Abstract

The drop in blood pressure during pregnancy may persist postpartum, but the impact of pregnancy on blood pressure across the life course is not known. In this study we examined blood pressure trajectories for women in the years preceding and following pregnancy and compared life course trajectories of blood pressure for parous and nulliparous women. We linked information on all women who participated in the population-based, longitudinal HUNT Study, Norway with pregnancy information from the Medical Birth Registry of Norway. A total of 23,438 women were included with up to 3 blood pressure measurements per woman. Blood pressure trajectories were compared using a mixed effects linear spline model. Before first pregnancy, women who later gave birth had similar mean blood pressure to women who never gave birth. Women who delivered experienced a drop after their first birth of − 3.32 mmHg (95% CI, − 3.93, − 2.71) and − 1.98 mmHg (95% CI, − 2.43, − 1.53) in systolic and diastolic blood pressure, respectively. Subsequent pregnancies were associated with smaller reductions. These pregnancy-related reductions in blood pressure led to persistent differences in mean blood pressure, and at age 50, parous women still had lower systolic (− 1.93 mmHg; 95% CI, − 3.33, − 0.53) and diastolic (− 1.36 mmHg; 95% CI, − 2.26, − 0.46) blood pressure compared to nulliparous women. The findings suggest that the first pregnancy and, to a lesser extent, successive pregnancies are associated with lasting and clinically relevant reductions in systolic and diastolic blood pressure.

Keywords Life course · Blood pressure · Parity · Pregnancy · Epidemiology

Introduction

Longitudinal studies have shown that blood pressure increases during a woman's life [1–3]. In the first half of pregnancy blood pressure substantially decreases and then rises towards term [4–6]. Limited evidence from longitudinal studies following women from before to after first

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pregnancy suggests a woman's first pregnancy is associated with a drop in blood pressure [6–8] that may persist for years postpartum [7]. The presence of a long-lasting drop in blood pressure after pregnancy has also been supported by some [9–12], but not all [13–15] studies that compared parous and nulliparous women at various time points after their first pregnancy. If long-lasting, this reduction in blood pressure may impact life course trajectories of blood pressure in parous women and reduce their cardiovascular disease (CVD) risk compared to men [16] and women who remain nulliparous [17, 18]. However, no study has followed women from pre-pregnancy to middle age to determine longitudinally whether the pregnancy-related drop in blood pressure persists into the age when CVD may emerge.

Using data from the population-based Nord-Trøndelag Health Study (the HUNT Study) linked with the Medical Birth Registry of Norway (MBRN) we examined blood pressure trajectories for women in the years preceding and following pregnancy and compared life course trajectories of blood pressure for parous and nulliparous women.

Methods

Study population

The HUNT Study is an ongoing longitudinal study in which all people aged 20 and above in Nord-Trøndelag county, Norway are invited to undergo an extensive health assessment, including clinical measurements and questionnaires [19]. So far three surveys have been conducted: HUNT1 (1984-86), HUNT2 (1995-97) and HUNT3 (2006-08). The population of Nord-Trøndelag is representative of Norway as a whole [20]. Participation rates for women were 89.9% in HUNT1 [21], 75.5% in HUNT2 [20] and 58.7% in HUNT3 [19].

HUNT data were linked with the MBRN to retrieve information on births using the unique personal identification numbers assigned to Norwegians at birth or immigration. All births in Norway since 1967 have been recorded in the MBRN [22], and data were available through 2012. Among 55,084 women who had taken part in at least one HUNT survey, we excluded 26,246 women who were born before 1940 or after 1974 since their complete reproductive history may not have been captured between 1967 and 2012. Among the remaining 28,838 women, 5400 (18.7%) were excluded for the following reasons: We excluded 3686 women who did not have their first birth registered in the MBRN and 25 women whose first recorded pregnancy was shorter than 20 weeks since it was uncertain whether these shorter pregnancies would cause lasting cardiovascular changes. Finally, we excluded 486 women whose only blood pressure measurements were performed in pregnancy or up to 3 months postpartum and 1203 women with incomplete information on blood pressure, smoking or education, leaving 23,438 women for analysis (Fig. 1). Descriptive characteristics of excluded versus included women are shown in Supplemental Table 1.

Blood pressure and covariates

In each HUNT survey, blood pressure was measured by trained staff after the person had rested. In HUNT1 [21] blood pressure was measured manually two times with a 1-min interval using a sphygmomanometer, and in HUNT2 [20] and HUNT3 [19] blood pressure was measured three times with 1-min intervals using an automatic oscillometric method (Dinamap, Critikon, Florida) with cuff size adjusted to arm circumference. We used the means of the 1st and 2nd (HUNT1) or 2nd and 3rd (HUNT2 and HUNT3) measurements in the analyses. In HUNT3, due to sick leave amongst staff, 2016 women did not have their 3rd blood pressure measurement taken, and for them we used the 2nd measurement. To account for bias due to use of antihypertensive medication, blood pressure measurements from women using antihypertensives were, according to recommendations by Cui et al. [23] and Tobin et al. [24], amended by adding 10 and 5 mmHg to the measured systolic and diastolic blood pressure, respectively. We excluded blood pressure measurements performed in pregnancy or within 3 months postpartum.

Body mass index (BMI; weight in kg divided by the squared height in m^2) was measured at each HUNT examination. The HUNT questionnaires included information on smoking and anti-hypertensive medication (all HUNT surveys), use of oral contraceptives and breastfeeding duration (HUNT2 and HUNT3), and highest obtained educational level (HUNT1 and HUNT2); lower secondary (up to 9 years), upper secondary (10–12 years) and tertiary education (college or university). Information on work titles (HUNT3) was obtained from a structured interview. Due to lack of educational information for women who participated only in HUNT3, we derived educational status from work titles for 4041 women based on recommendations from Statistics Norway [25].

Information on hypertensive disorders in pregnancy (preeclampsia, gestational hypertension, and pre-pregnancy chronic hypertension) was retrieved from the MBRN, which records these disorders from standardized forms filled in at the birth clinics and returned shortly after delivery. Validation studies within the HUNT population have shown that 88% of preeclampsia cases in the MBRN were confirmed by evidence in hospital records [26], and 74% of cases of gestational hypertension in the MBRN had

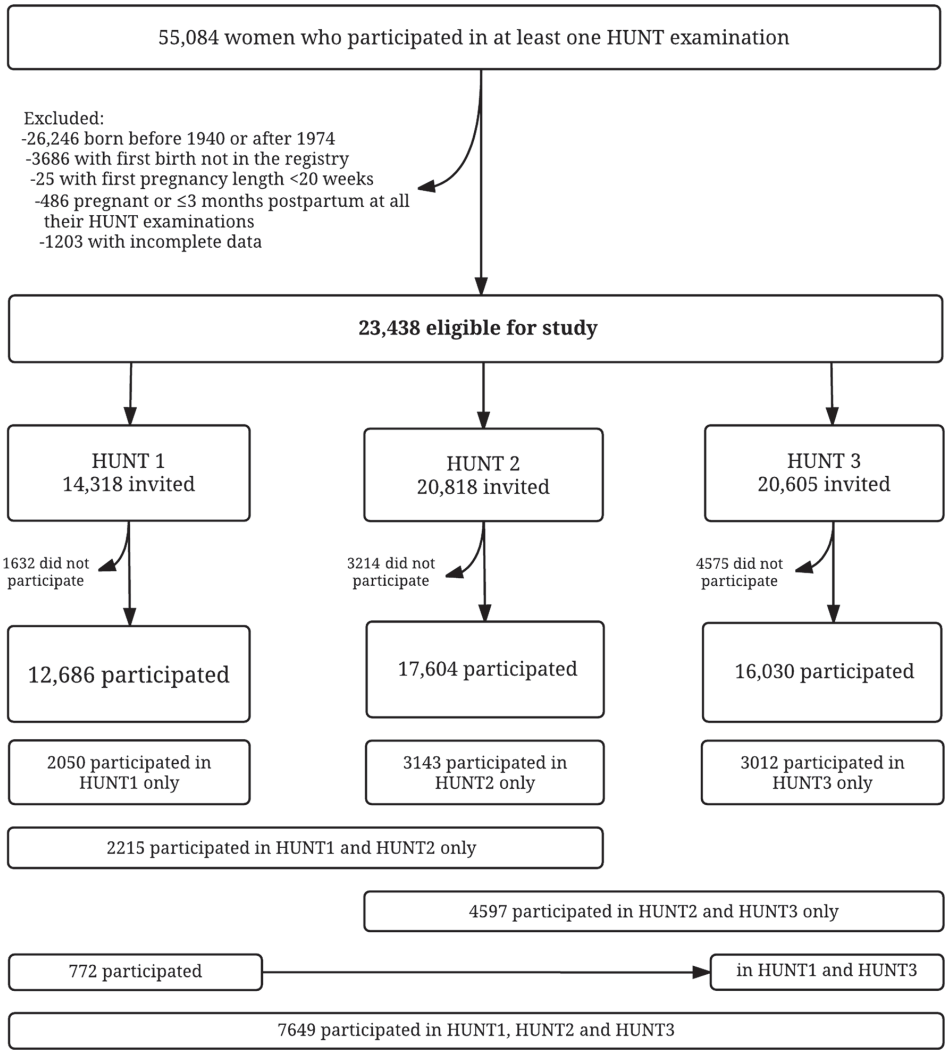

Fig. 1 Flow chart of the study population

evidence of gestational hypertension or preeclampsia in hospital records [27].

Statistical analysis

We used a linear spline mixed effects model [28] to estimate blood pressure trajectories for women who remained nulliparous or became parous at some point during 1967–2012, defined as having at least one pregnancy lasting beyond 20 weeks of gestation. To account for repeated observations (up to three per woman) and reflect the heterogeneity in the data, all models included a random intercept and a random slope. The effect of pregnancy was modeled using two variables: The first indicated whether the measurement occurred pre- versus post-pregnancy and provided an estimate of the immediate change in blood pressure following pregnancy, and the other indicated continuous time post pregnancy and gave an estimate of the change in blood pressure slope after pregnancy. Using linear splines allowed the change in blood pressure to vary by age interval, enabling non-linear trends in average blood pressure with age to be modeled. Knots (points at which the linear slope changed) were selected using the Bayesian Information Criterion (BIC) [29] to compare multivariable

models with different sets of knots (age intervals of 2, 4, 5, 6, 8, and 10 years). Knots were placed at 10-year age intervals as models with more knots did not prove superior. We included interaction terms to allow the age-dependent changes in blood pressure to vary between parous and nulliparous women, and to allow the effects of age and pregnancy on blood pressure to vary by levels of covariates. The estimates were adjusted for age, HUNT survey, education (as a proxy for socioeconomic status) and ever daily smoking. Blood pressure measurements up to 68 years of age were included, but blood pressure trajectories were presented for the age range 20–60 years due to limited data from older women. Predicted blood pressure trajectories are displayed for representative nulliparous women and parous women with first birth at 23, second at 27 and third at 30 years of age, corresponding to the median ages at births in our study population. In an analogous approach, we used logistic regression analysis to estimate trajectories of the prevalence of hypertension, defined as self-reported use of antihypertensives or blood pressure $\geq$ 140 mmHg systolic or $\geq$ 90 mmHg diastolic.

In analyses restricted to parous women, we examined whether the effect of pregnancy on blood pressure varied by age at first pregnancy. To confirm that the average blood pressure trajectories drawn using data from all examinations among all women were representative of within-woman changes in blood pressure across time, we performed a sensitivity analysis excluding women who had only one blood pressure measurement. Further to confirm that the trajectories represented the actual within-woman change in blood pressure due to pregnancy, we studied the difference in blood pressure change for women who had their pregnancy between HUNT2 and HUNT3 to women who remained nulliparous throughout the same interval and were 43 years or younger at HUNT2, the maximum age at HUNT2 of those who went on to have their first birth. To examine the extent of confounding by oral contraceptive use and BMI, the analysis of change in blood pressure between HUNT2 and HUNT3 was adjusted for change in BMI and oral contraceptive use between the HUNT surveys. Also, in order to investigate the potential mediating effect of breastfeeding upon the association between pregnancy and a drop in blood pressure, we also categorized women who delivered according to breastfeeding duration after first pregnancy. Lastly, we estimated the blood pressure trajectories for women with a hypertensive disorder and normotension in first pregnancy. All statistical analyses were carried out using Stata IC 13 (StataCorp, College Station, Texas) and MLwiN [30] version 2.34.

Results

Characteristics of the 21,513 parous and 1925 nulliparous women included in the analysis are given in Table 1. Compared to parous women, nulliparous women were more likely to be obese, but were less likely to report ever smoking or ever use of oral contraceptives. In total 46,320 blood pressure measurements were taken, 3417 from nulliparous and 42,903 from parous women, and of the latter, 2963 were collected pre-pregnancy and 39,940 post-pregnancy. A total of 7649 (33%) women participated in all three HUNT surveys and therefore had their blood pressure measured on three occasions, 7584 (33%) in two and 8199 (34%) in only one HUNT survey (Fig. 1). The distribution of blood pressure measurements by age group and HUNT survey is shown in Supplemental Figure 1. Median ages were 23 years at first birth, 27 at second and 30 at the third birth. Blood pressure measurements in HUNT covered time periods spanning from 20 years before to 40 years after the first pregnancy.

Figure 2 shows trajectories of systolic and diastolic blood pressure for parous and nulliparous women for the age interval 20–60 years. Women who became parous by the end of follow up and nulliparous women had indistinguishable mean blood pressure levels at age 20 (when both groups were nulliparous) until the first birth of the parous women, after which the blood pressures of the newly parous women fell abruptly (Fig. 2a, b). The mean adjusted changes in systolic and diastolic blood pressure from pre to post first pregnancy were − 3.32 mmHg (95% CI, − 3.93, − 2.71) and − 1.98 mmHg (95% CI, − 2.43, − 1.53), respectively (Table 2). Second and third pregnancies were also associated with blood pressure declines, though smaller than those seen in the first pregnancy (Fig. 2c–f, Table 2).

It took parous women roughly a decade to reach their mean pre-pregnancy blood pressure levels. From age 30 to 40 years, parous women had a faster rise in blood pressure compared with nulliparous women (Supplemental Table 2). Yet, the lower blood pressure in parous compared with nulliparous women lasted beyond 50 years of age (Fig. 2). Compared with nulliparous women, systolic blood pressure of parous women differed by − 1.93 mmHg (95% CI, − 3.33, − 0.53) at age 50 and − 1.38 mmHg (95% CI, − 3.56, 0.80) at age 60, while diastolic blood pressure differed by − 1.36 mmHg (95% CI, − 2.26, − 0.46) at age 50 and − 1.95 mmHg (95% CI, − 3.34, − 0.55) at age 60 (Supplemental Table 3).

Prior to pregnancy, the prevalence of hypertension was lower among future parous compared with never parous women. The prevalence among parous women declined after pregnancy, leading to a long-lasting greater difference

Table 1 Descriptive characteristics of the study population

Characteristics	Nulliparous (n = 1925)	Parous (n = 21,513)
Birthyear, median (IQR)	1958 (1949–1966)	1958 (1951–1965)
Ever smoked daily, n (%)		
No	924 (48)	8500 (40)
Yes	1001 (52)	13,013 (60)
Education, n (%)		
Lower secondary	437 (23)	3823 (18)
Upper secondary	814 (42)	10,061 (47)
Tertiary	674 (35)	7629 (35)
Ever used oral contraceptives, n (%)*		
No	693 (36)	4380 (20)
Yes	708 (37)	13,077 (61)
Missing	524 (27)	4056 (19)
Ever used blood pressure medication, n (%)		
No	1721 (89)	19,075 (89)
Yes	204 (11)	2434 (11)
Missing	0 (0)	4 (0)
Births, n (%)		
1	N/A	2577 (12)
2	N/A	9778 (46)
3 or more	N/A	9158 (42)
Age at 1st birth, median (IQR)	N/A	23 (20–26)
Year of 1st birth, median (IQR)	N/A	1981 (1973–1990)
Breastfeeding length of first child, n (%)*		
No breastfeeding	N/A	994 (5)
< 3 months	N/A	2864 (13)
3–6 months	N/A	5437 (25)
> 6 months	N/A	7401 (34)
Missing	N/A	4817 (22)
No. of HUNT exams, n (%)		
1	898 (47)	7307 (34)
2	562 (29)	7022 (33)
3	465 (24)	7184 (33)
Time varying covariates		
Number of observations, n (%)	3417 (7)	42,903 (93)
BMI at HUNT exam, kg/m^2		
< 25	1792 (52)	24,022 (56)
25–29.9	953 (28)	12,935 (30)
≥ 30	648 (19)	5881 (14)
Missing	24 (1)	65 (0.2)
Current use of oral contraceptives, n (%)*		
No	1684 (49)	22,686 (53)
Yes	234 (7)	2797 (7)
Missing	1499 (44)	17,420 (41)
Current use of blood pressure medication, n (%)		
No	3192 (93)	40,461 (94)
Yes	219 (6)	2338 (6)
Missing	6 (0.2)	104 (0.2)

*Queried at HUNT2 and HUNT3

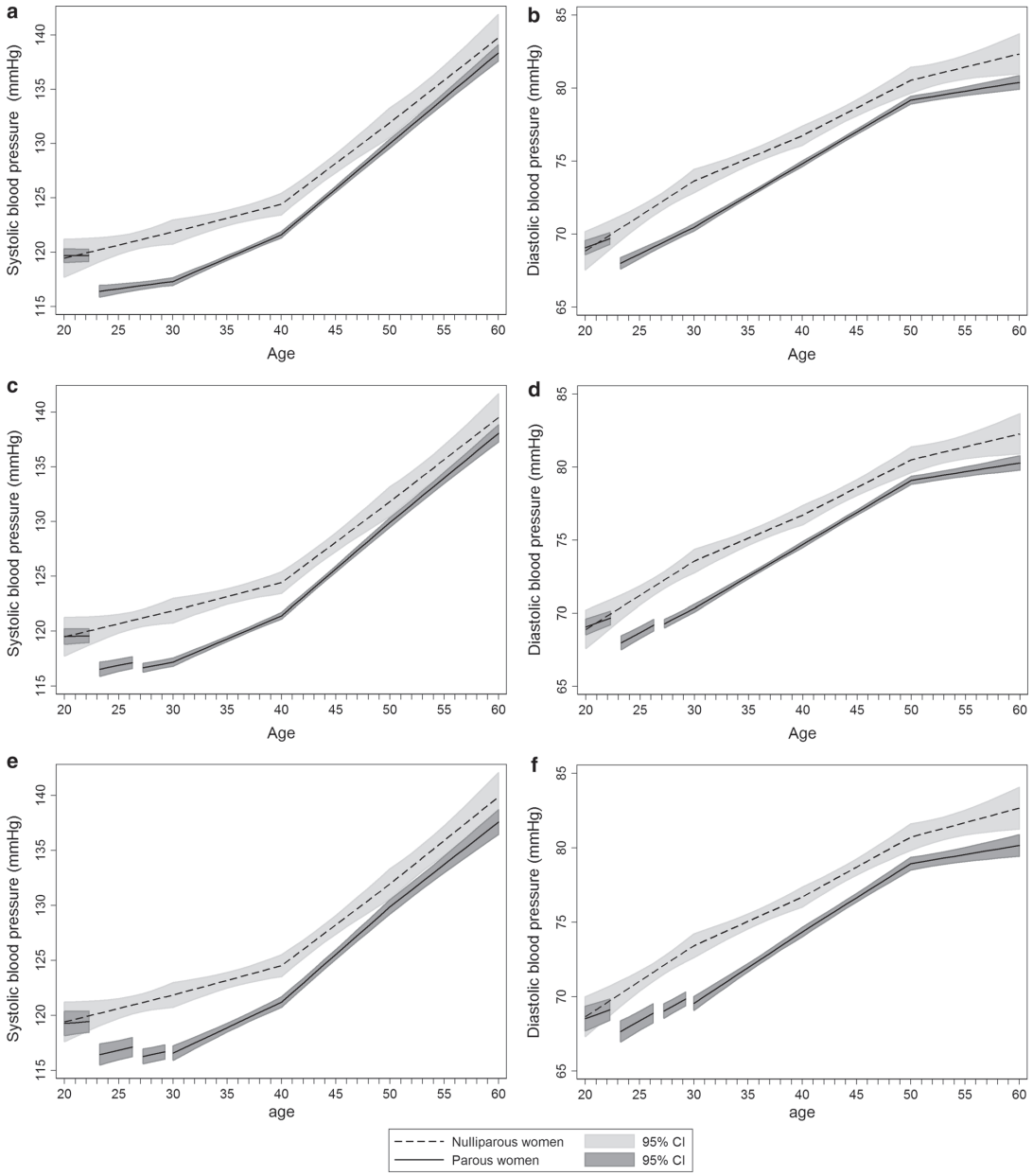

Fig. 2 Mean systolic and diastolic blood pressure life course trajectories for nulliparous and parous women with one or more births (**a** and **b**), two or more births (**c** and **d**) and three or more births (**e** and **f**). Trajectories are drawn for women with covariates fixed at their means and with gaps in the graph of parous women corresponding to pregnancy and 3-month postpartum periods with the 1st birth at age 23, 2nd at 27 and 3rd at 30 years. Estimates are adjusted for age, HUNT survey, education and ever daily smoking

in prevalence between parous and nullparous women that attenuated from 40 to 50 years of age (Supplemental Figure 2).

We examined whether the effect of pregnancy on blood pressure varied by age at first pregnancy. The blood pressure decline from pre to post first pregnancy was only

Table 2 Estimated mean change in systolic and diastolic blood pressure from pre- to post-pregnancy among parous women

	Pregnancy one[a]			Pregnancy two[b]			Pregnancy three[c]		
	Blood pressure change	95% CI	*p* value	Blood pressure change	95% CI	*p* value	Blood pressure change	95% CI	*p* value
Systolic (mmHg)									
Model 1[d]	− 3.42	[− 3.98, − 2.85]	< 0.001	− 0.68	[− 1.28, − 0.07]	0.028	− 0.22	[0.97, 0.53]	0.563
Model 2[e]	− 3.32	[− 3.93, − 2.71]	< 0.001	− 0.68	[− 1.30, − 0.06]	0.031	− 0.24	[− 1.00, 0.52]	0.537
Diastolic (mmHg)									
Model 1[d]	− 2.00	[− 2.42, − 1.59]	< 0.001	− 0.33	[− 0.77, 0.11]	0.138	− 0.62	[− 1.15, − 0.10]	0.021
Model 2[e]	− 1.98	[− 2.43, − 1.53]	< 0.001	− 0.31	[− 0.75, 0.14]	0.182	− 0.59	[− 1.13, − 0.06]	0.031

[a]Estimates are obtained from the trajectory models depicted in Fig. 2a and b where nulliparous women and all women with one or more children are included (n = 23,168)

[b]Estimates are obtained from the trajectory models depicted in Fig. 2c and d where nulliparous women and all women with two or more children are included (n = 20,861)

[c]Estimates are obtained from the trajectory models depicted in Fig. 2e and f where nulliparous women and all women with three or more children are included (n = 11,083)

[d]Estimates are adjusted for age and HUNT survey

[e]Estimates are adjusted for age, HUNT survey, education and ever daily smoking

slightly smaller (− 0.03 mmHg; 95% CI, − 0.18, 0.12) for systolic and slightly larger (0.06 mmHg; 95% CI, − 0.05, 0.17) for diastolic for each 1-year higher age at first pregnancy. When restricting our analysis to the 15,233 women with repeated (2 or 3) blood pressure measurements we observed similar trajectories as in our main analysis (Supplemental Figure 3), confirming that our main results were representative of within-woman changes in blood pressure. As a sensitivity analysis, we examined how the amendment for the effect of antihypertensive medication influenced our results and found that the shape of the trajectories remained essentially unchanged when we used the original, unamended blood pressure values in the analysis (Supplemental Figure 4).

Our analysis of within-woman change in blood pressure comparing the 621 women who gave birth to their first child between HUNT2 and HUNT3 to the 427 who remained nulliparous confirmed that pregnancy was associated with reductions in systolic and diastolic blood pressure similar to those observed in the main analysis (Supplemental Table 4); the estimated mean drop after pregnancy was − 3.99 mmHg (95% CI, − 5.98, − 1.99) for systolic and − 3.04 mmHg (95% CI, − 4.43, − 1.64) for diastolic blood pressure. Additional adjustment for oral contraceptive use and BMI did not substantially attenuate the estimated association between pregnancy and blood pressure change (Supplemental Table 5). The blood pressure change was broadly similar across categories of breastfeeding duration; however, 79% of women with first birth between HUNT2 and HUNT3 breastfed for > 6 -months after their first pregnancy, and the low number of women with no or short breastfeeding duration prevented precise estimates for those groups (Supplemental Table 6).

Among 21,513 parous women, 20,038 had normotension and 1475 had a hypertensive disorder in first pregnancy (preeclampsia, 994; gestational hypertension, 433; pre-pregnancy chronic hypertension, 48). There was some evidence that the blood pressure drop from pre to post first pregnancy differed between the two groups ($P_{interaction} = 0.195$ for systolic and 0.007 for diastolic blood pressure). In women with normotension in first pregnancy, the mean adjusted changes from pre to post first pregnancy were − 3.43 mmHg (95% CI, − 4.05, − 2.80) in systolic and − 2.15 mmHg (95% CI, − 2.62, − 1.69) in diastolic blood pressure. In women with a hypertensive disorder in first pregnancy, the corresponding changes were − 2.02 mmHg (95% CI, − 4.08, 0.04) systolic, but only 0.01 mmHg (95% CI, − 1.50, 1.51) diastolic. Women with a hypertensive disorder in first pregnancy had higher mean blood pressure throughout the age span, compared with both nulliparous women and women with a normotensive first pregnancy (Supplemental Figure 5).

Discussion

This study provides evidence that systolic and diastolic blood pressure drop after a woman's first birth and suggests that pregnancy itself induces differences in blood pressure between parous women post-pregnancy and nulliparous women. Our results also show that it takes approximately a decade for parous women to reach the levels they

experienced pre-pregnancy, and they do not reach the levels of nulliparous women until beyond menopause.

Our study is the first to include blood pressure measurements spanning from pre-pregnancy up to 40 years postpartum and is the first to examine blood pressure trajectories across a woman's life course taking into account the timing of pregnancy. The magnitude of drop in blood pressure associated with a woman's first pregnancy of − 3 mmHg systolic and − 2 mmHg diastolic is consistent with previous studies that examined changes in blood pressure from pre-pregnancy to postpartum [6–8]. In the longitudinal Cardia study of 2304 women, systolic and diastolic blood pressure dropped by − 2 mmHg over an interval of 2–20 years for women who had a first birth during the interval [7]. Similar differences between parous and nulliparous women were seen at age 36, but had disappeared by age 53 in a British cohort study of 2977 women [12]. In a Swiss cohort study [9], parity was associated with lower blood pressure before 60 years, but with a higher blood pressure after 60 years of age. Other cross-sectional studies examining blood pressure or risk of hypertension by parity status have reported either no significant association [13–15] or lower blood pressure among parous women [10, 11], with stronger association seen in premenopausal women [10, 11].

Our large study size, almost ten-fold more women than previous individual longitudinal studies, yielded precise blood pressure estimates. A major advantage of our study is that in addition to comparing parous women to women who remained nulliparous throughout their life, we were also able to compare pre- and post-pregnancy blood pressure among parous women. Most previous studies only compared parous to nulliparous women to estimate the long-term effect of pregnancy on blood pressure. This approach is susceptible to confounding by socioeconomic and behavioral factors and by health conditions such as polycystic ovary syndrome that impact fertility and may also affect blood pressure [31, 32]. In our data, the lack of difference in mean blood pressure in early adulthood between future parous and never parous women, the abrupt drop in blood pressure trajectory at the time of pregnancy, and the within-woman drop in blood pressure from pre to post first pregnancy all suggest that effects of parity explain most of the difference in blood pressure between parous and nulliparous women. Nonetheless, the higher prevalence of hypertension in early adulthood among never parous compared with future parous women suggests that early-onset factors influencing parity may also contribute to higher blood pressure in nulliparous women.

We used a mixed effects model [33] to account for correlated repeated measures of blood pressure in the same woman and model the subject variation in blood pressure levels and slopes between women. This allowed us to estimate within-woman blood pressure trajectories, avoiding the pitfalls of using purely cross-sectional information which may not correctly represent within-subject change over time. Two thirds of the study subjects participated in more than one HUNT exam and we obtained similar results when restricting to this exclusively longitudinal subgroup. The method for blood pressure measurement in HUNT1 differed from that in HUNT2 and HUNT3; therefore, we adjusted for HUNT survey in the analyses. Also, the pregnancy-related drop in blood pressure was confirmed when we examined within-woman change in blood pressure between HUNT2 and HUNT3 and found that women giving birth in this interval experienced drops in systolic and diastolic blood pressure comparable to the ones found in our main analysis.

In our main analysis, we controlled for age, education and smoking. Unfortunately, we were unable to adjust for pre-pregnancy BMI and oral contraceptive use, as these covariates were lacking for the majority of participants. However, in the analysis of within-woman change in blood pressure, adjustment for BMI and oral contraceptive use did not markedly attenuate the estimates, indicating that the lack of adjustment for these variables is not a source of substantial bias in the main analysis. We cannot exclude residual confounding due to other factors related to both parity and later blood pressure levels, for example infertility-associated health conditions. However, these factors are unlikely to explain the within-woman drop in blood pressure at the time of pregnancy. Non-participation in HUNT was related to age, socioeconomic factors and adverse health outcomes, including a higher prevalence of cardiovascular disease and diabetes, but not to use of antihypertensive medication [34] and we do not expect non-participation to have affected the shape of or differences between the trajectories.

There was a secular decrease in blood pressure between HUNT2 and HUNT3 [35], as also observed in other populations [36] over the same time period and this may be due to dietary changes and increased use of antihypertensive medication. Although we did add constants to the measured blood pressure values of individuals treated for hypertension, as recommended [23, 24], the slope in blood pressure with age may be underestimated. However, we have no reason to believe that this underestimate would substantially affect nulliparous differently from parous individuals and alter our overall findings. While the study population is fairly representative of the population of Norway [20], it is an ethnically homogenous population which may limit the generalizability of these findings. There is some evidence that the effect of pregnancy on blood pressure may be weaker for Black compared with White women [7]. It is also possible that the effect of pregnancy on blood pressure may differ by pregnancy characteristics. In our study, the

drop in diastolic pressure from pre to post pregnancy was absent among women with hypertensive pregnancy disorders, but their drop in systolic blood pressure did not convincingly differ from that observed in women with normotensive pregnancies.

One possible explanation for the longlasting differences in blood pressure between parous and nulliparous women is that changes in vascular function that occur in response to pregnancy persist postpartum. There are a number of cardiovascular adaptations to pregnancy that increase blood flow to organs, including a large increase in cardiac output and a corresponding decrease in vascular resistance [37]. Some of these adaptations, such as increased heart rate, appear to normalize quickly [6] while others such as reduced vascular resistance [6] and increased arterial compliance [8] appear to last at least 1 year postpartum. The decrease in vascular resistance following pregnancy at 1 year postpartum [6] may partly be explained by reduced arterial stiffness [8] which also was found to be present at 1 year postpartum. Pregnancy may impart lasting changes to cardiovascular structure and function in a similar manner to regular exercise [38].

Alternatively, other factors that accompany pregnancy may contribute to the lower post-pregnancy blood pressure. In two cross-sectional studies [39, 40], one of which was conducted within the HUNT study cohort [39], longer duration of breastfeeding was associated with lower blood pressure among parous women. Those results may suggest that breastfeeding mediates the association between parity and blood pressure, but could also have arisen due to higher pre-pregnancy blood pressure in women with short or no breastfeeding. In our longitudinal analysis, we saw no dose–response relationship between breastfeeding duration and blood pressure change from pre to post first pregnancy. Although our longitudinal sample was too small to make conclusive inferences, our results suggest breastfeeding does not mediate the drop in blood pressure observed after pregnancy. It is also possible that lifestyle changes post-pregnancy contribute to decreasing blood pressure. This would be consistent with findings from a British cohort that both women and men had lower blood pressure if they had one or more children compared with none, with little difference in magnitude by sex [12]. There is a small, lasting weight gain (mean, 0.5–3 kg) [41] associated with pregnancy; this would expectedly contribute to a higher blood pressure. In our data, adjustment for pre- to post-pregnancy change in BMI slightly attenuated the estimates.

A 2–3 mmHg lower blood pressure lasting from first pregnancy to beyond 50 years of age is likely to have a significant influence on risk of CVD, as even a 2 mmHg reduction in diastolic blood pressure was found to reduce the risk of coronary heart disease by 6% and the risk of stroke and transient ischemic attacks by 15% [42]. The pregnancy-related drop in blood pressure may contribute to the lower CVD risk observed in women compared with men at younger age. It has been estimated that sex differences in blood pressure may explain 20% of the sex difference in CVD mortality below 50 years of age, but little or no of the sex difference at older ages [16]. Finally, the pregnancy-related drop in blood pressure provides a possible explanation why the risk of pre-eclampsia is higher in the first compared with the second pregnancy since higher pre-pregnancy blood pressure is associated with increased risk of pre-eclampsia. The risk of pre-eclampsia is more than halved from the first to subsequent pregnancies [43] and this reduced risk is present for interpregnancy intervals up to approximately 10 years [43]. Our results are consistent with the hypothesis that lower blood pressure following a first pregnancy reduces the risk of preeclampsia and that this protective effect gradually diminishes but can remain for up to a decade [44, 45], at which time mean blood pressure approached its pre-pregnancy level in our data.

Conclusion

A woman's first pregnancy and to a lesser extent her subsequent pregnancies, are associated with reductions in systolic and diastolic blood pressure that persist over decades. The decreases in blood pressure resulting from pregnancies may provide a protective effect against hypertension and CVD. Our results may help explain CVD risk differences defined by parity and sex and why the risk of preeclampsia is higher in the first compared with later pregnancies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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Supplementary material

The impact of parity on life course blood pressure trajectories. The HUNT Study in Norway.

Supplemental Table 1. Descriptive characteristics of female HUNT participants born in the eligible birth cohorts 1940-1974, by inclusion status

Characteristics	Included in the analyses (n=23,438)	Excluded from the analyses (n=5400)
Birthyear, median (IQR)	1958 (1951 – 1965)	1945 (1942 - 1956)
Age at last HUNT participation, median (IQR)	45 (37 - 54)	53 (35 - 64)
Ever smoked daily, n (% of non-missing)		
No	9424 (40)	1582 (37)
Yes	14,014 (60)	2658 (63)
Missing, n (%)	0	1160 (22)
Education, n (% of non-missing)		
Lower Secondary	4260 (18)	1744 (43)
Upper Secondary	10875 (46)	1481 (37)
Tertiary	8303 (35)	831 (21)
Missing, n (%)	0	1344 (25)
Ever used oral contraceptives, n (% of non-missing)*		
No	5073 (27)	1680 (52)
Yes	13785 (73)	1572 (48)
Missing, n (%)	4580 (20)	2148 (40)
Ever used blood pressure medication, n (% of non-missing)		
No	20,796 (89)	4391 (81)
Yes	2638 (11)	1004 (19)
Missing, n (%)	4 (0.02)	5 (0.1)
Parity, n (%)		
Nulliparous	1925 (8)	269 (5)
Parous	21,513 (92)	5131 (95)
1 birth	2362 (10)	409 (8)
2 births	9500 (41)	1666 (31)
3 or more births	9651 (41)	3053 (57)
unknown number of births	0	3 (0.1)
Age at 1st birth, median (IQR)**	23 (20 - 26)	21 (19 - 23)
Missing, n (%)	0	1162 (22)
Year of 1st birth, median (IQR)**	1981 (1973–1990)	1966 (1964 - 1980)
Missing, n (%)	0	1590 (29)

* Queried at HUNT2 and HUNT3

** For women whose first birth was prior to the inception of Medical Birth Registry of Norway in 1967, information on age and year of first birth is based on the women's report at participation in HUNT

Supplemental Table 2. Predicted increase per year in systolic and diastolic pressure by age at follow-up in parous and nulliparous women.

	Nulliparous		Parous*		Difference		
Age interval	Blood pressure†	95% CI	Blood pressure†	95% CI	Blood pressure†	95% CI	p-value
Systolic (mmHg/year)							
20–23 years	0.242	[0.003 , 0.480]	0.012	[-0.076 , 0.100]	-0.230	[-0.483 , 0.023]	0.075
24–30 years	0.242	[0.003 , 0.480]	0.134	[0.047 , 0.220]	-0.108	[-0.361 , 0.144]	0.401
30–40 years	0.255	[0.098 , 0.412]	0.430	[0.383 , 0.476]	0.174	[0.012 , 0.337]	0.035
40–50 years	0.751	[0.584 , 0.918]	0.839	[0.792 , 0.886]	0.089	[-0.083 , 0.260]	0.310
50–60 years	0.781	[0.535 , 1.028]	0.836	[0.765 , 0.908]	0.055	[-0.198 , 0.308]	0.671
Diastolic (mmHg/year)							
20–23 years	0.478	[0.304 , 0.651]	0.280	[0.216 , 0.344]	-0.198	[-0.382 , -0.014]	0.035
24–30 years	0.478	[0.304 , 0.651]	0.364	[0.302 , 0.427]	-0.114	[-0.297 , 0.070]	0.226
30–40 years	0.312	[0.204 , 0.421]	0.437	[0.405 , 0.469]	0.125	[0.013 , 0.237]	0.029
40–50 years	0.379	[0.268 , 0.490]	0.435	[0.404 , 0.467]	0.056	[-0.058 , 0.170]	0.335
50–60 years	0.181	[0.017 , 0.344]	0.122	[0.075 , 0.168]	-0.059	[-0.226 , 0.109]	0.491

* Predicted for parous women having their first birth at age 23, corresponding to median age at first birth in our study population.

† Estimates are based on the trajectory models depicted in Figure 2a and 2b and adjusted for age, HUNT survey, education and ever daily smoking.

Supplemental Table 3. Predicted mean systolic and diastolic blood pressure by age at follow-up in parous and nulliparous women.

	Nulliparous		Parous*		Difference		
	Blood pressure†	95% CI	Blood pressure†	95% CI	Blood pressure†	95% CI	p-value
Systolic (mmHg)							
20 years	119.44	[117.69 , 121.19]	119.68	[119.03 , 120.33]	0.24	[-1.58 , 2.05]	0.797
1st birth in parous women occurs at age 23							
30 years	121.86	[120.75 , 122.97]	117.30	[116.95 , 117.65]	-4.56	[-5.70 , -3.42]	<0.001
40 years	124.41	[123.43 , 125.40]	121.60	[121.32 , 121.88]	-2.82	[-3.84 , -1.79]	<0.001
50 years	131.92	[130.56 , 133.28]	129.99	[129.58 , 130.40]	-1.93	[-3.33 , -0.53]	0.007
60 years	139.73	[137.59 , 141.88]	138.35	[137.62 , 139.09]	-1.38	[-3.56 , 0.80]	0.215
Diastolic (mmHg)							
20 years	68.85	[67.54 , 70.17]	69.07	[68.59 , 69.56]	0.22	[-1.14 , 1.58]	0.750
1st birth in parous women occurs at age 23							
30 years	73.63	[72.83 , 74.43]	70.46	[70.21 , 70.71]	-3.17	[-3.99 , -2.35]	<0.001
40 years	76.75	[76.09 , 77.41]	74.83	[74.64 , 75.02]	-1.92	[-2.61 , -1.23]	<0.001
50 years	80.54	[79.66 , 81.42]	79.18	[78.92 , 79.45]	-1.36	[-2.26 , -0.46]	0.003
60 years	82.35	[80.98 , 83.72]	80.40	[79.94 , 80.87]	-1.95	[-3.34 , -0.55]	0.006

*Predicted for parous women having their first birth at age 23, corresponding to median age at first birth in our study population.

† Estimates are based on the trajectory models depicted in Figure 2a and 2b and adjusted for age, HUNT survey, education and ever daily smoking.

Supplemental Table 4. Mean within-woman change in systolic and diastolic blood pressure between HUNT2 and HUNT3 (n=1048).

No. of births between HUNT2 and HUNT3	n	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
		change*	95% CI	p-value	change*	95% CI	p-value
None	426	ref.			ref.		
Any	620	-3.99	[-5.98 , -1.99]	<0.001	-3.04	[-4.43 , -1.64]	<0.001
1	139	-3.57	[-6.20 , -0.94]	0.008	-3.05	[-4.89 , -1.20]	0.001
2	334	-3.28	[-5.53 , -1.04]	0.004	-2.53	[-4.10 , -0.96]	0.002
≥ 3	147	-6.47	[-9.26 , -3.68]	<0.001	-4.34	[-6.28 , -2.39]	<0.001

*estimates are adjusted for age and education at baseline (HUNT2) and change in smoking status from HUNT2 to HUNT3.

Supplemental Table 5. Mean within-woman change in blood pressure (mmHg) due to pregnancy among 754[*] women who participated in both HUNT2 and HUNT3 and had complete data on all covariates.

No. of births between HUNT2 and HUNT3	Model 1[†]			Model 2[‡]			Model 3[§]			Model 4[‖]			Model 5[#]		
	change	95% CI	p-value	change	95% CI	p-value	change	95% CI	p-value	change	95% CI	p-value	change	95% CI	p-value
Systolic (mmHg)															
None (309)	ref.			ref.			ref.			ref.			ref.		
Any (431)	-3.25	[-5.61, -0.89]	0.007	-3.07	[-5.46, -0.69]	0.012	-3.13	[-5.52, -0.74]	0.010	-2.63	[-5.06, -0.21]	0.033	-2.47	[-4.86, -0.08]	0.043
1 (92)	-2.62	[-5.83, 0.59]	0.110	-2.54	[-5.77, 0.68]	0.123	-2.62	[-5.85, 0.62]	0.113	-2.12	[-5.38, 1.13]	0.201	-2.06	[-5.28, 1.15]	0.208
2 (226)	-2.63	[-5.34, 0.07]	0.056	-2.48	[-5.20, 0.24]	0.073	-2.52	[-5.24, 0.20]	0.069	-2.02	[-4.77, 0.73]	0.150	-1.92	[-4.63, 0.79]	0.165
≥ 3 (113)	-5.39	[-8.62, -2.16]	0.001	-5.15	[-8.42, -1.87]	0.002	-5.22	[-8.49, -1.94]	0.002	-4.72	[-8.01, -1.42]	0.005	-4.29	[-7.55, -1.03]	0.010
Diastolic (mmHg)															
None (309)	ref.			ref.			ref.			ref.			ref.		
Any (431)	-2.33	[-3.90, -0.75]	0.004	-2.37	[-3.96, -0.78]	0.004	-2.37	[-3.96, -0.77]	0.004	-2.04	[-3.66, -0.42]	0.014	-2.00	[-3.62, -0.39]	0.015
1 (92)	-2.17	[-4.31, -0.03]	0.047	-2.26	[-4.42, -0.11]	0.040	-2.21	[-4.38, -0.05]	0.045	-1.89	[-4.07, 0.29]	0.089	-1.88	[-4.05, 0.30]	0.091
2 (226)	-1.83	[-3.63, -0.02]	0.047	-1.86	[-3.67, -0.04]	0.045	-1.86	[-3.68, -0.05]	0.044	-1.53	[-3.37, 0.30]	0.102	-1.51	[-3.35, 0.32]	0.107
≥ 3 (113)	-3.60	[-5.76, -1.45]	0.001	-3.69	[-5.88, -1.50]	0.001	-3.72	[-5.91, -1.53]	0.001	-3.40	[-5.61, -1.20]	0.002	-3.31	[-5.51, -1.10]	0.003

[*] Sample size is lower than in Supplemental Table 3 predominantly due to incomplete information on oral contraceptive use from questionnaires retrieved by mail.

[†] estimates are adjusted for age at baseline (HUNT2).

[‡] estimates are adjusted for age and education at baseline (HUNT2).

[§] estimates are adjusted for age and education at baseline (HUNT2) and change in smoking status from HUNT2 to HUNT3.

[‖] estimates are adjusted for age and education at baseline (HUNT2) and change in smoking status and oral contraceptive use from HUNT2 to HUNT3.

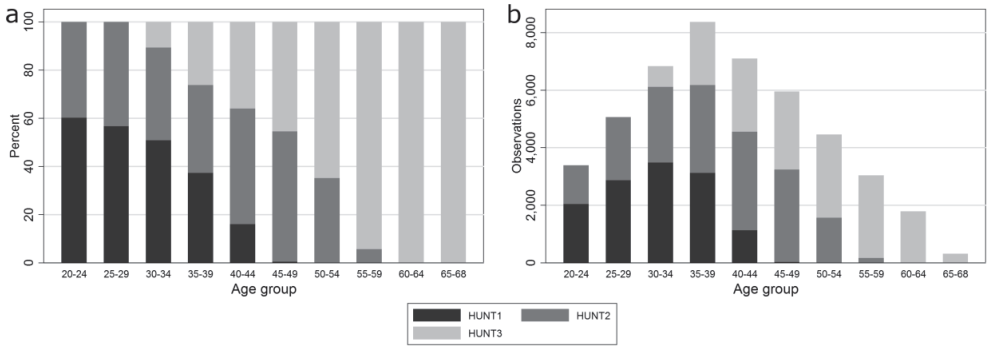
[#] estimates are adjusted for age and education at baseline (HUNT2) and change in smoking status, oral contraceptive use and BMI from HUNT2 to HUNT3.

Supplemental Table 6. Mean within-woman change in systolic and diastolic blood pressure between HUNT2 and HUNT3 by breastfeeding categories (n=702).*

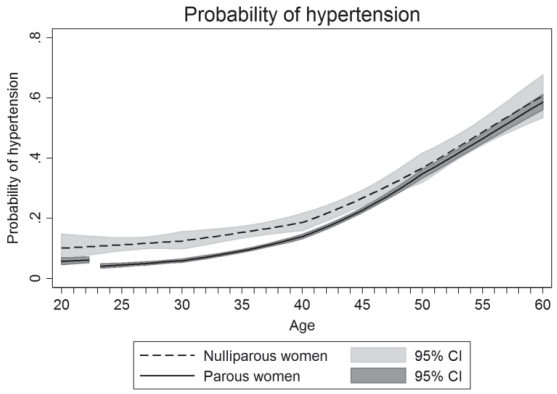
Breastfeeding status of first pregnancy	N	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)		
		change†	95% CI	p-value	change†	95% CI	p-value
No pregnancy	320	reference			reference		
No breastfeeding	15	-2.89	[-9.90 , 4.13]	0.420	-2.85	[-7.60 , 1.90]	0.239
> 0 to < 3 months	26	-2.35	[-7.80 , 3.09]	0.397	-2.72	[-6.40 , 0.97]	0.149
3 to 6 months	41	-1.42	[-5.93 , 3.10]	0.539	-1.11	[-4.17 , 1.95]	0.476
> 6 months	300	-2.71	[-5.32 , -0.10]	0.042	-2.46	[-4.23 , -0.70]	0.006

*sample is smaller than in Supplemental Table 4 due to missing information on breastfeeding length.

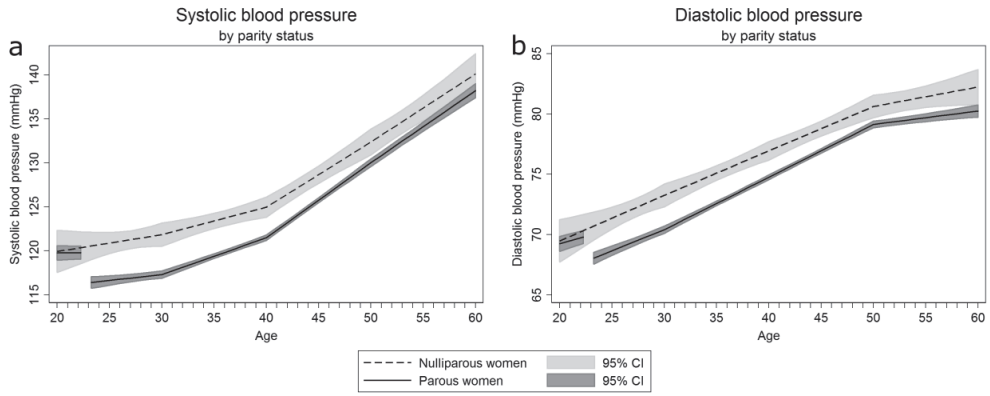
†estimates are adjusted for age and education at baseline (HUNT2) and change in smoking status, oral contraceptive use and BMI from HUNT2 to HUNT3.



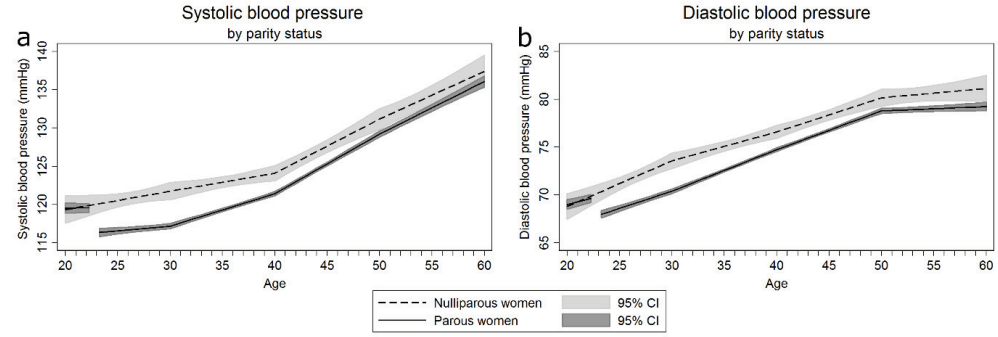
Supplemental Figure 1. **Proportion (a) and number (b) of blood pressure measurements according to age at participation and HUNT survey.**



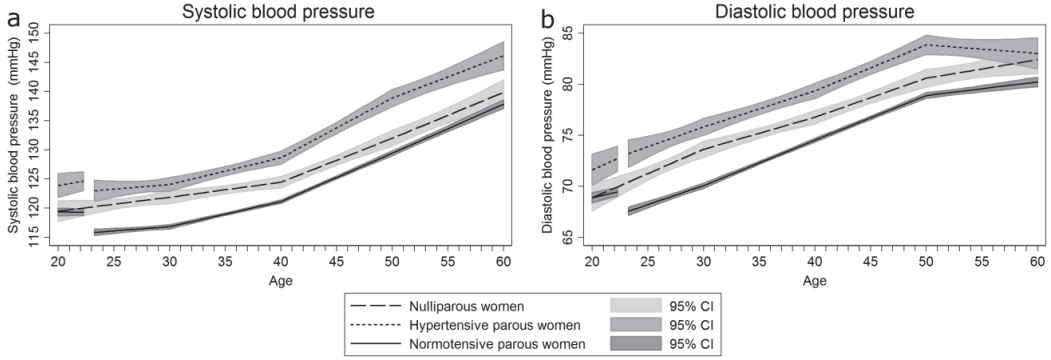
Supplemental Figure 2. Predicted probability of hypertension by age for nulliparous and parous women. The gap in the graph for parous women corresponds to the 1st pregnancy and 3-month postpartum period with the 1st birth at age 23. Estimates are adjusted for age, HUNT survey, education and ever daily smoking.



Supplemental Figure 3. **Mean systolic and diastolic blood pressure life course trajectories for nulliparous and parous women.** This strictly longitudinal sensitivity analysis includes only women with at least two blood pressure observations (n=15,233). Trajectories are drawn for women with covariates fixed at their means and with gaps in the graphs of parous women corresponding to the 1st pregnancy and 3-month postpartum period with the 1st birth at age 23. Estimates are adjusted for age, HUNT survey, education and ever daily smoking.



Supplemental Figure 4. **Mean systolic (a) and diastolic (b) blood pressure life course trajectories for nulliparous and parous women using original blood pressure data.** This sensitivity analysis is based on the original blood pressure values without adding constants in women who used antihypertensive medication, as was done in the main analysis. Trajectories are drawn for women with covariates fixed at their means and with gaps in the graphs of parous women corresponding to the 1st pregnancy and 3-month postpartum period with the 1st birth at age 23. Estimates are adjusted for age, HUNT survey, education and ever daily smoking.



Supplemental Figure 5. **Mean systolic (a) and diastolic (b) blood pressure life course trajectories for nulliparous women and parous women with or without a hypertensive disorder in their first pregnancy.** Trajectories are drawn for women with covariates fixed at their means and with gaps in the graphs of parous women corresponding to the 1st pregnancy and 3-month postpartum period with the 1st birth at age 23. Estimates are adjusted for age, HUNT survey, education and ever daily smoking.

Paper II

ORIGINAL RESEARCH

Life Course Trajectories of Cardiovascular Risk Factors in Women With and Without Hypertensive Disorders in First Pregnancy: The HUNT Study in Norway

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***Background*—**Women with hypertensive pregnancy disorders have adverse levels of cardiovascular risk factors. It is unclear how this adverse risk factor profile evolves during adult life. We compared life course trajectories of cardiovascular risk factors in women with preeclampsia or gestational hypertension in their first pregnancy to normotensive women.

***Methods and Results*—**We linked information on cardiovascular risk factors from the population-based HUNT (Nord-Trøndelag Health Study) surveys with pregnancy information from the Medical Birth Registry of Norway. Trajectories of cardiovascular risk factors were constructed for 22 308 women with a normotensive first pregnancy; 1092 with preeclampsia, and 478 with gestational hypertension in first pregnancy. Already before first pregnancy, women with preeclampsia in their first pregnancy had higher measures of adiposity, blood pressure, heart rate, and serum lipids and glucose compared with women with a normotensive first pregnancy. After first pregnancy, there was a parallel development in cardiovascular risk factor levels, but women with a normotensive first pregnancy had a time lag of >10 years compared with the preeclampsia group. There were no clear differences in risk factor trajectories between women with gestational hypertension and women with preeclampsia.

***Conclusions*—**Women with hypertensive pregnancy disorders in their first pregnancy had an adverse cardiovascular risk factor profile before pregnancy compared with normotensive women, and the differences persisted beyond 50 years of age. Hypertensive disorders in pregnancy signal long-term increases in modifiable cardiovascular risk factors, and may be used to identify women who would benefit from early prevention strategies. **(*J Am Heart Assoc*. 2018;7:e009250. DOI: 10.1161/JAHA.118.009250.)**

Key Words: cardiovascular risk factors • epidemiology • hypertensive disorders of pregnancy • life course

Cardiovascular disease (CVD) accounts for ≈1 in 3 deaths in women.[1] Hypertensive disorders of pregnancy (HDP), including preeclampsia and gestational hypertension, occur in up to 10% of all pregnancies.[2] Pregnancy may serve as a stress test of maternal cardiovascular health, where HDP may indicate a reduced ability to accommodate the extra cardiovascular and metabolic challenges of pregnancy.[3] HDP may reveal a phenotype predisposed to CVD, and may therefore be used to identify women who would benefit from early screening and preventive efforts. A history of HDP has been included as a cardiovascular risk factor in CVD prevention guidelines in the United States since 2011[4] and in Europe since 2016.[5] Yet there is little evidence and no consensus on how to tailor CVD screening and prevention in women with a history of HDP. Although previous studies reported adverse cardiovascular risk factor profiles in women with HDP both before and after pregnancy,[6–17] detailed knowledge on how different cardiovascular risk factors develop throughout life is lacking. In particular, it is unclear when in life the elevated cardiovascular risk profile manifests itself in women with a

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Accompanying Tables S1 through S5 and Figures S1 through S10 are available at http://jaha.ahajournals.org/content/7/15/e009250/DC1/embed/inline-supplementary-material-1.pdf

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Clinical Perspective

What Is New?

- In women with hypertensive disorders of pregnancy (HDP), adverse levels of adiposity, blood pressure, heart rate, serum lipids and glucose were present before first pregnancy and remained higher compared with other women beyond 50 years of age.
- Progression of cardiovascular risk factors throughout the age interval 20 to 60 years occurred mostly in parallel for women with and without a history of HDP, with greater increases in systolic blood pressure and adiposity in women with a history of HDP.

What Are the Clinical Implications?

- Women with a history of HDP may be expected to pass beyond treatment thresholds of cardiovascular risk factors at least 10 years earlier than women with normotensive pregnancy.
- Our results suggest that women with a history of HDP may benefit from early screening and intervention programs that seek to lower the levels of cardiovascular risk factors.

history of HDP, and whether and how this profile may change from before to after a pregnancy complicated with HDP, and also how differences in cardiovascular risk factors between women with and without HDP may evolve postpartum.

To our knowledge, no longitudinal studies have examined long-term trajectories of cardiovascular risk factors among women with a history of HDP from before first pregnancy until middle age. In the HUNT (Nord-Trøndelag Health Study) cohort in Norway, we recently observed that higher blood pressure in women with a history of HDP manifests before first pregnancy and lasts beyond 60 years of age.[18] In the present study, we examine the life course trajectories from before first pregnancy and until 60 years of age for a broad range of cardiovascular risk factors in women with and without HDP in their first pregnancy.

Methods

Data from the HUNT Study used in research projects will when reasonably requested by others be made available upon request to the HUNT Data Access Committee (hunt@medisin.ntnu.no). The HUNT data access information (available here: http://www.ntnu.edu/hunt/data) describes in detail the policy regarding data availability.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Study Population

The HUNT study is a longitudinal population study that has invited all adult inhabitants 20 years and older in Nord-Trøndelag county, Norway, to take part in health surveys since the 1980s. The surveys include questionnaires, interviews, blood sampling, and clinical measurements.[19–21] So far, 3 HUNT surveys have been conducted: HUNT1 1984–1986,[20] HUNT2 1995–1997,[21] and HUNT3 2006–2008.[19] The predominantly (>97% at the time of HUNT2) white population in Nord-Trøndelag is considered to be fairly representative for Norway as a whole.[21] The Medical Birth Registry of Norway (MBRN) has recorded all births in the country since 1967 and provides detailed information on maternal and child characteristics.[22] Information from the MBRN and HUNT was linked using the 11-digit unique personal identification number that is allocated to all Norwegian citizens. In total, 25 932 women whose first delivery had been recorded in the MBRN between its inception in 1967 and 2012 had also taken part in at least 1 HUNT survey between 1984 and 2008. Among them, we excluded 314 women whose first birth was a multiple and, since preeclampsia and gestational hypertension cannot be diagnosed before 20 weeks of gestation, we further excluded 56 women with either gestational length <20 weeks, offspring birth weight <350 g, or missing information on both gestational length and offspring birth weight. In addition, we excluded 88 women who had a pre-first pregnancy diagnosis of hypertension and 357 women who were pregnant or <3 months postpartum at all their HUNT examinations. Lastly, we excluded 1239 women because of incomplete information on smoking or education or because they had no cardiovascular risk factor measurements, leaving 23 878 women for statistical analysis (Figure 1).

Exposures and Covariates

Diagnoses of preeclampsia and gestational hypertension in first pregnancy were retrieved from the MBRN, which uses internationally recommended diagnostic criteria[2]: Gestational hypertension was generally defined as de novo hypertension (≥140 mm Hg systolic and/or ≥90 mm Hg diastolic) after 20 weeks of gestation, and preeclampsia also required proteinuria (300 mg/24 h or ≥1+ on the dipstick test). Validation studies[23,24] within the HUNT study population have estimated the positive predictive values of the preeclampsia and gestational hypertension diagnoses in the MBRN to be 88% and 68%, respectively.

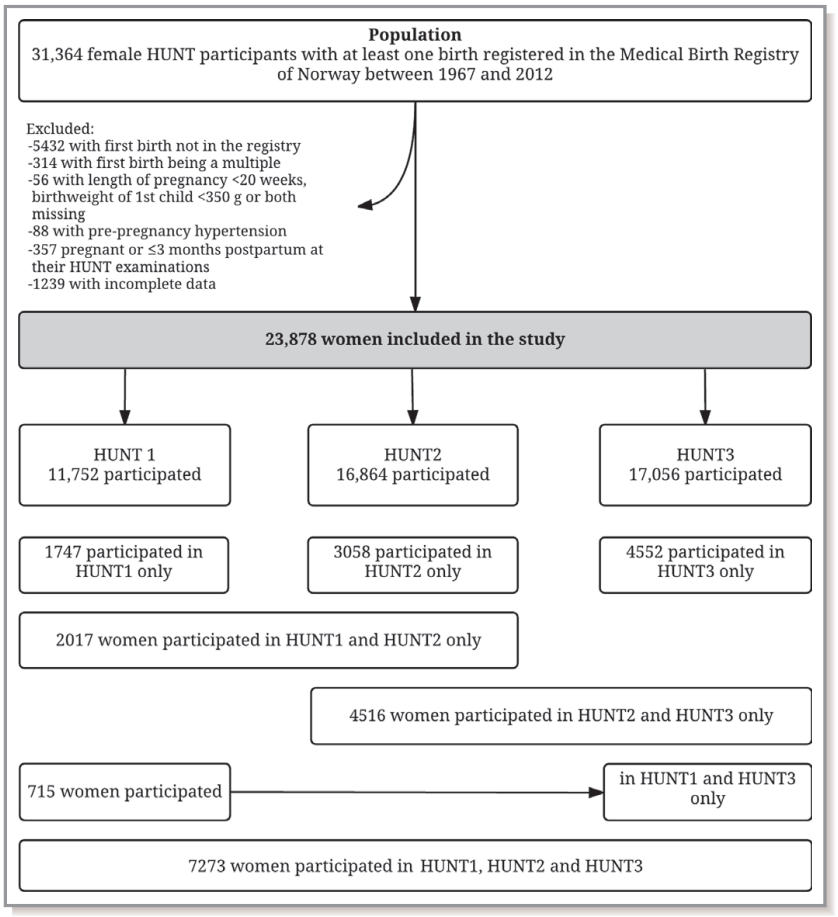

Figure 1. Flow chart of study population. HUNT indicates Nord-Trøndelag Health Study.

From the HUNT questionnaires and interviews, we retrieved self-reported information on use of antihypertensive medication, diabetes mellitus, ever daily smoking, hours since last meal, highest obtained educational level, and work titles. Since education level was not available in HUNT3, we derived educational level from work titles based on recommendations from Statistics Norway[25] for 5546 women.

Cardiovascular Risk Factors

Blood sampling and clinical measurements were performed by trained staff at the HUNT examination stations. Height and weight were measured with the person wearing light clothes and no shoes and were rounded to the nearest cm (height) and half kilo (weight). Body mass index (BMI) was calculated as weight (in kg) divided by the squared value of height (in m), and obesity was defined as BMI $\geq$30 kg/m^2. For 12 832 women in HUNT3, we also calculated BMI at age 18 years using self-reported height and weight at age 18 years. Blood pressure in HUNT1 was measured manually 2 times at 1-minute intervals using a sphygmomanometer after the person had come to rest, and we used the mean value of these 2 measurements in our analysis. In HUNT2 and HUNT3, blood pressure was measured 3 times at 1-minute intervals using an automatic oscillometric method (Dinamap, Critikon, FL) after the person had come to rest, with cuff size adjusted to arm circumference. We used the mean of the second and third measurement, except for 2135 women in HUNT3 who lacked the third measurement because of sick leave among staff; for them, we used the second measurement only. Based on recommendations by Cui et al[26] and Tobin et al,[27] we added 10 mm Hg to systolic and 5 mm Hg to diastolic blood

pressure levels for 2137 women who reported taking antihypertensive medication. We classified women as having hypertension if they reported taking antihypertensive medication, or whose blood pressure was either ≥140 mm Hg systolic or ≥90 mm Hg diastolic. Resting heart rate in beats/min was measured 1 time in HUNT1 and 3 times in HUNT2 and HUNT3 using the same devices as for blood pressure described above. For HUNT2 and HUNT3, we used the mean of the second and third measurements. Waist and hip circumference (available in HUNT2 and HUNT3) were measured to the nearest centimeter while the person was standing with arms hanging down at the height of the umbilicus (waist circumference) or at the thickest part of the hip (hip circumference).

All serum analyses were performed in nonfasting samples at the Central Laboratory, Levanger Hospital, Nord-Trøndelag Hospital Trust using a Hitachi 911 Autoanalyzer in HUNT2 and Architect cSystems ci8200 in HUNT3. All analyses were performed in fresh serum samples, except C-reactive protein (CRP) in HUNT2, which was measured after 2 years of serum storage at −80°C. Serum total and high-density lipoprotein (HDL) cholesterol and triglycerides were analyzed using enzymatic colorimetric methods (Boeheringer Mannheim, Germany) in HUNT2. In HUNT3, HDL cholesterol was measured with an accelerator selective detergent methodology, total cholesterol was analyzed by a cholesterol esterase methodology, and triglycerides were measured by a glycerol phosphate oxidase methodology, all by equipment from Abbott, Clinical Chemistry, USA. Non-HDL cholesterol was calculated as the difference between total and HDL cholesterol. High-sensitive CRP was measured in participants from 4 out of 24 municipalities (n=2766) in HUNT2 using a CRP ultrasensitive assay (Tina-quant(R); Roche, Basel, Switzerland). In HUNT3, CRP was measured in everyone using a latex immunoassay (Abbott, Clinical Chemistry, USA). In HUNT2 and HUNT3, serum glucose was measured for all persons using an enzymatic hexokinase method. In HUNT1, capillary glucose was measured at the examination stations in participants >40 years (Reflocheck-Glucose; Boehringer Mannheim, Germany), and for the analysis of mean glucose levels, we transformed capillary levels to equate serum values (in mmol/L) by multiplying by 1.11.[28] In HUNT1, fasting capillary glucose was measured in persons with capillary glucose ≥8.0 mmol/L at the initial examination, and a 2-hour oral glucose tolerance test was given if fasting capillary glucose was <7.0 mmol/L. If capillary glucose concentrations indicated diabetes mellitus (≥7.0 mmol/L fasting or ≥11.1 mmol/L after 2 hours), the corresponding serum glucose concentrations were measured. We defined diabetes mellitus by self-report (all HUNT surveys), nonfasting serum glucose ≥11.1 mmol/L (HUNT2 or HUNT3), or fasting serum glucose ≥7.0 mmol/L or 2-hour postload serum glucose ≥11.1 mmol/L (HUNT1). Serum creatinine was measured with the Jaffe method in HUNT2 (Roche Diagnostics, Mannheim, Germany) and with an alkaline picrate methodology in HUNT3 (Abbott, Clinical Chemistry, USA), and calibrated to isotope-dilution mass-spectroscopy level using an enzymatic method (Roche).[29] Estimated glomerular filtration rate in mL/min per 1.73 m^2 was calculated using the Chronic Kidney Disease Epidemiology consortium formula,[30] which takes account of creatinine, age, and sex.

Statistical Analysis

Life course trajectories of cardiovascular risk factors were modeled using linear spline mixed-effects models,[31] except for CRP, which had a limited number of repeated measurements and was modeled using a linear spline regression model with a cluster-robust estimate of variance (Huber/White sandwich estimate). The linear spline mixed-effects models included subject-specific (random) intercepts and slopes to account for up to 3 repeated dependent observations per woman and facilitated estimation of within-woman trajectories.[32] Linear splines defined by age intervals were used in order to allow for nonlinear change in the cardiovascular risk factor over time. The most appropriate age intervals were determined for each cardiovascular risk factor by comparing performance of models with 2, 4, 5, 6, 8, and 10 years age intervals using the Bayesian Information Criterion. On the basis of this, 10-year age intervals up to age 70 years were selected for all cardiovascular risk factors. All models adjusted for highest obtained education level (lower secondary [≤9 years], upper secondary [10–12 years], and tertiary [college or university]), ever daily smoking, HUNT survey, and age at first birth while also allowing the age-dependent change in cardiovascular risk factor (linear spline) to vary by exposure status and by different levels of these potential confounders. Analyses of glucose and triglycerides were additionally adjusted for number of hours since last meal (<1, 1, 2, 3, 4, 5, or ≥6 hours). We included 1 term describing the immediate change in cardiovascular risk factor level from pre- to post-first pregnancy, and another indicating the change in increase/decrease per year (slope) from pre- to post-first pregnancy. We allowed both terms to vary by whether the woman's first pregnancy was complicated by preeclampsia/gestational hypertension or was normotensive and by different levels of education, smoking, and age at first birth. All women aged 20 to 82 years old were included in the analysis, but because of limited data for women >60 years, we show predicted cardiovascular risk factor trajectories for the age range 20 to 60 years (18–60 for BMI, because of the available self-reported height and weight at age 18 years). We had insufficient data to model the risk factor

trajectories during pregnancy and placed gaps in the predicted trajectories corresponding to the first pregnancy and a 3 months postpartum period. We predicted the risk factor trajectories as if the woman had her first birth at age 23 years, the median age at first birth in our study population, and with all the remaining covariates set at their sample means. As a sensitivity analysis, we also modeled the same cardiovascular risk factor trajectories among women who had taken part in 2 or more HUNT surveys in order to examine the potential impact of including women with single measurements. In a separate analysis using logistic regression with cluster-robust variance, we also estimated the probability of being obese, having hypertension or diabetes mellitus as a function of age adjusting for highest obtained education level, ever daily smoking, age at first birth, and HUNT survey. In an additional analysis among women with at least 2 pregnancies, we examined whether repeat preeclampsia was associated with a more adverse cardiovascular risk profile. In this analysis, we contrasted cardiovascular risk trajectories in women having preeclampsia in both first and second pregnancy with women having preeclampsia in one of these pregnancies. Since the risk of preeclampsia is associated with pregnancy interval,[33,34] we additionally adjusted for time between the first and second pregnancy in this analysis. All analyses were performed using Stata IC 14 and MLwiN version 2.34[35] via the runmlwin[36] command in Stata.

Results

Characteristics of our study population are given in the Table. Among 23 878 women, 1092 (5%) had preeclampsia and 478 (2%) had gestational hypertension in their first pregnancy. Cardiovascular risk factors were measured within a time span of 20 years before to 40 years after first birth. In total, 7273 (30%) women participated in all 3 HUNT surveys, 7248 (30%) took part in 2 and 9357 (39%) only participated in 1 HUNT survey. Median age at first birth was similar for women with preeclampsia, gestational hypertension, and normotension in first pregnancy. Preterm delivery and small for gestational age offspring were more common in preeclamptic pregnancies. The numbers of women and measurements included in each of the cardiovascular risk factor analyses are given in Table S1, and Figure S1 displays the distribution of observations by participation age and HUNT survey.

For the sake of clarity and brevity, we focus the description of the results on risk factor trajectories in women with preeclampsia compared with normotension in first pregnancy. However, throughout the analyses, results for women with gestational hypertension in first pregnancy were comparable to those for women with preeclampsia; full results for gestational hypertension are given in Figures S2 and S3. Where no reference to the order of the pregnancy is made, it is implied that we mean the first pregnancy.

At the age of 20 years, women who later had a preeclamptic pregnancy had 5.2 mm Hg (95% confidence interval [CI], 3.2–7.2) higher systolic and 3.5 mm Hg (95% CI, 2.0–5.0) higher diastolic blood pressure compared with women who later had a normotensive pregnancy (Figure 2A and 2B, Table S2). From pre- to postpregnancy, systolic blood pressure decreased both in women with preeclampsia and normotensive pregnancies, whereas diastolic blood pressure decreased only in women with normotensive pregnancies (Table S3). In the years following pregnancy, the increase in blood pressure was similar among women with preeclampsia and normotensive pregnancy, except that women with preeclampsia had a steeper increase in systolic blood pressure from 40 to 50 years of age (Table S4). By age 60 years, systolic blood pressure was 9.0 mm Hg (95% CI, 6.2–11.8) higher and diastolic blood pressure was 2.8 mm Hg (95% CI, 1.0–4.6) higher in women with preeclampsia compared with normotensive pregnancy (Table S2). The prevalence of hypertension was higher in women with preeclampsia compared with normotensive pregnancy throughout the entire age range, and the prevalence in women with preeclampsia increased more strongly after age 30 years, a decade earlier than the corresponding increase among women with normotensive pregnancy (Figure 3A, Table S5). At age 60 years, 78% (95% CI, 70–84) of women with a first preeclamptic pregnancy had hypertension, compared with 58% (95% CI, 55–60) of women with normotensive pregnancy (Figure 3A, Table S5).

BMI was 1.1 kg/m^2 (95% CI, 0.8–1.3) higher at age 20 years in women with subsequent preeclampsia compared with women with a normotensive pregnancy (Figure 2C, Table S2). Up to pregnancy, and from pre- to immediately postpregnancy, BMI increased more steeply among women with preeclampsia (Tables S3 and S4). In the years after pregnancy, BMI increased linearly and in parallel in both groups, and at age 60 years, BMI was 2.4 kg/m^2 (95% CI, 1.8–3.0) higher among women with preeclampsia compared to women with a normotensive pregnancy (Table S2). By age 60 years, the prevalence of obesity was 18% (95% CI, 12–24) in women with preeclampsia and 11% (95% CI, 10–13) in women with a normotensive pregnancy (Figure 3B and Table S5). Waist circumference and waist-to-hip ratio, measures of abdominal adiposity, were also consistently higher in women with a preeclampsia pregnancy, and increased with age in a broadly parallel fashion in both groups (Figure 2D through 2F, Tables S2 and S4).

Non-HDL cholesterol was 0.24 mmol/L (95% CI, 0.05–0.43) higher at age 20 years among women with subsequent preeclampsia compared with a normotensive first pregnancy (Figure 4A, Table S2), and increased similarly in both groups

Table. Descriptive Characteristics of the Study Population

	Hypertension Status of First Pregnancy		
	Normotension (n=22 308)	Gestational Hypertension (n=478)	Preeclampsia (n=1092)
Maternal characteristics			
Birth year, median (IQR)	1959 (1951–1968)	1957 (1951–1966)	1962 (1953–1970)
Age at first birth, median (IQR)	23 (20–26)	24 (21–27)	24 (21–27)
Ever daily smoking, n (%)			
No	9132 (41)	240 (50)	585 (54)
Yes	13 176 (59)	238 (50)	507 (46)
Education, n (%)			
Lower secondary (≤9 y)	3737 (17)	89 (19)	177 (16)
Upper secondary (10–12 y)	10 540 (47)	217 (45)	551 (50)
Tertiary (>12 y)	8031 (36)	172 (36)	364 (33)
Ever use of antihypertensive medication, n (%)			
No	20 271 (91)	332 (69)	775 (71)
Yes	2033 (9)	146 (31)	317 (29)
Missing	4 (0)	0 (0)	0 (0)
Age at first HUNT exam, median (IQR)	31 (26–37)	31 (26–37)	31 (26–36)
No. of HUNT exams, n (%)			
1	8701 (39)	177 (37)	479 (44)
2	6799 (30)	125 (26)	324 (30)
3	6808 (31)	176 (37)	289 (26)
HUNT exams relative to first pregnancy, n (%)			
Before first pregnancy only	1927 (9)	50 (10)	113 (10)
After first pregnancy only	18 166 (81)	380 (79)	847 (78)
Before and after first pregnancy	2215 (10)	48 (10)	132 (12)
First pregnancy characteristics			
Gestational length in wks, n (%)			
<34	407 (2)	4 (1)	57 (5)
34–36	753 (3)	11 (2)	106 (10)
≥37	20 033 (90)	439 (92)	857 (78)
Missing	1115 (5)	24 (5)	72 (7)
Birth weight, n (%)*			
Small for gestational age	658 (3)	23 (5)	118 (11)
Normal	19 952 (89)	424 (89)	876 (80)
Large for gestational age	399 (2)	5 (1)	19 (2)
Missing	1299 (6)	26 (5)	79 (7)
Stillbirths, n (%)	193 (1)	2 (0)	21 (2)

IQR indicates interquartile range; HUNT, Nord-Trøndelag Health Study.
*Small and large for gestational age were defined as >2 standard deviations away from the established mean birth weights by gestational age in the Medical Birth Registry of Norway.[37]

until age 40 years (Figure 4A, Table S4). From 40 to 60 years, women with a normotensive pregnancy had a seemingly steeper rise, resulting in the 2 groups of women having similar non-HDL cholesterol levels by age 60 years (Figure 4A, Table S2). HDL cholesterol levels were similar between the groups prepregnancy (Figure 4B, Table S2) and immediately postpregnancy. Women with preeclampsia then had lower HDL cholesterol until beyond 50 years of age compared with women with normotensive pregnancy (Figure 4B, Table S2). Triglyceride levels were 0.18 mmol/L (95% CI, 0.05–0.32)

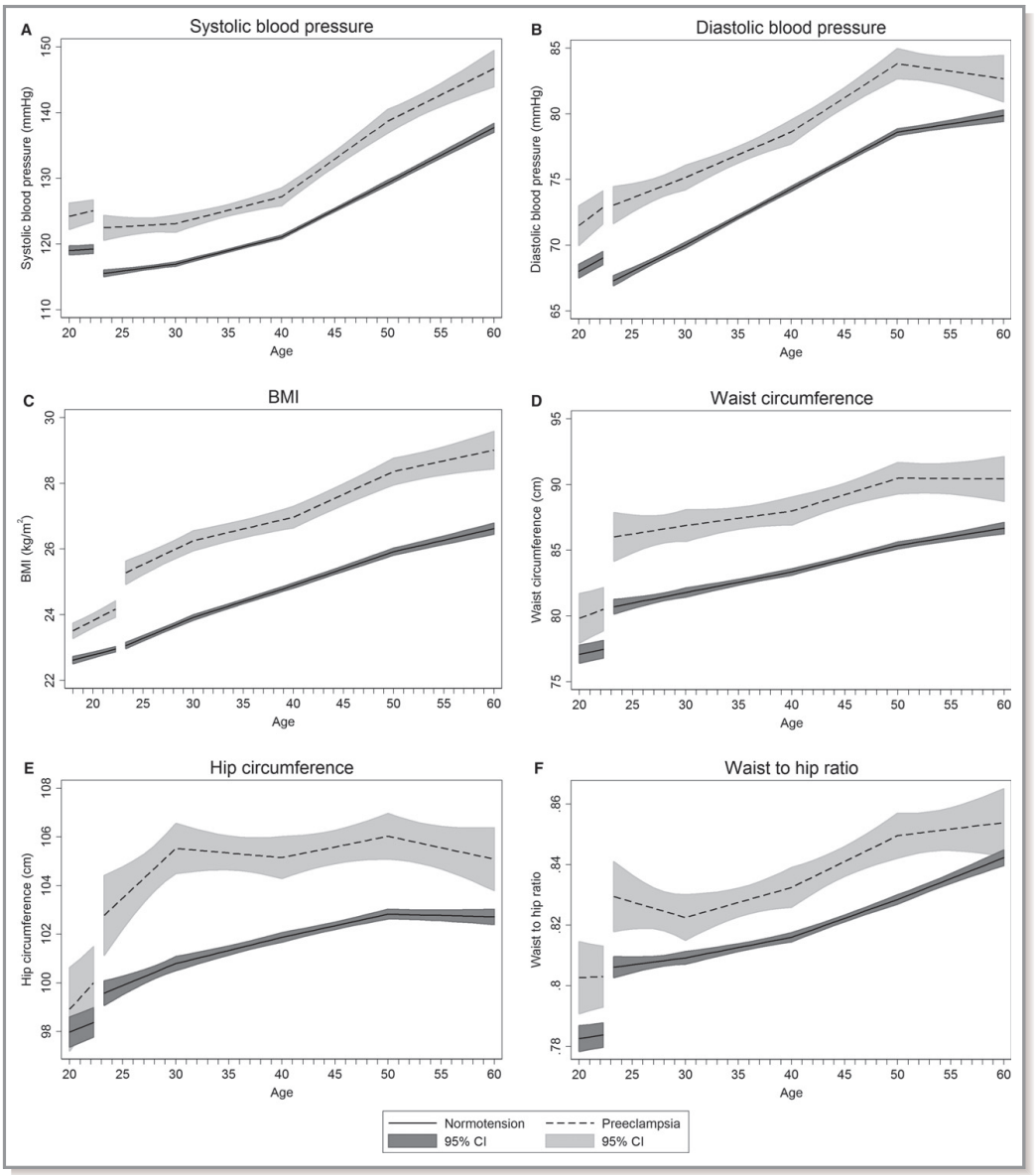

Figure 2. Life course trajectories of mean systolic blood pressure (A), diastolic blood pressure (B), BMI (C), waist circumference (D), hip circumference (E), and waist-to-hip ratio (F) for women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first birth, and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 years, and a 3-month postpartum period. BMI indicates body mass index; CI, confidence interval; HUNT, Nord-Trøndelag Health Study.

higher at age 20 in women who later had preeclampsia compared with normotensive pregnancy (Figure 4C, Table S2), and this difference between the groups remained broadly unchanged until 50 years of age. At age 60 years, the 2 groups of women had similar levels of all lipid subtypes (Figure 4A through 4C, Table S2).

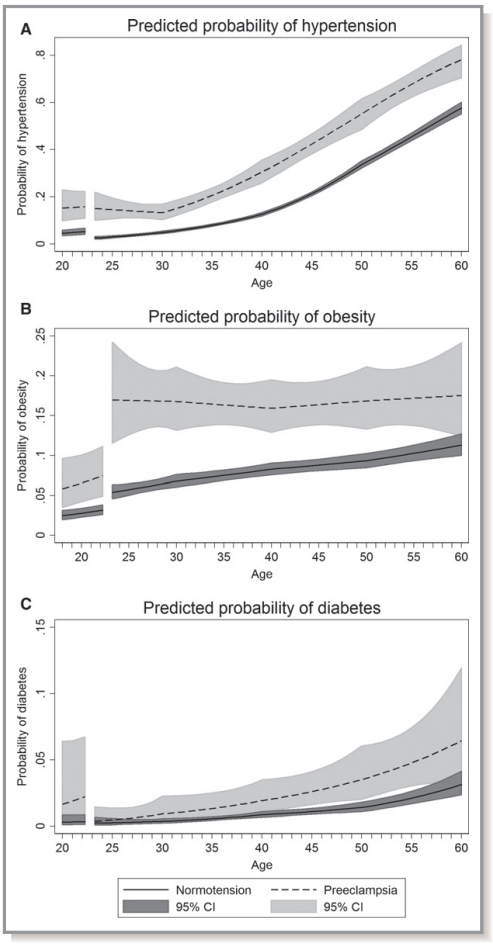

Figure 3. Population average predicted probabilities of hypertension (defined as current antihypertensive medication and/or blood pressure ≥140 mm Hg systolic or ≥90 mm Hg diastolic) (A), obesity (defined as a BMI ≥30 kg/m^2) (B), and diabetes mellitus (defined as self-reported diabetes mellitus, nonfasting serum glucose ≥11.1 mmol/L, fasting serum glucose ≥7.0 mmol/L, and/or 2-hour postload serum glucose ≥11.1 mmol/L) (C) by age in women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first birth, and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23, and a 3-month postpartum period. BMI indicates body mass index; CI, confidence interval; HUNT, Nord-Trøndelag Health Study.

Nonfasting serum glucose was ≈0.2 mmol/L higher in women with preeclampsia compared with normotensive pregnancies (Figure 4D, Table S2), and this difference was similar from ages 20 to 60 years. Diabetes mellitus prevalence rose faster in women with preeclampsia compared with normotensive pregnancy (Figure 3C). At age 60 years, 6% (95% CI, 3–12) of women with preeclampsia and 3% (95% CI, 2–4) of women with normotensive first pregnancies had diabetes mellitus (Table S5).

Resting heart rate was 2.4 beats/min (95% CI, 0.4–4.3) faster at age 20 in women with preeclampsia compared with normotensive pregnancy (Figure 4E, Table S2). After pregnancy, resting heart rate was 1 beat/min faster until 50 years of age in women with preeclampsia compared with normotensive pregnancy (Table S2). Prepregnancy CRP levels were similar in women with preeclampsia and normotensive pregnancy (Figure 4F, Table S2). Following pregnancy, CRP was higher in preeclamptic women, especially at age 30 to 55 years, but the CRP trajectories were less precise because of a lower number of measurements (Figure 4F, Table S2). Estimated glomerular filtration rate decreased in a linear fashion throughout the entire age-interval in all women without any noticeable differences between women with normotension or preeclampsia in their first pregnancy (Figure S4).

For all the above-described analyses except for CRP, we obtained similar results when restricting the analysis to women with 2 or more repeated measures (Figures S5 and S6).

The analysis of repeat exposure to preeclampsia included 121 women with preeclampsia in both first and second pregnancy, 929 women with preeclampsia in 1 of these pregnancies, and 18 577 women who were normotensive in both first and second pregnancy. Women with repeat preeclampsia had higher systolic and diastolic blood pressure, increased risk of hypertension and higher BMI, waist circumference, and serum glucose in midlife compared with women with only 1 occurrence of preeclampsia (Figures S7 through S10). Women with repeat preeclampsia also tended to have more adverse levels of all other cardiovascular risk factors except estimated glomerular filtration rate, but the low number of women with repeat preeclampsia precluded precise estimates. Life course trajectory of diabetes mellitus prevalence among women with repeat preeclampsia could not be estimated because of too few events.

Discussion

In this longitudinal population-based study, multiple cardiovascular risk factors were already elevated before first pregnancy in women who later experienced HDP compared with women with normotensive first pregnancies. Risk factor trajectories of women with HDP and normotensive first pregnancy displayed a roughly parallel pattern after pregnancy, but the increases in systolic blood pressure and measures of adiposity from 20 to 60 years of age were somewhat steeper among women with HDP. Although levels

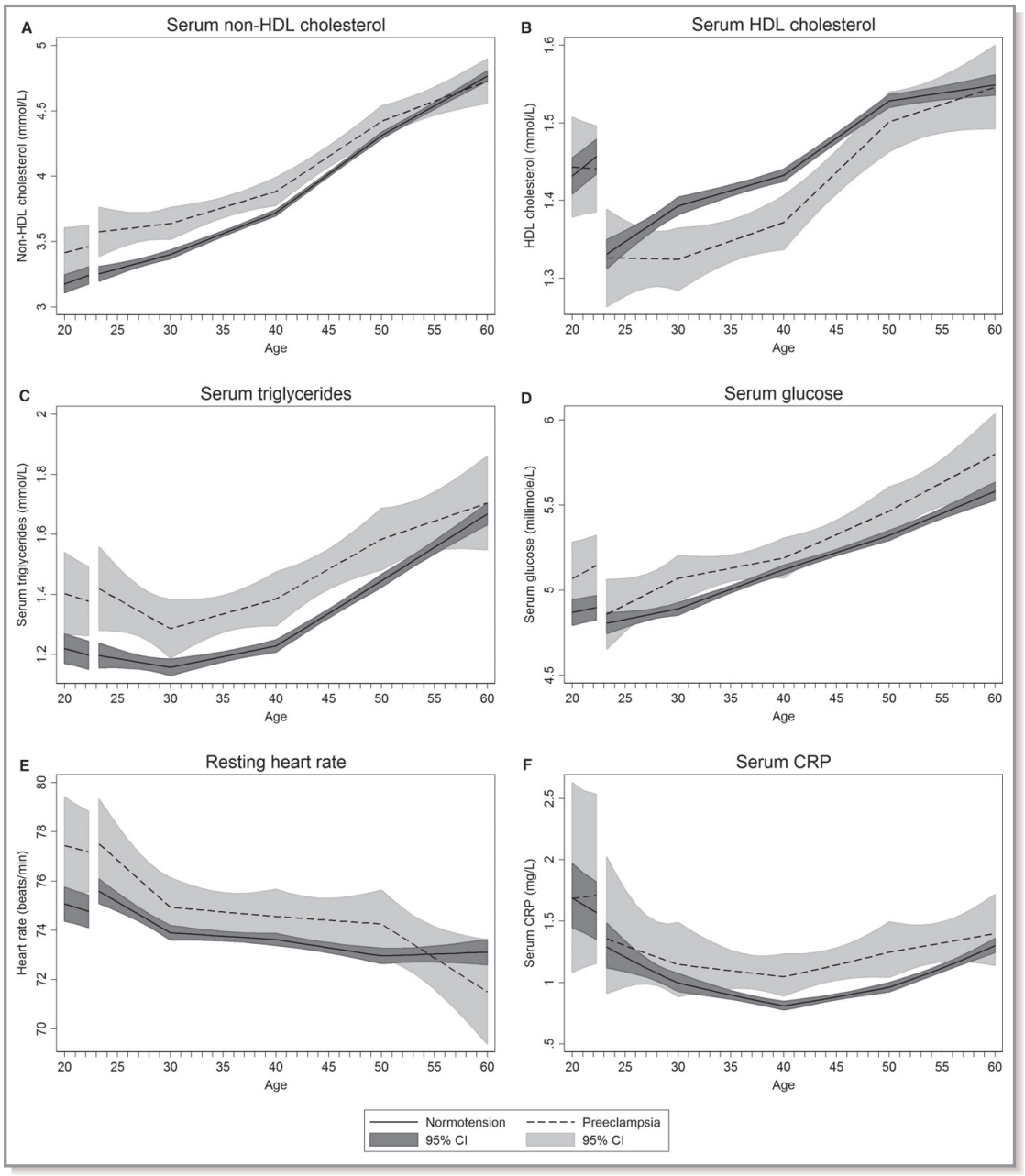

Figure 4. Life course trajectories of mean nonfasting serum non-HDL (A) and HDL (B) cholesterol, triglycerides (C), and glucose (D), resting heart rate (E), and serum CRP (F) for women with normotensive and preeclamptic first pregnancies. Estimates are adjusted for age at measurement, HUNT survey highest obtained education level, age at first birth and ever daily smoking. Analyses of glucose and triglycerides were additionally adjusted for time since last meal. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23, and a 3-month postpartum period. CRP is given as geometric mean. CI indicates confidence interval; CRP, C-reactive protein; HDL, high-density lipoprotein; HUNT, Nord-Trøndelag Health Study.

of blood pressure, adiposity, serum lipids, and glucose increased with age in both groups of women, there was a time lag of 10 years or more between mean levels observed among women with a history of HDP and women with normotensive first pregnancies. The time-related cardiovascular risk profiles were similar in women with preeclampsia and gestational hypertension. Women with repeat preeclampsia in their first and second pregnancy had a more adverse cardiovascular risk factor profile than women with only 1 occurrence of preeclampsia in their first 2 pregnancies.

In our previous analysis on parity and life course blood pressure trajectories from this cohort, we observed that women with HDP as a group had higher blood pressure from before first pregnancy until beyond 60 years of age.[18] In the present study, we examined a wide range of cardiovascular risk factors separately among women with preeclampsia and gestational hypertension. We are not aware of other studies that have constructed and contrasted life course trajectories of common cardiovascular risk factors in women with a history of HDP and women with normotensive pregnancies. Our work builds on previous studies by Magnussen et al, who examined the associations between pre- and postpregnancy cardiovascular risk factors and HDP; however, those studies were restricted to data from the HUNT1 and HUNTT2 surveys.[6,9,38]

Our results were generally consistent with previous studies in showing that women with HDP had adverse levels of cardiovascular risk factors at various time points from before first pregnancy and until menopause,[6–17] with correspondingly increased risks of hypertension, obesity, and diabetes mellitus.[13–15,39–42] Our study adds to the limited evidence beyond age 50 years, confirming that except for lipids, for which trajectories converge by age 60 years, other differences in cardiovascular risk factors persist until age 60 years. Our findings also support the theoretical cardiovascular risk factor trajectories in women with HDP proposed by Sattar and Greer,[3] giving credence to the concept of pregnancy as a stress test of cardiometabolic function. Additionally, the observation that most cardiovascular risk factors increase nearly monotonically with advancing age in women is also consistent with previous life course trajectory studies on selected cardiovascular risk factors.[43]

We were able to describe risk factor trajectories in normotensive and HDP women with high precision and with a longer follow-up than previous studies, by applying mixed-effects models.[32] The use of repeated observations of cardiovascular risk factors pre- and post–first pregnancy was one of the major advantages of our study over previous ones, enabling the estimation of within-woman trajectories and hence the ability to assess when higher levels of cardiovascular risk factors in HDP women were present. Our sensitivity analyses among women with 2 or more observations only confirmed that the trajectories including the full sample can be interpreted as within-woman life course trajectories.

Our aim was to describe and contrast life course trajectories of cardiovascular risk factors in order to inform CVD screening and ultimately prevention in women with HDP. For that purpose, confounder adjustment was less relevant compared with studies aiming to examine the causal association of cardiovascular risk factors with HDP. Nevertheless, we adjusted for educational level and smoking, which are well established and easily identified prepregnancy factors potentially part of a common cause of HDP and cardiovascular risk factor elevation. Prepregnancy BMI may also be part of this common cause, but incomplete information prevented us from examining the impact of prepregnancy BMI on the life course trajectories. We adjusted for age and HUNT survey occasion, which should reduce the potential impact that secular trends in blood pressure,[44] BMI,[45] waist circumference,[46] and cholesterol[47] during our study period may have had on the observed difference between HDP and normotensive women. Antihypertensive treatment was used more frequently in women with a history of HDP, and although we attempted to remedy this by adding constants to the observed blood pressure measurements, as recommended by Cui et al[26] and Tobin et al,[27] antihypertensive use could have lowered blood pressure in HDP more than in normotensive women and attenuated the estimated difference between the groups. The use of statin treatment has increased substantially in Norway starting in the late 1990s[48] and could have lowered non-HDL cholesterol levels in women attending HUNT3 (2006–2008). In a similar way, the use of β-blockers could have lowered the resting heart rate of women with HDP to a larger extent than for women without HDP. This may have contributed to the smaller differences in non-HDL cholesterol levels and resting heart rate between HDP and normotensive women who we observed after 50 years of age, when statin and β-blocker use is more frequent.

Participation declined in the more recent HUNT surveys and was lower among people with lower socioeconomic status and certain adverse health outcomes. However, the use of antihypertensive medication was similar in participants and nonparticipants,[49] and nonparticipants had lower BMI than participants.[49] It also seems unlikely that participation was related to HDP. For these reasons we do not expect nonparticipation to have violated the missing at random assumption implicit in mixed effects models nor caused substantial bias in the differences in cardiovascular risk factors between normotensive and HDP women. The MBRN provided accurate information on the reproductive histories, and the validity of the preeclampsia diagnosis within this population was generally good with a positive predictive value of 88%.[23] For gestational hypertension, the positive predictive value was 68%, but most women with an MBRN diagnosis of

gestational hypertension had evidence of either gestational hypertension or preeclampsia in medical records.[23]

The absence of noticeable differences between cardiovascular risk factor profiles in women with preeclampsia and gestational hypertension could in part be explained by most (84%) of the women diagnosed with preeclampsia having a mild form, as indicated by term delivery (gestational length ≥37 weeks). We did not have a sufficient number of women with preterm preeclampsia to examine whether this form of preeclampsia was associated with different cardiovascular risk trajectories. A validation study[23] conducted within the same cohort also noted that some women diagnosed with gestational hypertension displayed signs of preeclampsia (ie, proteinuria), a finding that indicates overlap between the 2 groups of women.

Our and others' observations that women with subsequent HDP have adverse cardiovascular risk factors in young adult life, before first pregnancy, support the hypothesis that adverse cardiovascular risk profiles observed in women with HDP originate early in life. These findings could be consistent with a genetic origin of HDP, but while the familial clustering of preeclampsia is well documented,[50] there is limited knowledge about a possible genetic basis for the disorder.[51] The higher risk of HDP in women who were born prematurely or with low birthweight[52] supports that the elevated cardiovascular risk factor levels in women with HDP may be attributed to genes or to adverse in utero conditions.[53] Alternatively, women who go on to develop HDP may have different dietary and lifestyle patterns in childhood and adolescence that set them on a divergent adult cardiovascular risk factor trajectory.

Although women with subsequent HDP have an adverse cardiovascular risk factor profile even before first pregnancy, this does not exclude an additional causal contribution by HDP.[3] However, pre- to postpregnancy changes in most cardiovascular risk factors were similar between women with HDP and normotensive women, suggesting that HDP itself did not contribute to the adverse levels of these risk factors. The observation that BMI increased more in pregnancies with HDP is consistent with previous findings of increased risk of HDP with higher gestational weight gain,[54] but it does not imply that HDP necessarily caused the higher pre- to postpregnancy increase in BMI.

As expected from the higher BMI, blood pressure, and glucose levels in women with HDP, the prevalence of obesity, hypertension, and diabetes mellitus remained elevated in women with HDP compared with women with normotensive pregnancies for the entire age range of 20 to 60 years. From a clinical perspective, it may be interesting to note that the probability of hypertension in preeclamptic women started increasing more rapidly at around age 30, approximately a decade earlier than in normotensive women, creating a time lag in the prevalence of hypertension of around 10 years. Obesity, hypertension, and diabetes mellitus are well known to increase the risk of CVD.[55] Given the substantial body of evidence showing higher levels of cardiovascular risk factors in women with HDP, it is highly likely that a substantial proportion of the excess CVD risk in women with HDP[56] is mediated through these traditional cardiovascular risk factors.

Research suggests that a reduction of 2 mm Hg in diastolic blood pressure could reduce the risk of coronary heart disease by 6% and the risk of stroke and transient ischemic attacks by 15%.[57] Even such small reductions in blood pressure as that obtainable by lifestyle modification programs could be beneficial in women with a history of HDP. As the adverse cardiovascular risk profile in women with a history of HDP in most cases is already established in early adulthood, our findings suggest that HDP may be included in early CVD screening, and that women with HDP may particularly benefit from early lifestyle modification programs that target cardiometabolic risk factors following a pregnancy complicated by HDP.

Conclusion

This longitudinal population-based study shows that the adverse cardiovascular risk factor profiles in women with HDP are present before first pregnancy and remain higher compared with other women beyond 50 years of age. Progression of cardiovascular risk factors throughout the age interval 20 to 60 years occurs mostly in parallel for women with and without a history of HDP, with greater increases in systolic blood pressure and adiposity in women with a history of HDP. Women with a history of HDP may be expected to pass beyond treatment thresholds of blood pressure, adiposity, serum lipids, and glucose at least 10 years earlier than women with normotensive pregnancy. HDP signals long-term increases in modifiable cardiovascular risk factors that may warrant early screening and preventive efforts.

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Disclosures

Disclosures are correct.

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SUPPLEMENTAL MATERIAL

Table S1. Number of women and measurements included in analysis by CVD risk factor.

	Number of women			Number of measurements		
CVD risk factor	**Normotension**	**Preeclampsia**	**Gestational hypertension**	**Normotension**	**Preeclampsia**	**Gestational hypertension**
Systolic blood pressure	22 061	1077	474	42 357	1976	947
Diastolic blood pressure	22 061	1077	474	42 356	1976	947
BMI	22 298	1091	478	54 422	2519	1177
Waist circumference	20 409	1009	433	31 361	1510	678
Hip circumference	20 410	1009	433	31 362	1510	678
Waist to hip ratio	20 409	1009	433	31 360	1510	678
Non-HDL cholesterol	20 283	1007	432	30 977	1493	668
HDL cholesterol	20 283	1007	432	30 977	1493	668
Triglycerides	19 858	977	427	30 715	1470	666
Glucose	19 836	983	429	31 156	1510	683
Resting heart rate	21 530	1049	467	40 406	1875	895
CRP	16 335	791	330	17 983	885	370

Table S2. Predicted mean levels of cardiovascular disease risk factors by age at follow-up in women with normotensive and preeclamptic first pregnancies.

	Normotensive		Preeclampsia		Difference		
Linear prediction*	estimate	95% CI	estimate	95% CI	estimate	95% CI	p-value
Systolic blood pressure (mmHg)							
20 years	119.03	[118.33 – 119.73]	124.23	[122.21 – 126.24]	5.20	[3.20 – 7.20]	<0.001
			1st birth occurs at age 23				
30 years	116.95	[116.62 – 117.29]	123.10	[121.78 – 124.42]	6.15	[4.81 – 7.48]	<0.001
40 years	121.08	[120.79 – 121.38]	127.20	[125.85 – 128.56]	6.12	[4.74 – 7.50]	<0.001
50 years	129.32	[128.91 – 129.72]	138.69	[136.90 – 140.49]	9.38	[7.55 – 11.20]	<0.001
60 years	137.72	[137.03 – 138.41]	146.72	[143.94 – 149.49]	8.99	[6.20 – 11.79]	<0.001
Diastolic blood pressure (mmHg)							
20 years	68.03	[67.50 – 68.57]	71.49	[69.97 – 73.02]	3.46	[1.95 – 4.97]	<0.001
30 years	69.99	[69.75 – 70.23]	75.15	[74.20 – 76.10]	5.16	[4.20 – 6.12]	<0.001
40 years	74.29	[74.09 – 74.49]	78.63	[77.71 – 79.54]	4.33	[3.40 – 5.27]	<0.001
50 years	78.61	[78.35 – 78.87]	83.82	[82.66 – 84.98]	5.21	[4.03 – 6.38]	<0.001
60 years	79.86	[79.43 – 80.30]	82.68	[80.91 – 84.45]	2.82	[1.03 – 4.60]	0.002
BMI (kg/m^2)							
20 years	22.78	[22.69 – 22.86]	23.82	[23.61 – 24.04]	1.05	[0.84 – 1.26]	<0.001
30 years	23.92	[23.83 – 24.00]	26.25	[25.95 – 26.56]	2.34	[2.03 – 2.65]	<0.001
40 years	24.89	[24.81 – 24.97]	26.97	[26.64 – 27.30]	2.08	[1.75 – 2.41]	<0.001
50 years	25.92	[25.81 – 26.03]	28.36	[27.95 – 28.77]	2.44	[2.03 – 2.85]	<0.001
60 years	26.62	[26.45 – 26.79]	29.01	[28.44 – 29.58]	2.39	[1.82 – 2.96]	<0.001
Waist circumference (cm)							
20 years	77.08	[76.39 – 77.78]	79.82	[77.93 – 81.72]	2.74	[0.86 – 4.62]	0.004
30 years	81.79	[81.44 – 82.13]	86.88	[85.67 – 88.10]	5.09	[3.86 – 6.33]	<0.001
40 years	83.35	[83.11 – 83.60]	87.99	[86.92 – 89.06]	4.64	[3.55 – 5.73]	<0.001
50 years	85.37	[85.10 – 85.63]	90.49	[89.28 – 91.69]	5.12	[3.89 – 6.35]	<0.001
60 years	86.69	[86.26 – 87.11]	90.43	[88.72 – 92.13]	3.74	[2.02 – 5.46]	<0.001
Hip circumference (cm)							
20 years	97.98	[97.35 – 98.60]	98.91	[97.19 – 100.63]	0.93	[-0.77 – 2.63]	0.281
30 years	100.80	[100.50 – 101.09]	105.53	[104.49 – 106.57]	4.73	[3.68 – 5.79]	<0.001
40 years	101.88	[101.68 – 102.07]	105.15	[104.29 – 106.02]	3.28	[2.40 – 4.16]	<0.001
50 years	102.83	[102.63 – 103.04]	106.03	[105.10 – 106.97]	3.20	[2.25 – 4.15]	<0.001
60 years	102.72	[102.40 – 103.04]	105.09	[103.79 – 106.38]	2.37	[1.06 – 3.67]	<0.001
Waist to hip ratio							
20 years	0.78	[0.78 – 0.79]	0.80	[0.79 – 0.81]	0.02	[0.01 – 0.03]	0.001
30 years	0.81	[0.81 – 0.81]	0.82	[0.82 – 0.83]	0.01	[0.01 – 0.02]	0.001
40 years	0.82	[0.81 – 0.82]	0.83	[0.83 – 0.84]	0.02	[0.01 – 0.02]	<0.001
50 years	0.83	[0.83 – 0.83]	0.85	[0.84 – 0.86]	0.02	[0.01 – 0.03]	<0.001
60 years	0.84	[0.84 – 0.84]	0.85	[0.84 – 0.87]	0.01	[0.00 – 0.02]	0.045

*Linear predictions are estimated with all covariates set at their means and as if the woman has her first birth at age 23.

Table S2 continued. Predicted mean levels of cardiovascular disease risk factors by age at follow-up in women with normotensive and preeclamptic first pregnancies.

	Normotensive		Preeclampsia		Difference		
Linear prediction*	estimate	95% CI	estimate	95% CI	estimate	95% CI	p-value
Non-HDL cholesterol (mmol/L)							
20 years	3.18	[3.11 – 3.24]	3.42	[3.22 – 3.61]	0.24	[0.05 – 0.43]	0.013
			1st birth occurs at age 23				
30 years	3.40	[3.37 – 3.44]	3.64	[3.52 – 3.76]	0.24	[0.11 – 0.36]	<0.001
40 years	3.72	[3.70 – 3.74]	3.88	[3.78 – 3.99]	0.16	[0.05 – 0.27]	0.003
50 years	4.31	[4.29 – 4.34]	4.42	[4.30 – 4.54]	0.11	[-0.01 – 0.23]	0.073
60 years	4.77	[4.73 – 4.81]	4.73	[4.56 – 4.90]	-0.04	[-0.21 – 0.13]	0.663
HDL cholesterol (mmol/L)							
20 years	1.43	[1.41 – 1.46]	1.44	[1.38 – 1.51]	0.01	[-0.05 – 0.08]	0.724
30 years	1.39	[1.38 – 1.40]	1.32	[1.28 – 1.36]	-0.07	[-0.11 – -0.03]	0.001
40 years	1.43	[1.42 – 1.44]	1.37	[1.34 – 1.41]	-0.06	[-0.10 – -0.03]	0.001
50 years	1.53	[1.52 – 1.54]	1.50	[1.46 – 1.54]	-0.03	[-0.07 – 0.01]	0.175
60 years	1.55	[1.54 – 1.56]	1.55	[1.49 – 1.60]	0.00	[-0.06 – 0.05]	0.923
Triglycerides (mmol/L)							
20 years	1.22	[1.170 – 1.269]	1.40	[1.266 – 1.540]	0.18	[0.05 – 0.32]	0.008
30 years	1.16	[1.13 – 1.18]	1.29	[1.188 – 1.384]	0.13	[0.03 – 0.23]	0.011
40 years	1.23	[1.21 – 1.25]	1.39	[1.30 – 1.48]	0.16	[0.06 – 0.25]	0.001
50 years	1.45	[1.42 – 1.47]	1.58	[1.48 – 1.69]	0.14	[0.03 – 0.24]	0.009
60 years	1.67	[1.63 - 1.70]	1.70	[1.55 - 1.86]	0.04	[-0.12 – 0.19]	0.649
Glucose (mmol/L)							
20 years	4.87	[4.79 – 4.95]	5.07	[4.85 – 5.28]	0.20	[-0.01 – 0.41]	0.068
30 years	4.89	[4.85 – 4.93]	5.07	[4.94 – 5.20]	0.18	[0.04 – 0.32]	0.010
40 years	5.12	[5.09 – 5.15]	5.19	[5.07 – 5.31]	0.07	[-0.05 – 0.19]	0.268
50 years	5.32	[5.29 – 5.35]	5.47	[5.32 – 5.61]	0.14	[-0.00 – 0.29]	0.052
60 years	5.58	[5.53 – 5.63]	5.80	[5.56 – 6.04]	0.22	[-0.02 – 0.46]	0.076
Resting heart rate (beats/min)							
20 years	75.07	[74.38 – 75.76]	77.45	[75.48 – 79.42]	2.38	[0.42 – 4.33]	0.017
30 years	73.90	[73.60 – 74.20]	74.94	[73.74 – 76.13]	1.03	[-0.18 – 2.25]	0.095
40 years	73.63	[73.38 – 73.87]	74.56	[73.45 – 75.67]	0.93	[-0.20 – 2.06]	0.105
50 years	72.96	[72.65 – 73.27]	74.26	[72.88 – 75.64]	1.30	[-0.10 – 2.70]	0.068
60 years	73.12	[72.61 – 73.63]	71.50	[69.39 – 73.62]	-1.61	[-3.75 – 0.53]	0.139
CRP† (mg/L)							
20 years	1.69	[1.45 – 1.97]	1.69	[1.08 – 2.63]	1.00	[0.64 – 1.56]	0.997
30 years	1.00	[0.93 – 1.07]	1.15	[0.89 – 1.49]	1.15	[0.88 – 1.50]	0.297
40 years	0.81	[0.78 – 0.85]	1.05	[0.89 – 1.23]	1.29	[1.09 – 1.53]	0.003
50 years	0.96	[0.92 – 1.00]	1.25	[1.04 – 1.49]	1.30	[1.08 – 1.56]	0.005
60 years	1.30	[1.24 – 1.36]	1.40	[1.14 – 1.72]	1.08	[0.87 – 1.33]	0.487

*Linear predictions are estimated with all covariates set at their means and as if the woman has her first birth at age 23.

†CRP is given as geometric mean values where the difference equates to the ratio of geometric mean CRP between women with preeclamptic and normotensive first pregnancy.

Table S3. Predicted change in cardiovascular disease risk factor level from pre- to post-first pregnancy in women with normotensive or preeclamptic first pregnancy.

	Normotension		Preeclampsia		Difference		
	Change	95 % CI	Change	95 % CI	Change	95 % CI	p-value
Systolic blood pressure (mmHg)	-3.81	[-4.65 – -2.97]	-2.99	[-5.32 – -0.67]	0.82	[-1.47 – 3.11]	0.485
Diastolic blood pressure (mmHg)	-2.17	[-2.81 – -1.53]	-0.44	[-2.17 – 1.29]	1.72	[0.03 – 3.42]	0.046
BMI (kg/m^2)	0.03	[-0.08 – 0.15]	0.95	[0.51 – 1.40]	0.92	[0.46 – 1.37]	<0.001
Waist circumference (cm)	3.06	[2.19 – 3.93]	5.21	[2.86 – 7.57]	2.15	[-0.17 – 4.47]	0.070
Hip circumference (cm)	1.03	[0.24 – 1.81]	2.29	[0.21 – 4.38]	1.27	[-0.78 – 3.31]	0.226
Waist to hip ratio	0.02	[0.02 – 0.03]	0.03	[0.01 – 0.04]	0.00	[-0.01 – 0.02]	0.549
Non-HDL cholesterol (mmol/L)	-0.02	[-0.10 – 0.07]	0.09	[-0.14 – 0.33]	0.11	[-0.12 – 0.34]	0.363
HDL cholesterol (mmol/L)	-0.14	[-0.17 – -0.11]	-0.11	[-0.19 – -0.03]	0.02	[-0.06 – 0.10]	0.567
Triglycerides (mmol/L)	0.01	[-0.06 – 0.07]	0.05	[-0.12 – 0.23]	0.04	[-0.13 – 0.22]	0.614
Glucose (mmol/L)	-0.10	[-0.20 – -0.01]	-0.32	[-0.58 – -0.07]	-0.22	[-0.47 – 0.03]	0.090
Resting heart rate (beats/min)	0.94	[0.11 – 1.77]	0.44	[-1.77 – 2.65]	-0.50	[-2.66 – 1.66]	0.649
CRP* (mg/L)	0.85	[0.69 – 1.05]	0.79	[0.45 – 1.39]	0.93	[0.53 – 1.63]	0.797

*CRP is given as geometric mean values where the difference equates to the ratio of geometric mean CRP between women with preeclampsia and normotensive women.

Table S4. Predicted change per year in cardiovascular disease risk factors by age interval in women with normotensive and preeclamptic first pregnancies.

	Normotension		Preeclampsia		Difference		
Change per year	estimate	95% CI	estimate	95% CI	estimate	95% CI	p-value
Systolic blood pressure (mmHg/year)							
20-23 years	0.09	[-0.04 – 0.22]	0.38	[0.03 – 0.73]	0.29	[-0.05 – 0.63]	0.097
23-30 years	0.21	[0.12 – 0.30]	0.09	[-0.25 – 0.43]	-0.12	[-0.46 – 0.23]	0.500
30-40 years	0.43	[0.37 – 0.50]	0.41	[0.21 – 0.61]	0.00	[-0.21 –0.20]	0.981
40-50 years	0.84	[0.79 – 0.89]	1.15	[0.93 – 1.36]	0.33	[0.11 – 0.54]	0.004
50-60 years	0.84	[0.77 – 0.91]	0.80	[0.50 – 1.11]	-0.04	[-0.35 – 0.27]	0.811
Diastolic blood pressure (mmHg/year)							
20-23 years	0.44	[0.34 – 0.54]	0.62	[0.36 – 0.87]	0.17	[-0.07 – 0.42]	0.170
23-30 years	0.40	[0.33 – 0.47]	0.31	[0.06 – 0.56]	-0.09	[-0.34 – 0.16]	0.489
30-40 years	0.44	[0.39 – 0.48]	0.35	[0.21 – 0.49]	-0.08	[-0.22 – 0.06]	0.249
40-50 years	0.44	[0.41 – 0.47]	0.52	[0.38 – 0.66]	0.09	[-0.06 – 0.23]	0.239
50-60 years	0.13	[0.08 – 0.17]	-0.11	[-0.32 – 0.09]	-0.24	[-0.45 – -0.03]	0.023
BMI (kg/m^2/year)							
18-23 years	0.08	[0.06 – 0.10]	0.16	[0.11 – 0.20]	0.08	[0.03 – 0.12]	0.001
23-30 years	0.13	[0.11 – 0.14]	0.14	[0.09 – 0.20]	0.02	[-0.03 – 0.07]	0.502
30-40 years	0.10	[0.09 – 0.12]	0.07	[0.04 – 0.11]	-0.03	[-0.06 – 0.01]	0.151
40-50 years	0.10	[0.09 – 0.11]	0.14	[0.10 – 0.17]	0.04	[-0.00 – 0.07]	0.052
50-60 years	0.07	[0.06 – 0.08]	0.07	[0.02 – 0.12]	0.00	[-0.06 – 0.05]	0.850
Waist circumference (cm/year)							
20-23 years	0.17	[0.05 – 0.29]	0.30	[-0.02 – 0.62]	0.13	[-0.18 – 0.45]	0.401
23-30 years	0.16	[0.06 – 0.26]	0.13	[-0.19 – 0.44]	-0.03	[-0.35 – 0.28]	0.835
30-40 years	0.18	[0.12 – 0.23]	0.11	[-0.05 – 0.27]	-0.05	[-0.21 – 0.11]	0.576
40-50 years	0.18	[0.15 – 0.21]	0.25	[0.10 – 0.39]	0.05	[-0.10 – 0.20]	0.522
50-60 years	0.13	[0.09 – 0.17]	-0.01	[-0.18 – 0.17]	-0.14	[-0.32 – 0.04]	0.135
Hip circumference (cm/year)							
20-23 years	0.18	[0.07 – 0.28]	0.48	[0.21 – 0.76]	0.31	[0.04 – 0.58]	0.027
23-30 years	0.18	[0.10 – 0.26]	0.41	[0.14 – 0.68]	0.23	[-0.05 – 0.50]	0.105
30-40 years	0.13	[0.09 – 0.18]	-0.04	[-0.17 – 0.09]	-0.15	[-0.28 – -0.01]	0.032
40-50 years	0.09	[0.06 – 0.12]	0.09	[-0.03 – 0.21]	-0.01	[-0.13 – 0.11]	0.899
50-60 years	-0.01	[-0.04 - 0.02]	-0.09	[-0.24 – 0.05]	-0.08	[-0.23 – 0.06]	0.258

Table S4 continued. Predicted change per year in cardiovascular disease risk factors by age interval in women with normotensive and preeclamptic first pregnancies.

	Normotension		Preeclampsia		Difference		
Change per year	estimate	95% CI	estimate	95% CI	estimate	95% CI	p-value
Non-HDL cholesterol (mmol/L/year)							
20-23 years	0.03	[0.02 – 0.04]	0.02	[-0.01 – 0.05]	-0.01	[-0.04 – 0.02]	0.647
23-30 years	0.02	[0.01 – 0.03]	0.01	[-0.02 – 0.04]	-0.01	[-0.05 – 0.02]	0.442
30-40 years	0.03	[0.02 – 0.04]	0.02	[0.01 – 0.04]	-0.01	[-0.02 – 0.01]	0.410
40-50 years	0.06	[0.06 – 0.06]	0.05	[0.04 – 0.07]	-0.01	[-0.02 – 0.01]	0.514
50-60 years	0.05	[0.04 – 0.05]	0.03	[0.01 – 0.05]	-0.01	[-0.03 – 0.01]	0.150
HDL cholesterol (mmol/L/year)							
20-23 years	0.01	[0.01 – 0.02]	0.00	[-0.01 – 0.01]	-0.01	[-0.02 – -0.00]	0.024
23-30 years	0.01	[0.01 – 0.01]	0.00	[-0.01 – 0.01]	-0.01	[-0.02 – 0.00]	0.085
30-40 years	0.00	[0.00 – 0.01]	0.00	[-0.00 – 0.01]	0.00	[-0.00 – 0.01]	0.780
40-50 years	0.01	[0.01 – 0.01]	0.01	[0.01 – 0.02]	0.00	[-0.00 – 0.01]	0.176
50-60 years	0.00	[0.00 – 0.00]	0.00	[-0.00 – 0.01]	0.00	[-0.00 – 0.01]	0.428
Triglycerides (mmol/L/year)							
20-23 years	-0.01	[-0.02 – -0.00]	-0.01	[-0.04 – 0.01]	0.00	[-0.03 – 0.02]	0.884
23-30 years	-0.01	[-0.01 – 0.00]	-0.02	[-0.04 – 0.01]	-0.01	[-0.04 – 0.01]	0.283
30-40 years	0.01	[0.00 – 0.01]	0.01	[-0.00 – 0.02]	0.00	[-0.01 – 0.02]	0.708
40-50 years	0.02	[0.02 – 0.02]	0.02	[0.01 – 0.03]	0.00	[-0.02 – 0.01]	0.804
50-60 years	0.02	[0.02 – 0.03]	0.01	[-0.01 – 0.03]	-0.01	[-0.03 – 0.01]	0.274
Glucose (mmol/L/year)							
20-23 years	0.01	[-0.00 – 0.03]	0.03	[-0.00 – 0.07]	0.02	[-0.01 – 0.06]	0.238
23-30 years	0.01	[0.00 – 0.02]	0.03	[-0.01 – 0.07]	0.02	[-0.02 – 0.06]	0.319
30-40 years	0.02	[0.02 – 0.03]	0.01	[-0.01 – 0.03]	-0.01	[-0.03 – 0.01]	0.286
40-50 years	0.02	[0.02 – 0.02]	0.03	[0.01 – 0.05]	0.01	[-0.01 – 0.03]	0.469
50-60 years	0.03	[0.02 – 0.03]	0.03	[0.01 – 0.06]	0.01	[-0.02 – 0.04]	0.609
Resting heart rate (beats/min/year)							
20-23 years	-0.13	[-0.26 – -0.01]	-0.12	[-0.44 – 0.21]	0.02	[-0.30 – 0.33]	0.920
23-30 years	-0.25	[-0.33 – -0.16]	-0.38	[-0.69 – -0.07]	-0.13	[-0.45 – 0.18]	0.409
30-40 years	-0.01	[-0.07 – 0.04]	-0.04	[-0.21 – 0.13]	-0.01	[-0.18 – 0.16]	0.909
40-50 years	-0.07	[-0.11 – -0.03]	-0.03	[-0.21 – 0.15]	0.04	[-0.14 – 0.22]	0.687
50-60 years	0.02	[-0.04 – 0.07]	-0.28	[-0.53 – -0.02]	-0.29	[-0.55 – -0.04]	0.026
CRP* (mg/L/year)							
20-23 years							
23-30 years	0.97	[0.94 – 1.00]	1.01	[0.93 – 1.09]	1.04	[0.97 – 1.12]	0.296
30-40 years	0.96	[0.94 – 0.99]	0.98	[0.91 – 1.05]	1.01	[0.94 – 1.09]	0.725
40-50 years	0.98	[0.97 – 0.99]	0.99	[0.96 – 1.02]	1.01	[0.98 – 1.05]	0.503
50-60 years	1.01	[1.01 – 1.02]	1.02	[0.99 – 1.04]	1.00	[0.97 – 1.03]	0.974

*CRP is given as geometric mean values where the difference equates to the ratio of geometric mean CRP between women with preeclampsia and normotensive women.

Table S5. Population average predicted probabilities* of hypertension, obesity and diabetes by age at follow-up in women with normotension, preeclampsia and gestational hypertension in first pregnancy.

	First pregnancy					
	Normotension		Preeclampsia		Gestational hypertension	
Age	probability	95% CI	probability	95% CI	probability	95% CI
Hypertension						
20 years	0.05	[0.04 – 0.06]	0.15	[0.10 – 0.23]	0.15	[0.07 – 0.29]
30 years	0.05	[0.04 – 0.06]	0.13	[0.10 – 0.17]	0.25	[0.18 – 0.32]
40 years	0.13	[0.12 – 0.13]	0.31	[0.26 – 0.36]	0.34	[0.28 – 0.41]
50 years	0.34	[0.32 – 0.35]	0.55	[0.49 – 0.62]	0.52	[0.43 – 0.60]
60 years	0.58	[0.55 – 0.60]	0.78	[0.70 – 0.84]	0.79	[0.69 – 0.87]
Obesity						
20 years	0.03	[0.02 , 0.03]	0.07	[0.04 , 0.10]	0.06	[0.03 , 0.11]
30 years	0.07	[0.06 , 0.08]	0.17	[0.13 , 0.21]	0.18	[0.13 , 0.25]
40 years	0.08	[0.08 , 0.09]	0.16	[0.13 , 0.20]	0.20	[0.16 , 0.26]
50 years	0.09	[0.08 , 0.10]	0.17	[0.13 , 0.21]	0.21	[0.15 , 0.28]
60 years	0.11	[0.10 , 0.13]	0.18	[0.12 , 0.24]	0.21	[0.13 , 0.31]
Diabetes						
20 years	0.003	[0.001 – 0.009]	0.02	[0.00 – 0.06]	0.000	[0.00 – 0.000]
30 years	0.004	[0.002 – 0.006]	0.01	[0.00 – 0.02]	0.015	[0.002 – 0.10]
40 years	0.01	[0.01 – 0.01]	0.02	[0.01 – 0.04]	0.002	[0.000 – 0.02]
50 years	0.01	[0.01 – 0.02]	0.04	[0.02 – 0.06]	0.02	[0.01 – 0.05]
60 years	0.03	[0.02 – 0.04]	0.06	[0.03 – 0.12]	0.10	[0.05 – 0.21]

*Population average proportions are estimated with all covariates set at their means and as if the woman has her first birth at age 23.

Figure S1. Number (a) and proportion (b) of HUNT participants according to age at participation and HUNT survey.

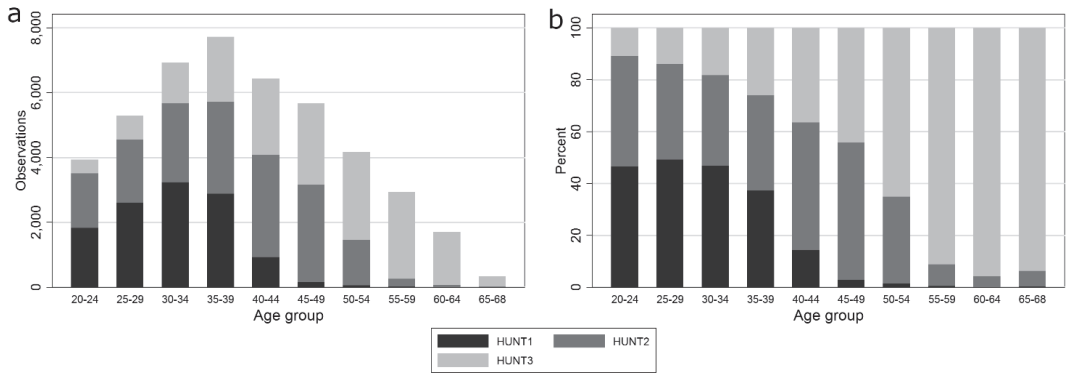
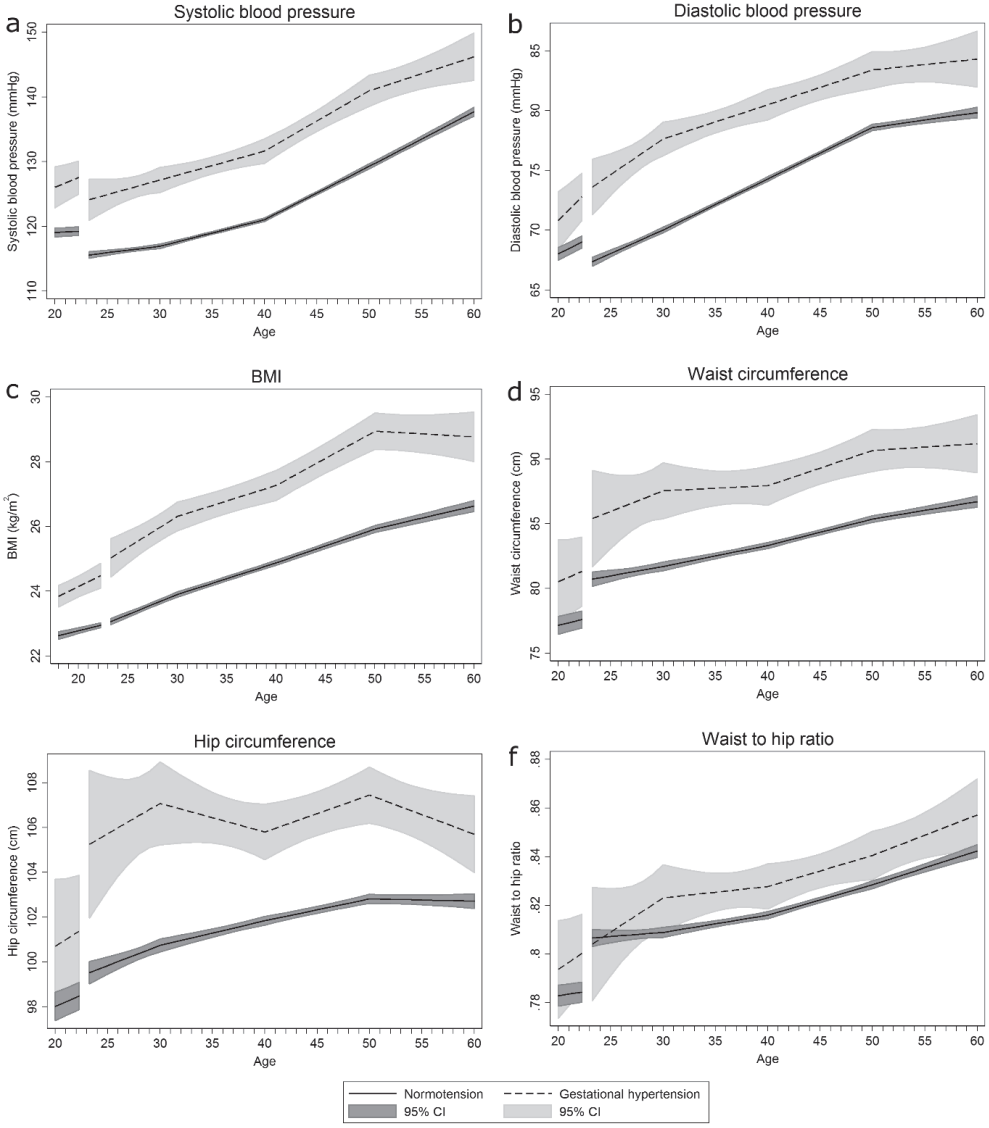
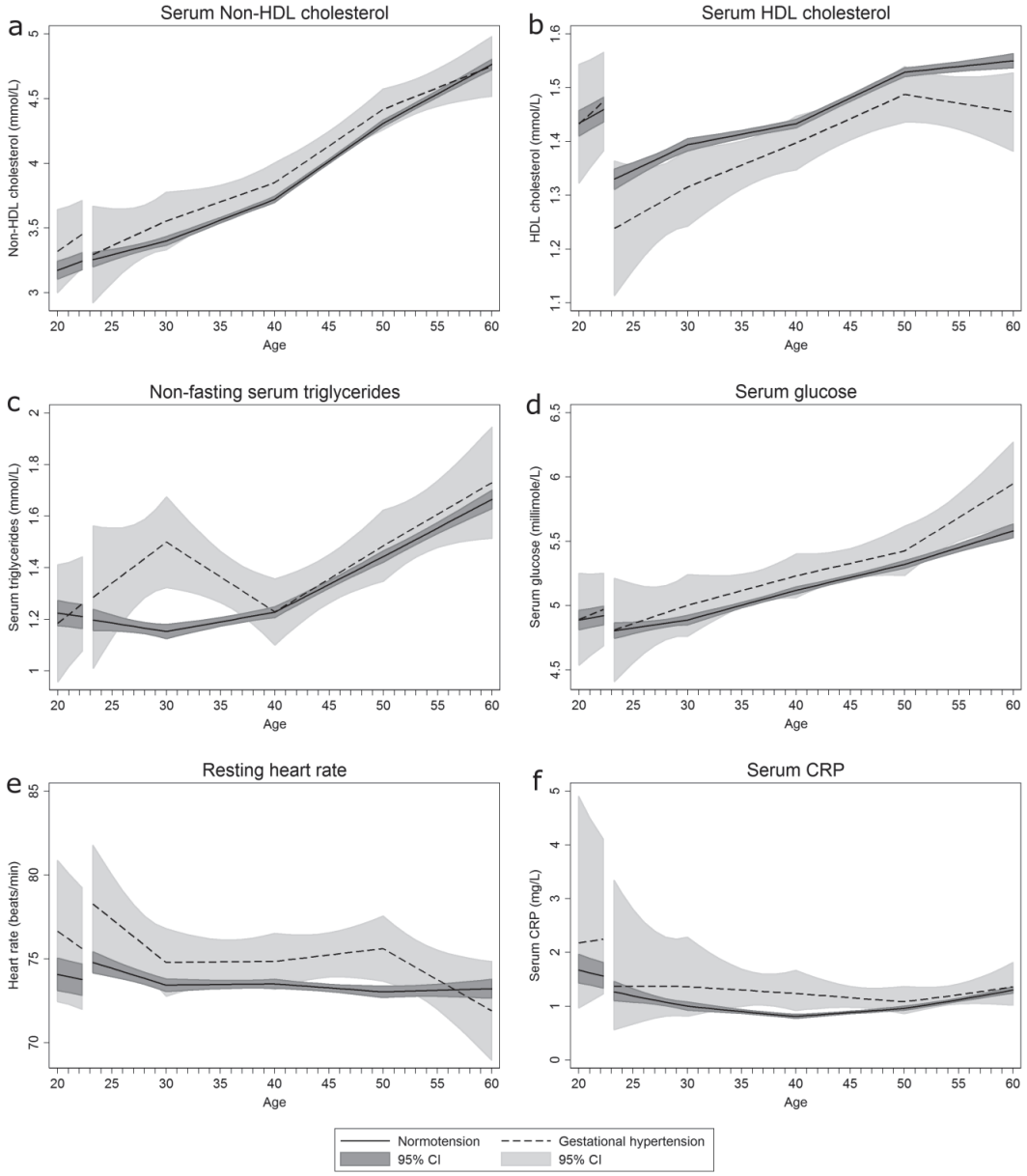


Figure S2. Life course trajectories of mean systolic blood pressure (a), diastolic blood pressure (b), BMI (c), waist circumference (d), hip circumference (e) and waist to hip ratio (f) for women with normotension and gestational hypertension in their first pregnancies.



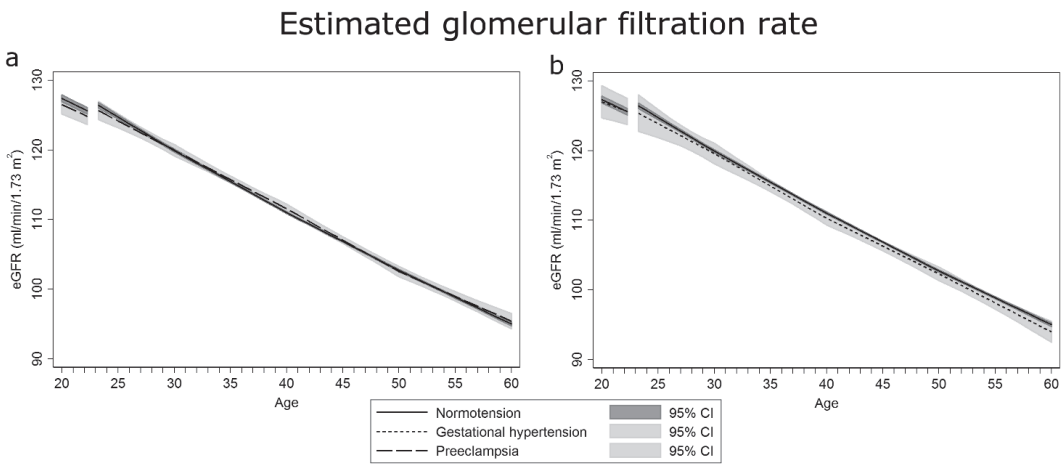
Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first birth and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period.

Figure S3. Life course trajectories of mean non-fasting non-HDL (a) and HDL (b) cholesterol, triglycerides (c), and glucose (d), resting heart rate (e), and serum CRP (f) for women with normotension and gestational hypertension in their first pregnancies.



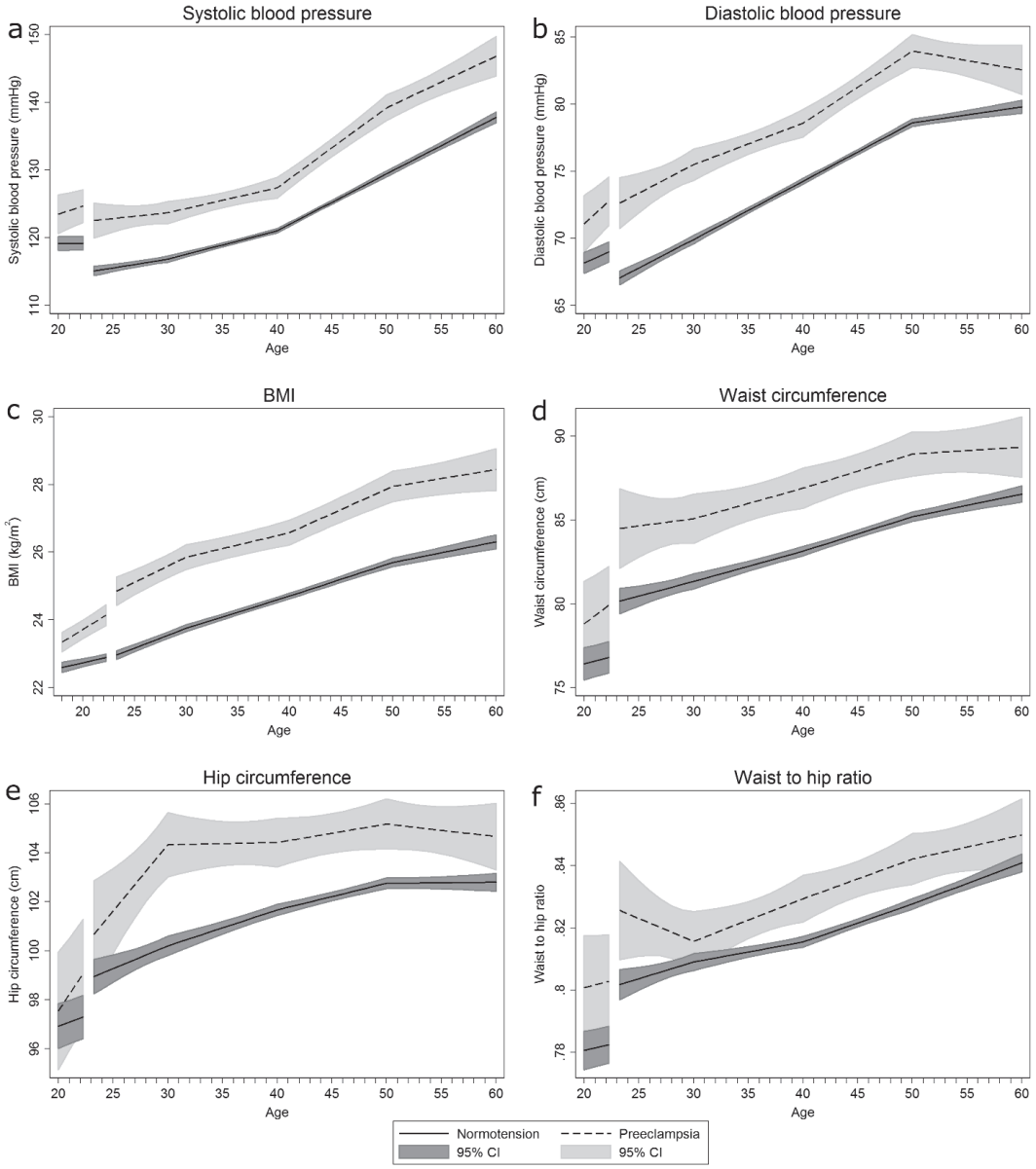
Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first pregnancy and ever daily smoking. Analyses of glucose and triglycerides were additionally adjusted for time since last meal. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period. CRP is given as geometric mean.

Figure S4. Life course trajectories of mean estimated glomerular filtration rate (eGFR) for women with normotension, preeclampsia (a) or gestational hypertension (b) in their first pregnancies.



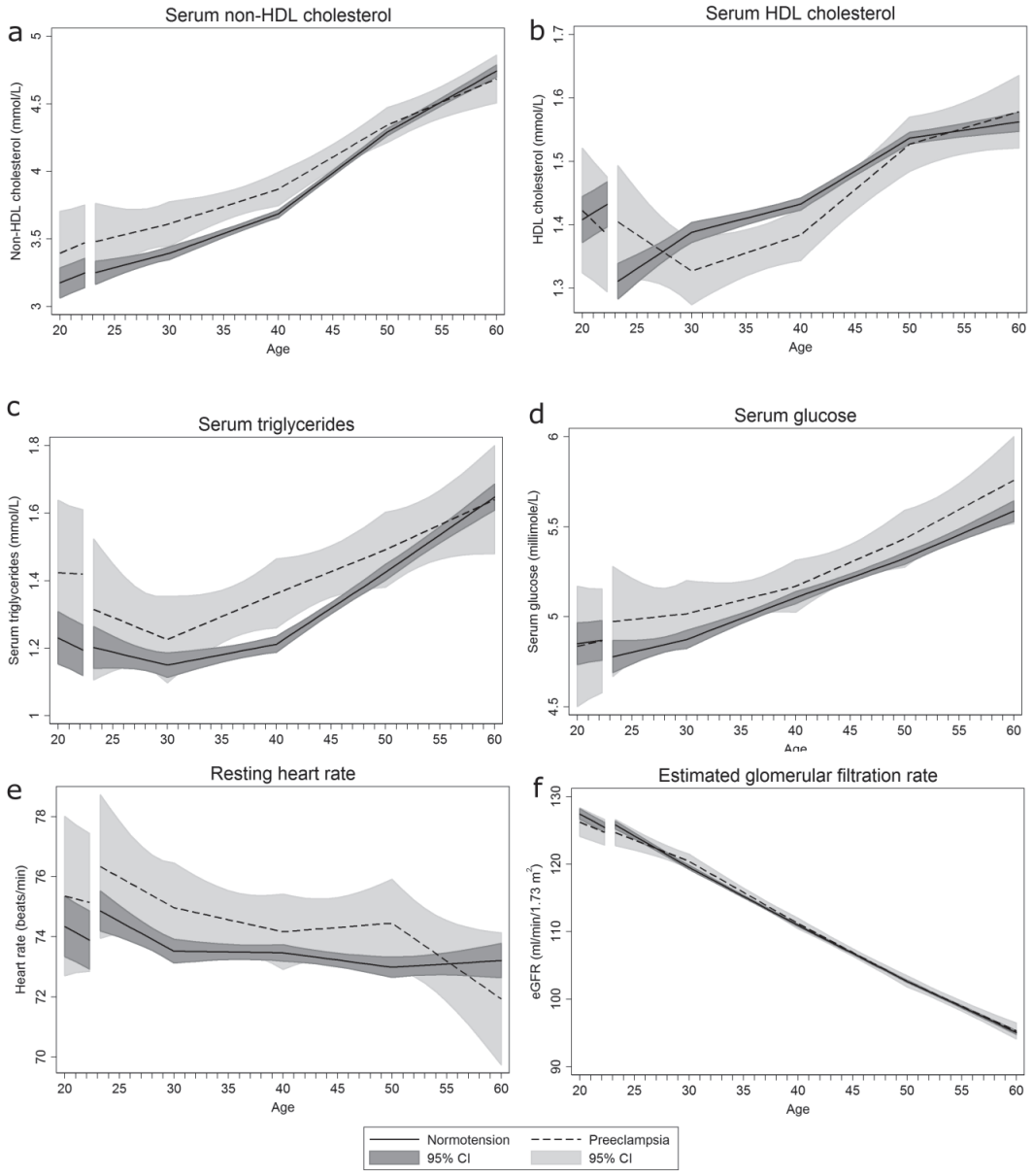
Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period.

Figure S5. Life course trajectories of mean systolic blood pressure (a), diastolic blood pressure (b), BMI (c), waist circumference (d), hip circumference (e) and waist to hip ratio (f) for women with normotensive and preeclamptic first pregnancies who had two or more observations.



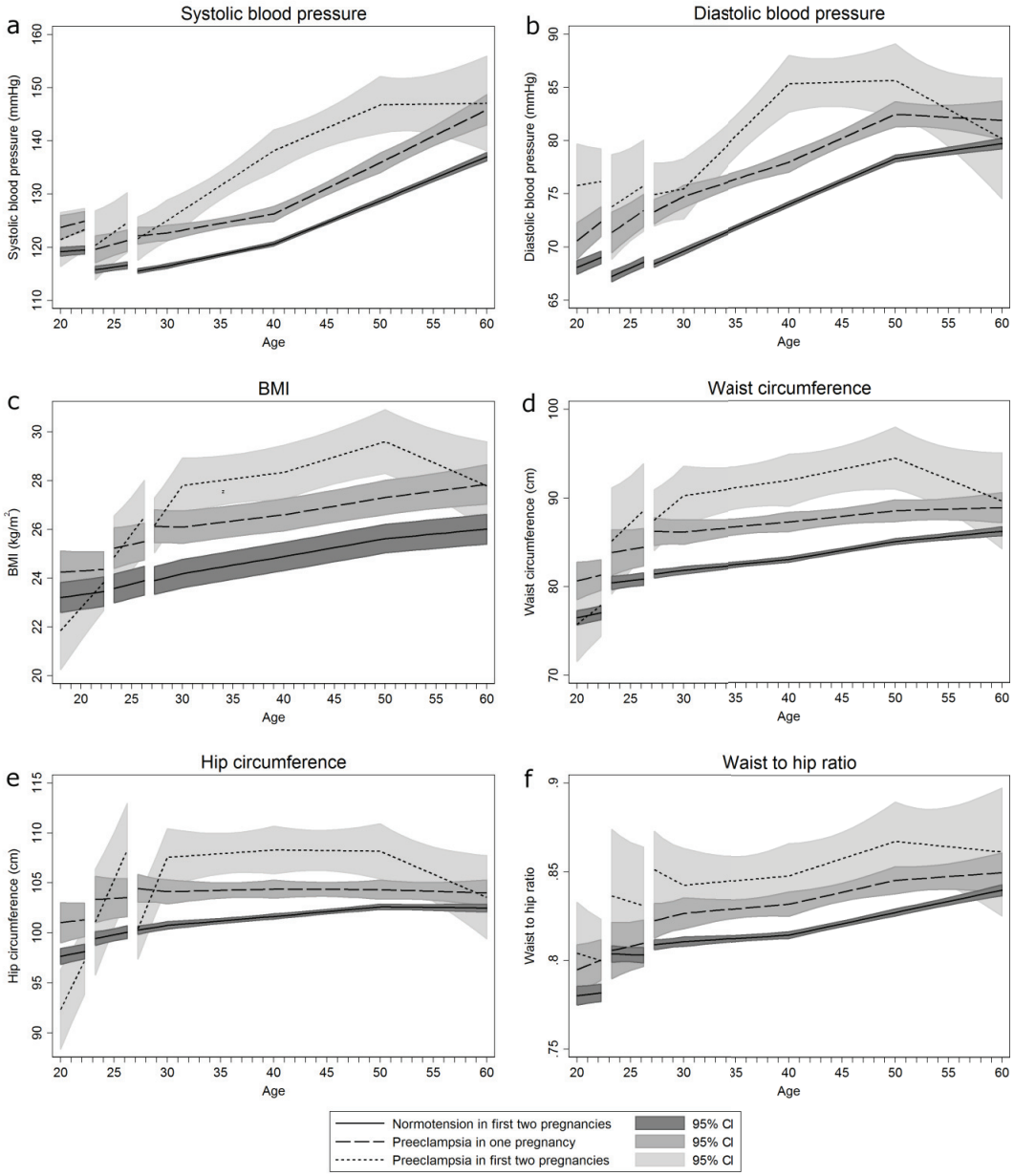
Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period.

Figure S6. Life course trajectories of mean non-fasting serum non-HDL (a) and HDL (b) cholesterol, triglycerides (c) and glucose (d), resting heart rate (e), and estimated glomerular filtration rate (f) for women with normotensive and preeclamptic first pregnancies who had two or more observations.



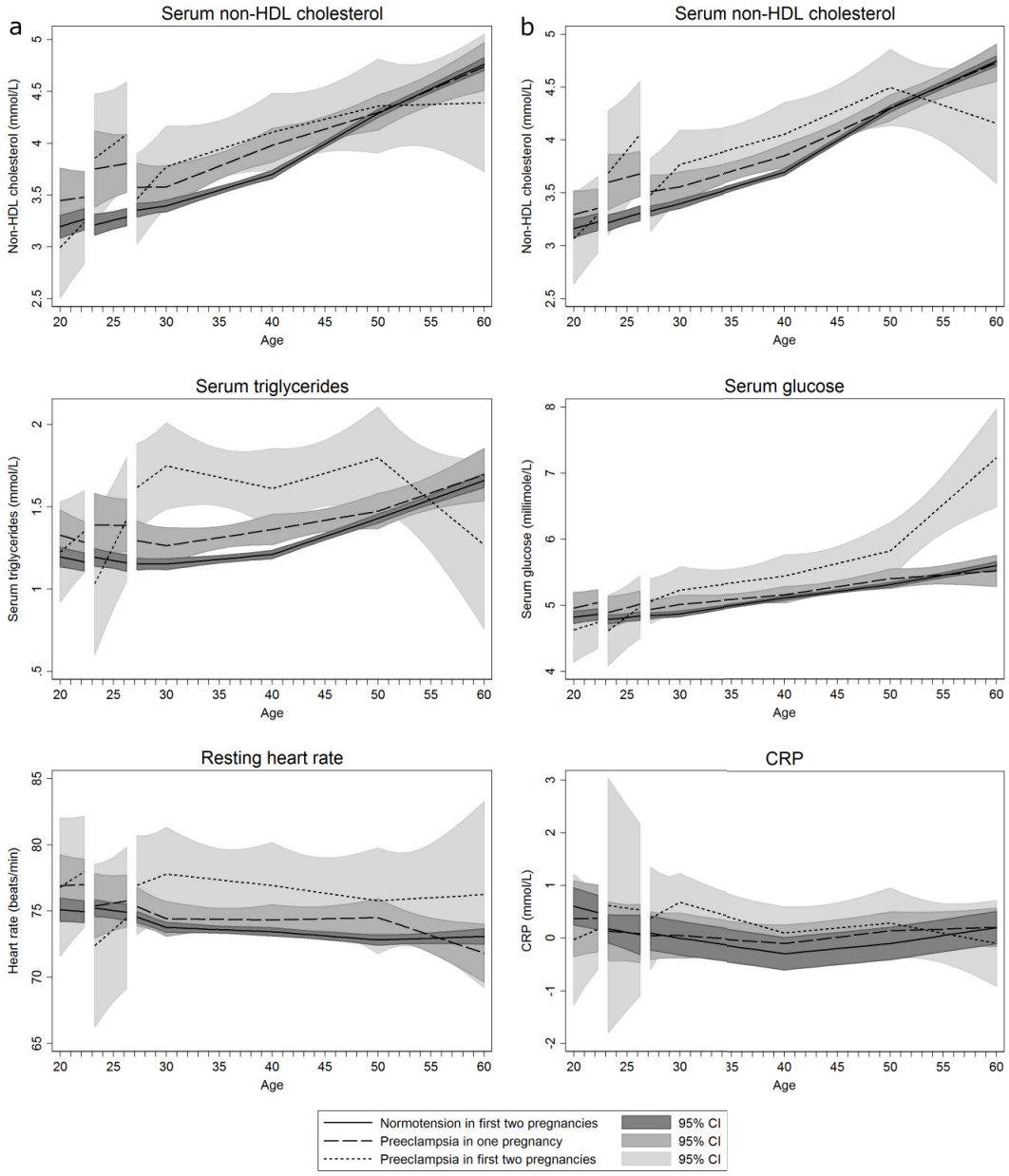
Estimates are adjusted for age at measurement, HUNT survey, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period.

Figure S7. Life course trajectories of mean systolic blood pressure (a), diastolic blood pressure (b), BMI (c), waist circumference (d), hip circumference (e) and waist to hip ratio (f) for women with normotensive first and second pregnancy, preeclampsia in one of their first two pregnancies and preeclampsia in both the first and second pregnancy.



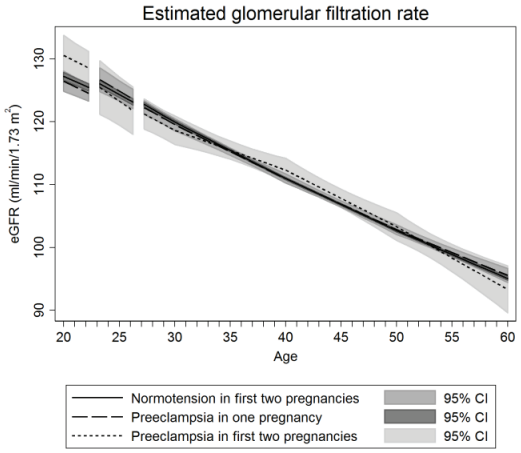
Estimates are adjusted for age at measurement, HUNT survey, time between first and second pregnancy, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first and second pregnancy, birth at age 23 and 27 and three-month postpartum periods.

Figure S8. Life course trajectories of mean non-fasting serum non-HDL (a) and HDL (b) cholesterol, triglycerides (c) and glucose (d), resting heart rate (e) and serum CRP (f) for women with normotensive first and second pregnancy, preeclampsia in one of their first two pregnancies and preeclampsia in both the first and second pregnancy.



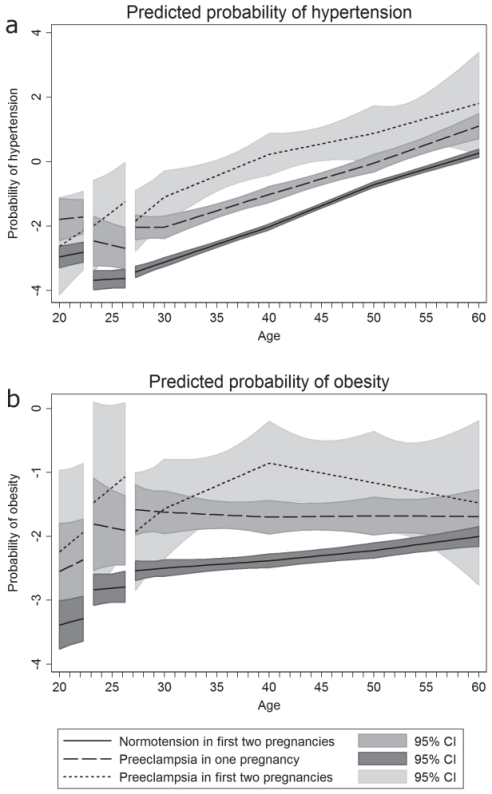
Estimates are adjusted for age at measurement, HUNT survey, time between first and second pregnancy, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first and second pregnancy, birth at age 23 and 27 and three-month postpartum periods.

Figure S9. Life course trajectories of mean estimated glomerular filtration rate (eGFR) for women with normotensive first and second pregnancy, preeclampsia in one of their first two pregnancies and preeclampsia in both the first and second pregnancy.



Estimates are adjusted for age at measurement, HUNT survey, time between first and second pregnancy, highest obtained education level, age at first pregnancy and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first and second pregnancy, birth at age 23 and 27 and three-month postpartum periods.

Figure S10. Population average predicted probabilities of hypertension (defined as current antihypertensive medication and/or blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic) (a) and obesity (defined as a BMI ≥30 kg/m^2) (b) by age in women with normotensive 1st and 2nd pregnancy, preeclampsia in one of their first two pregnancies and preeclampsia in both the 1st and 2nd pregnancy.



Estimates are adjusted for age at measurement, HUNT survey, time between 1st and 2nd pregnancy, highest obtained education level, age at first birth and ever daily smoking. Covariates are fixed at their means with gaps in the graphs corresponding to the woman's first pregnancy, birth at age 23 and a three-month postpartum period.

Paper III

Is not included due to copyright

Appendixes

I Questionnaires from HUNT1

II Questionnaires from HUNT2

III Questionnaires from HUNT3

IV Notification form for the Medical Birth Registry of Norway 1967-1998

V Notification form for the Medical Birth Registry of Norway 1999-

MELDING OM SKJERMBILDEFOTOGRAFERING OG UNDERSØKELSE AV BLODTRYKK OG BLODSUKKER

Skjermbildefotograferingen kommer nå til ditt distrikt. Denne gangen inngår fotograferingen i en større helseundersøkelse, og vi viser til orienteringen som er gitt i den vedlagte brosjyre.

Tid og sted for frammøte vil du finne nedenfor.

Vennligst fyll ut spørreskjemaet på baksiden og ta det med til undersøkelsen. Ta også med skjermbildebevis, tuberkulinkort eller helsebok om du har.

Det er viktig at du møter fram selv om du nylig har fått kontrollert blodtrykk eller blodsukker, og selv om du er under behandling for høyt blodtrykk eller for sukkersyke.

Med vennlig hilsen

Statens skjermbildefotografering

Postboks 8155 Dep, Oslo 1

Fylkeslegen • Helserådet • Statens Institutt For Folkehelse

Født dato | Personr. | Kommune | Kretsnr.

Møtested | Kjønn | Første bokstav etternavn | Dag og dato | Klokkeslett

H. 14 | V. 18 | SBT_1 21 | DBT_1 24 | PULS 27 | SBT_2 30 | DBT_2 33 | SYKEPL 35

TID 36 | $GLUC_1$ 39 | $GLUC_2$ 42 | $GLUC_3$ 45 | HG 46 | BT 47 | P 48 | Ø.M. 49

A. Hvordan er helsa di for tida?
(Sett kryss i bare *en* rute.)

Dårlig	50	1
Ikke helt god		2
God		3
Svært god		4

B. Har du i løpet av de siste 12 måneder vært hos?

	JA	NEI
Almenpraktiserende lege (distriktslege, privatpraktiserende lege,turnuskandidat)	51	
Bedriftslege	52	
Militærlege	53	
Lege ved sykehus (uten at du var innlagt)	54	
Annen lege	55	

C. Har du vært innlagt i sykehus de siste 5 åra? 56

D. Bruker du, eller har du brukt, medisin for høyt blodtrykk? 57

E. Har du eller har du hatt noen av disse sykdommene?

	JA	NEI
Sukkersyke	58	
Hjerteinfarkt	59	
Angina pectoris (hjertekrampe)	60	
Hjerneslag eller hjernebløding	61	

F. Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? (Med langvarig menes at det har vart, eller vil vare i minst ett år.) 62

Hvis «JA», vil du si at dine funksjoner er litt, middels eller mye nedsatt?

	LITT	MIDDELS	MYE
Er bevegelseshemmet	63		
Har nedsatt syn	64		
Har nedsatt hørsel	65		
Hemmet pga. kroppslig sykdom	66		
Hemmet pga. psykiske plager	67		

G. Har du noen søsken? (Nålevende eller døde) 68

Hvis «JA», har en eller flere av dem hatt noen av disse sykdommene?

	JA	NEI	VET IKKE
Sukkersyke	69		
Hjerteinfarkt/hjertekrampe	70		
Forhøyet blodtrykk	71		

H. Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?
(Sett kryss i bare *en* rute.)

Svært fornøyd	72	1
Meget fornøyd		2
Ganske fornøyd		3
Både/og		4
Nokså misfornøyd		5
Meget misfornøyd		6
Svært misfornøyd		7

SE BILDET AV BLODTRYKKSMÅLINGEN I DEN VEDLAGTE BROSJYREN

	JA	NEI	VET IKKE
I. Er blodtrykket ditt målt noen gang før? 73 **Hvis «NEI», gå videre til spørsmål M**			

J. Hvilket år ble blodtrykket målt siste gang?

19 ☐☐ vet ikke 74

Skriv årstallet her (ca.)

K. Hvor ble blodtrykket målt siste gang?
(Sett kryss i bare *en* rute.)

Hos almenpraktiserende lege (distriktslege, privatpraktiserende lege, turnuskandidat	76	1
Hos bedriftslege		2
Hos militærlege		3
På sykehus		4
Hos annen lege		5
Vet ikke		6

L. Hva ble resultatet av målingen?
(Sett kryss i bare *en* rute.)

Jeg skulle begynne med eller fortsette med medisin for høyt blodtrykk	77	1
Jeg skulle komme til kontroll, men skulle *ikke* ta medisin		2
Jeg skulle *ikke* ta medisin og *ikke* komme til kontroll		3

M. Dersom denne helseundersøkelsen viser at du bør undersøkes nærmere: Hvilken almenpraktiserende lege ønsker du da å bli henvist til?

Skriv navnet på legen her

IKKE SKRIV HER

Ingen spesiell lege 78

OM ARBEIDET DITT

N. Er du i arbeid for tida?
(Sett kryss i bare *en* rute.)

Ja, heltidsarbeid (utenom husarbeid)	81	1
Ja, deltidsarbeid (utenom husarbeid)		2
Ja, heltids husarbeid		3
Nei, ikke i arbeid		4

O. Hvis du ikke er i heltids arbeid, er det på grunn av:
(Sett kryss i bare *en* rute.)

Arbeidsløshet, permittering	82	1
Pensjon eller trygd		2
Utdanning eller militærtjeneste		3
Annet		4

HVIS DU ER I ARBEID, VENNLIGST SVAR PÅ DE NESTE TO SPØRSMÅLENE

P. Er det mye stress og mas på arbeidet ditt?
(Sett kryss i bare *en* rute.)

Nei, ikke i det hele tatt	83	1
Sjelden		2
Ja, en god del		3
Ja, nesten hele tida		4

Q. Kan du sjøl bestemme hvordan arbeidet ditt skal legges opp? (Sett kryss i bare *en* rute)

Nei, ikke i det hele tatt	84	1
I liten grad		2
Ja, stort sett		3
Ja, det bestemmer jeg sjøl		4

Vi takker for frammøtet til undersøkelsen.

Vi vil også be deg være vennlig å fylle ut dette spørreskjemaet. Opplysninger vil bli brukt i et større forskningsarbeid om forhold som har betydning for helsen.

Svar etter beste skjønn. Kryss av for bare en av svar-mulighetene (dersom det ikke står nevnt noe annet). Det utfylte skjema returneres i vedlagte svarkonvolutt. Porto er betalt.

Alle opplysningene er underlagt streng taushetsplikt.

Med hilsen

Statens skjermbildefotografering
Fylkeslegen ● Helserådet ● Statens Institutt For Folkehelse
Institutt for anvendt sosialvitenskapelig forskning/
Institutt for samfunnsforskning

Til etikett

Navn: _____

Adr.: _____

_____

_____

Postnr. Postkontor

F.nr.: _____

MOSJON

Med mosjon mener vi at du f.eks. går tur, går på ski, svømmer eller driver trening/idrett.

Hvor ofte driver du mosjon?
(Ta et gjennomsnitt)

Aldri	12	1
Sjeldnere enn en gang i uka		2
En gang i uka		3
2–3 ganger i uka		4
Omtrent hver dag		5

Dersom du driver slik mosjon så ofte som en eller flere ganger i uka:
Hvor hardt mosjonerer du?
(Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett	13	1
Tar det så hardt at jeg blir andpusten og svett		2
Tar meg nesten helt ut		3

Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

Mindre enn 15 minutter	14	1
16–30 minutter		2
30 minutter–1 time		3
Mer enn 1 time		4

SALT

Hvor ofte bruker du salt kjøtt eller salt fisk/sild til middag?

Aldri, eller sjeldnere enn en gang i måneden	15	1
1–2 ganger i måneden		2
Opptil en gang i uka		3
Opptil to ganger i uka		4
Mer enn to ganger i uka		5

Hvor ofte pleier du å strø ekstra salt på middagsmaten?

Sjelden eller aldri	16	1
Av og til		2
Ofte		3
Alltid eller nesten alltid		4

RØYKEVANER

		JA	NEI
Røyker du daglig for tiden?	17		
Hvis du svarte «JA», røyker du DAGLIG for tiden:		JA	NEI
Sigaretter?	18		
Pipe?	19		
Sigarer (eller serutter/sigarillos)?	20		
Hvis du IKKE røyker SIGARETTER daglig for tiden: Har du røykt SIGARETTER daglig tidligere?	21	JA	NEI

Hvis du svarte «JA», hvor lenge er det siden du sluttet å røyke sigaretter daglig?

Mindre enn 3 måneder	22	1
3 måneder– 1 år		2
1–5 år		3
Mer enn 5 år		4

Hvis du røyker SIGARETTER daglig nå, eller har gjort det tidligere:

Hvor mange sigaretter røyker eller røykte du pr. dag? (Oppgi antall pr. dag medregnet håndrullede) ..... 23 — Antall

Besvares av dem som røyker daglig nå eller har røykt daglig tidligere:
(Gjelder både sigarett-, pipe- og sigar-røykere)

Hvor gammel var du da du begynte å røyke daglig?	25	år
Hvor mange år tilsammen har du røykt daglig?	27	år

ALKOHOLBRUK

Hvor ofte har du drukket alkohol (øl, vin eller brennevin) de SISTE 14 DAGENE?

Jeg har ikke drukket alkohol, men er ikke totalavholdende	29	1
Jeg har drukket 1–4 ganger		2
Jeg har drukket 5–10 ganger		3
Jeg har drukket mer enn 10 ganger		4
Jeg er totalavholdende, drikker aldri alkohol		5

		JA	NEI
Dersom du har drukket alkohol de siste 14 dagene, har det ført til at du noen gang har følt deg beruset?	30		

Har det vært perioder i livet ditt da du har drukket for mye, eller i hvert fall i meste laget?

Nei	31	1
I tvil, kanskje		2
Ja		3

BOSITUASJONEN

Bor du alene eller sammen med andre?
Kryss av for de du bor sammen med. (Her kan du sette flere kryss.)

Bor alene	32	
Ektefelle eller samboer	33	
Foreldre eller svigerforeldre	34	
Andre voksne personer	35	
Barn under 5 år	36	
Barn 6–15 år	37	
Barn over 15 år	38	

Bor du fast i institusjon?
(sykehjem, aldershjem eller liknende) 39

JA | NEI

UTDANNINGEN

Hvilken utdanning har du fullført?
Oppgi bare høyest fullførte utdanning.

7-årig folkeskole eller kortere	40	1
Framhalds- eller fortsettelsesskole		2
9-årig grunnskole		3
Real- eller middelskole, grunnskolens 10. år		4
Ett- eller to-årig videregående skole		5
Artium, økonomisk gymnas eller almenfaglig retning i videregående skoler		6
Høyskole eller universitet, mindre enn 4 år		7
Høyskole eller universitet, 4 år eller mer		8

Har du fullført annen heldags utdanning, og i tilfelle i hvor mange år?

Skriv antall år her .... 41 ____ år

ARBEID

Hvis du er eller har vært i inntektsgivende arbeid, kan du angi hvilken av disse yrkesgruppene ditt yrke faller innenfor? (Hvis du ikke er i arbeid nå, svarer du ut fra det yrket du hadde sist.)

Hvis du har en ektefelle (eller samboer) som er i inntektsgivende arbeid nå, eller har vært det tidligere, angi tilsvarende hvilken yrkesgruppe han/hun tilhører. (Evt. angi om han/hun *ikke* har hatt inntektsgivende arbeid.)

		Deg selv	Ektefellen
Spesialarbeider, ufaglært arbeider	43, 44		1
Fagarbeider, håndverker, formann			2
Underordnet funksjonær (butikk, kontor, offentlige tjenester)			3
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)			4
Overordnet stilling i offentlig eller privat virksomhet			5
Gårdbruker eller skogeier			6
Fisker			7
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)			8
Selvstendig næringsdrivende (Industi, transport, handel)			9
Har *ikke* hatt inntektsgivende arbeid (f.eks. pga. heltids husarbeid, studier, trygd)			0

Hvis du er i arbeid (gjelder også heltids husarbeid), **ber vi deg fylle ut de neste spørsmålene:**

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?

Ja, nesten alltid	45	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag?

Ja, nesten alltid	46	1
Ganske ofte		2
Ganske sjelden		3
Aldri, eller nesten aldri		4

Hvordan trives du alt i alt med arbeidet ditt?

Veldig godt	47	1
Ganske godt		2
Godt		3
Ikke særlig godt		4
Dårlig		5

Hvis du er gårdbruker eller annen selvstendig næringsdrivende, har du noen ansatte som arbeider fast for deg?

Ingen fast ansatte	48	1
1–2 fast ansatte		2
3–10 fast ansatte		3
Mer enn 10 fast ansatte		4

HVORDAN HAR DU DET?

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen, eller er du stort sett misfornøyd?

Svært fornøyd	49	1
Meget fornøyd		2
Nokså fornøyd		3
Både - og		4
Nokså misfornøyd		5
Meget misfornøyd		6
Svært misfornøyd		7

Føler du deg stort sett sterk og opplagt, eller trett og sliten?

Meget sterk og opplagt	50	1
Sterk og opplagt		2
Ganske sterk og opplagt		3
Både - og		4
Ganske trett og sliten		5
Trett og sliten		6
Svært trett og sliten		7

MEDISIN/PLAGER

Har du vanligvis:

		JA	NEI
Hoste om morgenen?	51		
Oppspytt fra brystet om morgenen?	52		

Hvor ofte har du brukt smertestillende medisin den siste måneden?

Daglig	53	1
Hver uke, men ikke hver dag		2
Sjeldnere enn hver uke		3
Aldri		4

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden?

Daglig	54	1
Hver uke, men ikke hver dag		2
Sjeldnere enn hver uke		3
Aldri		4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)**?**

Nesten hele tida	55	1
Ofte		2
Av og til		3
Aldri		4

Har du i løpet av siste måned hatt innsoving- eller søvnproblemer?

Nesten hver natt	56	1
Ofte		2
Av og til		3
Aldri		4

Har du i det store og hele en rolig og god følelse inne i deg?

Nesten hele tida	57	1
Ofte		2
Av og til		3
Aldri		4

VENNER/HJELP

Dersom du ble syk og måtte holde senga i lengre tid, hvor sannsynlig tror du det er at du kunne få nødvendig hjelp og støtte av familie, venner eller naboer?

Svært sannsynlig	58	1
Nokså sannsynlig		2
Usikkert		3
Usannsynlig		4
Helt usannsynlig		5

Hender det ofte at du føler deg ensom?

Meget ofte	59	1
Ofte		2
Av og til		3
Meget sjelden		4
Aldri		5

HVORDAN ER DU?

Har du tendens til å ta dine oppgaver mer alvorlig enn folk flest?

Ja, nettopp slik er jeg	60	1
Ja, stort sett		2
Både - og		3
Nei, stort sett ikke		4
Nei, tvert imot		5

		JA	NEI	VET IKKE
Har du i løpet av det siste året ofte følt at du har presset deg, eller stadig drevet deg selv framover?	61			

Føler du deg alltid under tidspress, også når det gjelder daglige gjøremål?

Alltid, eller nesten alltid	62	1
Noen ganger		2
Aldri		3

Er du vanligvis glad eller nedstemt?

Svært nedstemt	63	1
Nedstemt		2
Nokså nedstemt		3
Både - og		4
Nokså glad		5
Glad		6
Svært glad		7

HVA ER VIKTIG?

Synes du det er viktig at man prøver å være fornøyd med det man har?

Dette er særlig viktig	64	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Synes du det er viktig at man kan slå av på kravene?

Dette er særlig viktig	65	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Synes du det er viktig at man alltid er i godt humør?

Dette er særlig viktig	66	1
Dette er viktig		2
Både - og		3
Dette er mindre viktig		4
Dette er overhodet ikke viktig		5

Tusen takk for den hjelp du har gitt oss ved å fylle ut dette skjema.

HELSEUNDERSØKELSEN
I NORD-TRØNDELAG

Personlig innbydelse

Spørreskjemaet er en viktig del av Helseundersøkelsen. Her finner du spørsmål om tidligere sykdom og om andre forhold som har betydning for helsa. Vennligst fyll ut skjemaet på forhånd og ta det med til Helseundersøkelsen. Dersom enkelte spørsmål er uklare, lar du dem bare stå ubesvarte til du møter fram, og drøfter dem med personalet som gjennomfører undersøkelsen. Alle svar vil bli behandlet strengt fortrolig.

Flere steder i skjemaet ber vi deg oppgi din alder da eventuell sykdom inntrådte. Hvis du ikke husker nøyaktig hvor gammel du var, skriver du et tall som er nærmest det du antar er korrekt.

Når resultatene fra undersøkelsen foreligger, vil det være enkelte som trenger ny undersøkelse hos egen lege. Dette vil du få beskjed om i det brevet som vi sender deg om dine resultater. Samtidig sender vi melding om resultatene dine til legen din. Det er derfor om å gjøre at du i rubrikken helt til slutt i skjemaet oppgir navnet på den allmennpraktiserende lege, kommunelege eller det helsesenter som du ønsker skal ta hånd om eventuell etterundersøkelse, og som vi skal sende resultatene til.

Med vennlig hilsen

Helsetjenesten i Nord-Trøndelag • Statens helseundersøkelser • Statens Institutt for Folkehelse

DET HANDLER OM HELSA DI

Hvordan er helsa di nå?

Bare ett kryss

Dårlig	12	☐ 1
Ikke helt god		☐ 2
God		☐ 3
Svært god		☐ 4

LUFTVEGSPLAGER

	JA	NEI
Hoster du daglig i perioder av året?		
Hvis JA:		
Er hosten vanligvis ledsaget av oppspytt? 14		
Har du hatt hoste med oppspytt i minst 3 mnd. sammenhengende i hvert av de to siste åra?		
Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder? 16		

	JA	NEI	Alder første gang
Har du eller har du hatt astma? 17			år

	JA	NEI
Har du brukt eller bruker du astmamedisiner? 20		

HJERTE-KARSYKDOMMER, DIABETES

Har du, eller har du hatt:	JA	NEI	Alder første gang
Hjerteinfarkt 21			år
Angina pectoris (hjertekrampe) 24			år
Hjerneslag/hjerneblødning 27			år
Diabetes (sukkersyke) 30			år

Hva ble resultatet siste gang du målte blodtrykket ditt?

Bare ett kryss

Begynne med/fortsette med blodtrykksmedisin	33	☐ 1
Komme til kontroll, men ikke ta blodtrykksmedisin		☐ 2
Ingen kontroll og ingen medisin nødvendig		☐ 3
Har aldri fått målt blodtrykket		☐ 4

Bruker du medisin mot høyt blodtrykk?

Bare ett kryss

Nå	34	☐ 1
Før, men ikke nå		☐ 2
Aldri brukt		☐ 3

	JA	NEI	VET IKKE
Har en eller flere av foreldre eller søsken hatt hjerteinfarkt (sår på hjertet) eller angina pectoris (hjertekrampe)?			

STOFFSKIFTE

Har du noen gang fått påvist:	JA	NEI	Alder første gang
for høyt stoffskifte 36			år
for lavt stoffskifte 39			år
struma 42			år
annen sykdom i skjoldbruskkjertelen			år
Bruker du eller har du brukt noen av disse medisinene:			
Thyroxin 48			år
Neo-Mercazole 51			år
Er du operert i skjoldbruskkjertelen			år
Har du fått radiojodbehandling 57			år

MUSKEL/SKJELETT-PLAGER

	JA	NEI
Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd som har vart i minst 3 måneder sammenhengende? 60		

Hvis NEI, gå videre til neste side øverst.

Hvis JA, svar på følgende:

Hvor har du hatt disse plagene?	JA	NEI
Nakke 61		
Skuldre (aksler)		
Albuer		
Håndledd, hender		
Bryst/mage 65		
Øvre del av ryggen		
Korsryggen		
Hofter		
Knær		
Ankler, føtter 70		

Hvis du har hatt plager i flere områder i minst 3 mnd. det siste året, setter du ring rundt det ja-krysset hvor plagene har vart lengst

Hvor lenge har plagene vart sammenhengende?

Svar for det området hvor plagene har vart lengst

	Antall mnd.	Antall år
Hvis under 1 år, oppgi antall mnd. 71		
Hvis 1 år eller mer, oppgi antall år. 73		

Har plagene redusert din arbeidsevne det siste året?

Gjelder også hjemmearbeidende. Bare ett kryss

Nei/ubetydelig	I noen grad	I betydelig grad	Vet ikke
☐	☐	☐	☐

	JA	NEI	IKKE I ARBEID
Har du vært sykmeldt pga. disse plagene det siste året? 76			

	JA	NEI
Har plagene ført til redusert aktivitet i fritida?		

Har lege noen gang sagt at du har/har hatt noen av disse sykdommene:

		JA	NEI
Beinskjørhet (osteoporose)	78		
Fibromyalgi (fibrositt/kronisk smertesyndrom)			
Leddgikt (reumatoid artritt)			
Slitasjegikt (artrose)			
Bechterews sykdom	82		
Andre langvarige skjelett- eller muskelsykdommer			

Har du noen gang hatt:

		JA	NEI	Alder *siste* gang
Lårhalsbrudd	84			år
Brudd i håndledd/underarm	87			år
Nakkesleng (whiplash)	90			år
Skade som førte til sykehusinnleggelse				år

ANDRE PLAGER

I hvilken grad har du hatt disse plagene i de siste 12 månedene?

		Ikke plaget	Litt plaget	Mye plaget
Kvalme	96	☐	☐	☐
Brystbrann/sure oppstøt		☐	☐	☐
Diaré		☐	☐	☐
Treg mage		☐	☐	☐
Hjertebank		☐	☐	☐
Åndenød	101	☐	☐	☐

ANDRE SYKDOMMER

Har du eller har du noen gang hatt:

		JA	NEI	Alder første gang
Epilepsi	102			år
Psykiske plager hvor du har søkt hjelp				år
Kreftsykdom	108			år
Annen langvarig sykdom	111			

DAGLIGE FUNKSJONER

Har du noen langvarig sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? ... 112

JA	NEI

Langvarig: minst ett år

Hvis JA:

Hvor mye vil du si at dine funksjoner er nedsatt?

		Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	113	☐	☐	☐
Har nedsatt syn		☐	☐	☐
Har nedsatt hørsel		☐	☐	☐
Hemmet pga. kroppslig sykdom.		☐	☐	☐
Hemmet pga. psykiske plager...	117	☐	☐	☐

MENN fortsetter øverst neste spalte

BESVARES BARE AV KVINNER

Hvor mange barn har du født? 118
Sett 0 hvis du ikke har født barn

Antall barn

Hvis du har født barn, besvar:

Hvor gammel var du da du fødte ditt første barn? 120

Alder: ____ år

Hvor gammel var du da du fødte ditt siste barn? 122
Besvares ikke hvis du har født bare ett barn

____ år

Hvor gammel var du da du fikk menstruasjon? 124
Sett 0 hvis du ikke noen gang har hatt menstruasjon

____ år

Fortsett neste spalte øverst

RØYKING

Røykte noen av de voksne hjemme da du vokste opp? 126

JA	NEI

Bor du, eller har du bodd, sammen med noen dagligrøykere etter at du fylte 20 år? 127

JA	NEI

Hvor lenge er du vanligvis daglig til stede i røykfylt rom? 128
Sett 0 hvis du ikke oppholder deg i røykfylt rom

Antall timer

Røyker du selv?

		JA	NEI
Sigaretter daglig?	130		
Sigarer/sigarillos daglig?			
Pipe daglig?	132		

Aldri røykt daglig ..... *(Sett kryss)* ☐

Hvis du har røykt daglig tidligere, hvor lenge er det siden du sluttet? 134

Antall år

Hvis du røyker daglig nå eller har røykt tidligere:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? 136

Antall sigaretter

Hvor gammel var du da du begynte å røyke daglig? 140

Alder ____ år

Hvor mange år tilsammen har du røykt daglig? 142

Antall år

KAFFE/TE/ALKOHOL

Hvor mange kopper kaffe/te drikker du daglig?
Sett 0 hvis du ikke drikker kaffe/te daglig

		Antall kopper
Kokekaffe	144	
Annen kaffe	146	
Te	148	

Alkohol:
Er du total avholdsmann/-kvinne? 150

JA	NEI

Hvor mange ganger i måneden drikker du vanligvis alkohol? 151
Regn ikke med lettøl. Sett 0 hvis mindre enn 1 gang i mnd.

Antall ganger

Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av to uker?

Regn ikke med lettøl.
Sett 0 hvis du ikke drikker alkohol 153

Øl	Vin	Brennevin
glass	glass	glass

FYSISK AKTIVITET

I FRITIDA

Hvordan har din fysiske aktivitet i fritida vært det siste året? *Tenk deg et ukentlig gjennomsnitt for året.*

Arbeidsveg regnes som fritid

		Timer pr. uke: Ingen	Under 1	1-2	3 og mer
Lett aktivitet *(ikke svett/andpusten)*	159	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	160	☐ 1	☐ 2	☐ 3	☐ 4

UNDER ARBEID
Hvis du er i lønnet eller ulønnet arbeid:

Hvorledes vil du beskrive arbeidet ditt?
Bare ett kryss

For det meste stillesittende arbeid
(f.eks. skrivebordsarbeid, montering) ..... 161 ☐ 1

Arbeid som krever at du går mye
(f.eks. ekspeditørarb., lett industriarb., undervisning) ..... ☐ 2

Arbeid hvor du går og løfter mye
(f.eks. postbud, pleier, bygningsarbeid) ..... ☐ 3

Tungt kroppsarbeid
(f.eks. skogsarbeid, tungt jordbruksarb.,tungt bygningsarb.) ☐ 4

Bla om!

HVORLEDES FØLER DU DEG?

Har du de siste to ukene følt deg:

	Nei	Litt	En god del	Svært mye
Trygg og rolig? 162	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Har du følt deg:				
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst? 165	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom? 168	☐ 1	☐ 2	☐ 3	☐ 4

Her kommer noen flere spørsmål om hvorledes du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser ***den siste uka.*** *Ikke tenk for lenge på svaret - de spontane svarene er best*

Jeg gleder meg fortsatt over ting slik jeg pleide før 169
Avgjort like mye ..... ☐ 1 Bare lite grann ..... ☐ 3
Ikke fullt så mye ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har en urofølelse som om noe forferdelig vil skje 170
Ja, og noe svært ille .... ☐ 1 Litt, bekymrer meg lite . ☐ 3
Ja, ikke så veldig ille ... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan le og se det morsomme i situasjoner 171
Like mye nå som før .... ☐ 1 Avgjort ikke som før .... ☐ 3
Ikke like mye nå som før ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg har hodet fullt av bekymringer 172
Veldig ofte ..... ☐ 1 Av og til ..... ☐ 3
Ganske ofte ..... ☐ 2 En gang i blant ..... ☐ 4

Jeg er i godt humør 173
Aldri ..... ☐ 1 Ganske ofte ..... ☐ 3
Noen ganger ..... ☐ 2 For det meste ..... ☐ 4

Jeg kan sitte i fred og ro og kjenne meg avslappet 174
Ja, helt klart ..... ☐ 1 Ikke så ofte ..... ☐ 3
Vanligvis ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg som om alt går langsommere 175
Nesten hele tiden ..... ☐ 1 Fra tid til annen ..... ☐ 3
Svært ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg føler meg urolig som om jeg har sommerfugler i magen 176
Ikke i det hele tatt ..... ☐ 1 Ganske ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært ofte ..... ☐ 4

Jeg bryr meg ikke lenger om hvordan jeg ser ut 177
Ja, har sluttet å bry meg ☐ 1 Kan hende ikke nok .... ☐ 3
Ikke som jeg burde ..... ☐ 2 Bryr meg som før ..... ☐ 4

Jeg er rastløs som om jeg stadig må være aktiv 178
Uten tvil svært mye ..... ☐ 1 Ikke så veldig mye ..... ☐ 3
Ganske mye..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg ser med glede frem til hendelser og ting 179
Like mye som før ..... ☐ 1 Avgjort mindre enn før . ☐ 3
Heller mindre enn før ... ☐ 2 Nesten ikke i det hele tatt ☐ 4

Jeg kan plutselig få en følelse av panikk 180
Uten tvil svært ofte ..... ☐ 1 Ikke så veldig ofte ..... ☐ 3
Ganske ofte ..... ☐ 2 Ikke i det hele tatt ..... ☐ 4

Jeg kan glede meg over gode bøker, radio og TV 181
Ofte ..... ☐ 1 Ikke så ofte ..... ☐ 3
Fra tid til annen ..... ☐ 2 Svært sjelden ..... ☐ 4

UTDANNING

Hvilken utdanning er den høyeste du har fullført?

Grunnskole 7-10 år, framhaldsskole, folkehøgskole ..... 182 ☐ 1
Realskole, middelskole, yrkesskole, 1-2 årig videregående skole..... ☐ 2
Artium, øk.gymnas, allmennfaglig retning i videregående skole ..... ☐ 3
Høgskole/universitet, mindre enn 4 år ..... ☐ 4
Høgskole/universitet, 4 år eller mer ..... ☐ 5

ARBEID

Hva slags arbeidssituasjon har du nå?
Ett eller flere kryss

Lønnet arbeid ..... 183 ☐
Selvstendig næringsdrivende..... ☐
Heltids husarbeid ..... ☐
Utdanning, militærtjeneste ..... ☐
Arbeidsledig, permittert..... ☐
Pensjonist/trygdet..... 188 ☐

Hvor mange timer lønnet arbeid har du i uka? ..... 189 Antall timer

	JA	NEI
Har du skiftarbeid, nattarbeid eller går vakt?		

ALT I ALT

Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd?
Bare ett kryss

Svært fornøyd ..... 192 ☐ 1
Meget fornøyd ..... ☐ 2
Ganske fornøyd..... ☐ 3
Både/og..... ☐ 4
Nokså misfornøyd ..... ☐ 5
Meget misfornøyd..... ☐ 6
Svært misfornøyd..... ☐ 7

DIN LEGE

Hvis denne helseundersøkelsen viser at du bør undersøkes nærmere, hvilken allmennpraktiserende lege/kommunelege ønsker du skal foreta undersøkelsen?

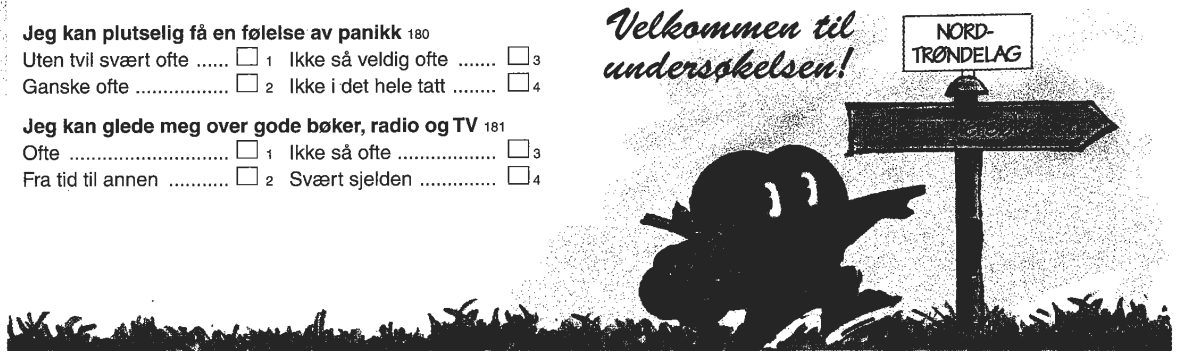
Skriv navnet på legen her: 193

	Ikke skriv her

Takk for utfyllingen!

Nok en gang:

Velkommen til undersøkelsen!



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Helseundersøkelsen i Nord-Trøndelag

SKJEMA FOR KVINNER 20–69 ÅR

Takk for frammøtet til undersøkelsen!
Vi vil også be deg fylle ut dette spørreskjemaet. Opplysningene vil bli brukt i større forskningsarbeider om forebyggende helsearbeid. Noen av spørsmålene likner på spørsmål du har svart på i det skjemaet du fylte ut heime og leverte ved frammøte til helseundersøkelsen. Det er likevel viktig at du svarer på alle spørsmålene også i dette skjemaet. Det utfylte skjemaet returneres i vedlagte svarkonvolutt. Porto er betalt.
Alle opplysningene er underlagt streng taushetsplikt.

Vennlig hilsen
Helsetjenesten i Nord-Trøndelag
Statens Institutt for Folkehelse Statens helseundersøkelser

Hvis du ikke ønsker å besvare spørreskjemaet, sett kryss her og returner skjemaet. Da slipper du purring.
Jeg ønsker ikke å besvare skjemaet ○

UTFYLLING

Dato for utfylling av skjema: / 19 (19)

OPPVEKST

I hvilken kommune bodde du da du fylte 1 år?
*Hvis du ikke bodde i Norge, oppgi **land** i stedet for kommune.*

(24)

ARBEID

Nåværende eller tidligere arbeid:
Hva slags inntektsgivende arbeid har du og event. din ektefelle/samboer? *Hvis du/dere ikke har inntektsgivende arbeid nå: Oppgi det siste yrket.*

	Deg selv	Ektefelle/ samboer
Spesialarbeider eller ufaglært arbeider (25)	☐	☐ (36)
Fagarbeider, handverker, formann	☐	☐
Underordnet funksjonær (f.eks. butikk, kontor, off. tjenester)	☐	☐
Fagfunksjonær (f.eks. sykepleier, tekniker, lærer)	☐	☐
Overordnet stilling i off. eller privat virksomhet	☐	☐
Sjåfør (30)	☐	☐ (41)
Gårdbruker eller skogeier	☐	☐
Fisker	☐	☐
Selvstendig i akademisk erverv (f.eks. tannlege, advokat)	☐	☐
Annen selvstendig næringsvirksomhet	☐	☐
Har ikke vært i inntektsgivende arbeid (35)	☐	☐ (46)

Hvis du NÅ ikke har inntektsgivende arbeid eller du ikke har heltids husarbeid: Gå til BOLIG.

Har du i løpet av de siste 12 månedene hatt sykefravær:	Ja	Nei
med egenmelding (47)	☐	☐
med sykmelding fra lege (48)	☐	☐

Hvis «Ja»: **Hvor lenge *tilsammen*?** *Bare ett kryss*

2 uker eller mindre (49)	☐ 1
2-8 uker	☐ 2
Mer enn 8 uker	☐ 3

Har du i løpet av de siste 12 månedene vurdert å skifte yrke eller arbeidsplass? (50)	Ja ☐	Nei ☐

Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag? *Bare ett kryss* (51)

Ja, nesten alltid	☐ 1	Ganske sjelden	☐ 3
Ganske ofte	☐ 2	Aldri, eller nesten aldri	☐ 4

Krever arbeidet ditt så mye konsentrasjon og oppmerksomhet at du ofte føler deg utslitt etter en arbeidsdag? (52)

Ja, nesten alltid	☐ 1	Ganske sjelden	☐ 3
Ganske ofte	☐ 2	Aldri, eller nesten aldri	☐ 4

Hvordan trives du alt i alt med arbeidet ditt? (53)

Veldig godt	☐ 1	Ikke særlig godt	☐ 3
Godt	☐ 2	Dårlig	☐ 4

BOLIG

Hvem bor du sammen med?
Ett kryss for hver linje og angi antall

	Ja	Nei	Antall
Ektefelle/samboer (54)	☐	☐	
Andre personer over 18 år (55)	☐	☐	
Personer under 18 år (58)	☐	☐	

Hvor mange av barna har plass i barnehage? (61) Antall

Hvilken type bolig bor du i? *Bare ett kryss*

Enebolig/villa (63)	☐	1
Gårdsbruk	☐	2
Blokk/terrasseleilighet	☐	3
Rekkehus/2-4 mannsbolig	☐	4
Annen bolig	☐	5

Hvor stor er din boenhet? (64) kvm

	Ja	Nei
Er det heldekkende tepper i stua? (67)	☐	☐
Er det heldekkende tepper på ditt soverom?	☐	☐
Er det katt i boligen? (69)	☐	☐
Er det hund i boligen?	☐	☐
Er det andre pelskledde dyr eller fugler i boligen?	☐	☐

ØKONOMI

Mottar du noen av følgende *offentlige* ytelser?	Ja	Nei
Sykepenger/sykelønn/rehabiliteringspenger (72)	☐	☐
Ytelser under yrkesrettet attføring	☐	☐
Uførepensjon (74)	☐	☐
Alderspensjon	☐	☐
Sosialstøtte	☐	☐
Arbeidsløshetstrygd	☐	☐
Overgangsstønad	☐	☐
Etterlattepensjon (79)	☐	☐
Andre ytelser	☐	☐

Har det i løpet av det siste året hendt at husholdningen har hatt vansker med å klare de løpende utgifter til mat, transport, bolig og liknende? *Bare ett kryss* (81)

Ja, ofte	☐ 1	Ja, en sjelden gang	☐ 3
Ja, av og til	☐ 2	Nei, aldri	☐ 4

VENNER

Hvor mange gode venner har du?
Regn med de du kan snakke fortrolig med og som kan gi deg god hjelp når du trenger det (82) Antall

Tell ikke med de du bor sammen med, men regn med andre slektninger

	Ja	Nei
Føler du at du har mange nok gode venner? (84)	☐	☐

Hvor ofte tar du vanligvis del i foreningsvirksomhet som f.eks. syklubb, idrettslag, politiske lag, religiøse eller andre foreninger? (85)

Aldri, eller noen få ganger i året	☐ 1	Omtrent en gang i uka	☐ 1
1-2 ganger i måneden	☐ 2	Mer enn en gang i uka	☐ 2

DER DU BOR

Svar ut fra nærmiljøet, dvs. nabolaget/grenda:
Ett kryss for hvert spørsmål

Jeg føler et sterkt fellesskap med de som bor her 86
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

Selv om noen tar initiativ, er det ingen som blir med på det som settes i gang her 87
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Hvis jeg flytter herfra, vil jeg lengte tilbake 88
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Man kan ikke stole på hverandre her 89
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Når noe skal gjøres her, er det lett å få folk med 90
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er vanskelig å få kontakt med folk her 91
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er godt samhold her 92
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Ingen orker å ta initiativ til noe lenger her 93
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk trives godt her 94
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk her kan ha store problemer uten at naboen vet noe 95
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Det er alltid noen som tar initiativ til å løse nødvendige oppgaver her 96
Helt enig ☐ Delvis enig ☐ Usikker ☐ Delvis uenig ☐ Helt uenig ☐

Folk snakker lite med hverandre her 97
Helt enig ☐ 1 Delvis enig ☐ 2 Usikker ☐ 3 Delvis uenig ☐ 4 Helt uenig ☐ 5

SYKDOM I FAMILIEN

Kryss av for de slektningene som har eller har hatt noen av sykdommene. Kryss av for "ingen" hvis ingen av slektningene har hatt denne sykdommen: *Evt. flere kryss på hver linje*

	Mor	*Far*	*Bror*	*Søster*	*Barn*	*Ingen*
Hjerneslag eller hjerneblødning 98	☐	☐	☐	☐	☐	☐
Hjerteinfarkt før 60 års alder..... 104	☐	☐	☐	☐	☐	☐
Astma..... 110	☐	☐	☐	☐	☐	☐
Allergi 116	☐	☐	☐	☐	☐	☐
Kreftsykdom..... 122	☐	☐	☐	☐	☐	☐
Høyt blodtrykk..... 128	☐	☐	☐	☐	☐	☐
Psykiske plager..... 134	☐	☐	☐	☐	☐	☐
Osteoporose (benskjørhet)..... 140	☐	☐	☐	☐	☐	☐
Diabetes (sukkersyke) 146	☐	☐	☐	☐	☐	☐
Alder da de fikk diabetes 152	år	år	år	år	år	

Har du *selv* høysnue eller neseallergi?..... 162 ☐ Ja ☐ Nei

BRUK AV HELSETJENESTER

Har du i løpet av de siste 12 månedene vært hos:
Ett kryss på hver linje

	Ja	*Nei*
allmennpraktiserende lege (kommunelege, privatpraktiserende lege, turnuskandidat) 163	☐	☐
bedriftslege.....	☐	☐
lege ved sykehus (uten at du var innlagt)	☐	☐
annen lege	☐	☐
fysioterapeut.....	☐	☐
kiropraktor	☐	☐
homøopat 169	☐	☐
annen behandler (naturmedisiner, fotsoneterapeut, håndspålegger, "healer", "synsk", e.l.)	☐	☐

Har du vært innlagt i sykehus de siste 5 åra?.....171 ☐ Ja ☐ Nei

ALKOHOL

Hvis du er totalavholdskvinne: Gå til KOSTHOLD.

Ett kryss for hver spørsmål

Har du noen gang følt at du burde redusere alkoholforbruket ditt?.....172 ☐ Ja ☐ Nei

Har andre noen gang kritisert alkoholbruken din?.....173 ☐ Ja ☐ Nei

Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din?.....174 ☐ Ja ☐ Nei

Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker? .....175 ☐ Ja ☐ Nei

KOSTHOLD

Hvor mange måltider spiser du vanligvis daglig (middag og brødmåltid)?.....176 Antall

Hvor mange dager i uka spiser du varm middag?

Hva slags type brød (kjøpt eller hjemmebakt) spiser du vanligvis? *Inntil to kryss*

Brødtypen ligner mest på 178	*Loff*	*Fint brød*	*Kneipp-brød*	*Grov-brød*	*Knekke-brød*
	☐	☐	☐	☐	☐

Hva slags *fett* blir vanligvis brukt i din husholdning?
Ett kryss for matlaging og ett kryss for brød

	Til matlaging	*På brød*
Bruker *ikke* smør eller margarin	183 ☐ 1	184 ☐ 1
Meierismør.....	☐ 2	☐ 2
Hard margarin.....	☐ 3	☐ 3
Bløt (soft) margarin	☐ 4	☐ 4
Smør/margarin blanding	☐ 5	☐ 5
Lettmargarin	☐ 6	☐ 6
Oljer	☐ 7	

MEDISINBRUK

Har du i deler av de siste 12 måneder brukt noen medisiner daglig eller nesten daglig? .....185 ☐ Ja ☐ Nei

Hvis «Ja»:
Angi hvor mange måneder du brukte følgende medisiner: *Sett 0 hvis du ikke har brukt medisinene*

	Antall mndr.		Antall mndr.
smertestillende 186		hjertemedisin (ikke blodtrykksmedisin)	
sovemedisin..... 188		annen medisin	
beroligende medisin		*Kosttilskudd:*	
medisin mot depresjon		jerntabletter..... 202	
allergimedisin..... 194		vitamintilskudd	
astmamedisin 196		tran/fiskeoljer 206	

Hvor ofte har du brukt avslappende/beroligende medisin eller sovemedisin den siste måneden? 208
Daglig..... ☐ 1 Sjeldnere enn hver uke ☐ 3
Hver uke, men ikke hver dag . ☐ 2 Aldri..... ☐ 4

HODEPINE

Har du vært plaget av hodepine i løpet av de siste 12 måneder? 209
Ja, anfallsvis (migrene)..... ☐ 1
Ja, annen slags hodepine.... ☐ 2
Nei ..... ☐ 3

Antall anfall siste 12 mndr. 210 ☐☐☐

Hvis «Nei»: Gå til MUSKEL-/SKJELETTPLAGER

Omtrent hvor mange dager i pr. måned har du hodepine?
Mindre enn 7 dager ☐1 7 til 14 dager ☐2 Mer enn 14 d. ☐3

Hvor lenge varer hodepinen vanligvis hver gang? 213
Mindre enn 4 timer ☐1 4 timer–3 døgn ☐2 Mer enn 3 døgn ☐3

Hvor ofte er hodepinen preget av eller ledsaget av:

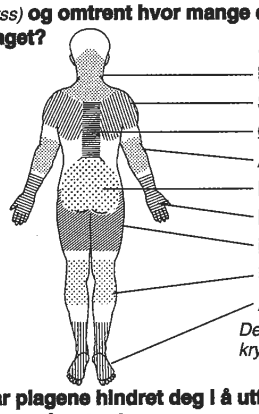
Ett kryss på hver linje	*Sjelden eller aldri*	*Av og til*	*Ofte*
bankende/dunkende smerte 214	☐	☐	☐
pressende smerte	☐	☐	☐
halvsidighet, alltid samme side	☐	☐	☐
halvsidighet, vekselvis h. og v. side	☐	☐	☐
smerter i «hele hodet»	☐	☐	☐
kvalme 219	☐	☐	☐
lys- og/eller lydskyhet	☐	☐	☐
forverring ved fysisk aktivitet.....	☐	☐	☐
synsforstyrrelser *før* hodepine 222	☐	☐	☐

Hvor mange tabletter/stikkpiller har du eventuelt brukt av disse medisinene *alt i alt i løpet av den siste måneden*?
Skriv 0 hvis du ikke har brukt medisinen.
Cafergot 223 ☐☐ Anervan 225 ☐☐ Imigran 227 ☐☐

MUSKEL-/SKJELETTPLAGER

Har du hatt plager (smerter, verk, ubehag) i muskler og/eller ledd i *den siste måneden*? 229 Ja ☐ Nei ☐

Hvis «Ja»: **Hvor har du hatt disse plagene** *(ett eller flere kryss)* **og omtrent hvor mange dager tilsammen var du plaget?**



Plager (Sett kryss)	Antall dager
Nakke 230	☐☐
Skuldre/aksler.....233	☐☐
Øvre del av ryggen	☐☐
Albuer 239	☐☐
Korsryggen 242	☐☐
Handledd/hender 245	☐☐
Hofter.....248	☐☐
Knær.....251	☐☐
Ankler/føtter 254	☐☐

*Dersom flere kryss: Sett **ring** rundt krysset **der plagen var verst***

Har plagene hindret deg i å utføre daglige aktiviteter den siste måneden?

	Ja	*Nei*
I arbeidet.....257	☐	☐
I fritida 258	☐	☐

SMERTER I BEINA

	Ja	*Nei*
Har du sår på tå, fot eller ankel som ikke vil gro? 259	☐	☐
Har du smerter i det ene eller i begge beina når du går? 260	☐	☐
Har du oppsøkt lege p.g.a. smerter i beina? 261	☐	☐

Hvis «NEI» på disse spørsmålene: Gå til MENSTRUASJON

	Ja	*Nei*
Kan du gå lenger enn 50 meter? 262	☐	☐
Forsvinner smerten når du står stille en stund? 263	☐	☐
Må du sette deg for at smerten skal gå over? 264	☐	☐

Hvor gjør det mest vondt? *Ett kryss* 265
Fot ☐ Legg ☐ Lår ☐ Hofte ☐

	Ja	*Nei*
Har du smerter i beina når du er i ro? 266	☐	☐
Er smertene verst når du ligger i senga? 267	☐	☐
Blir søvnen forstyrret av smertene? 268	☐	☐
Får du mindre vondt når beinet ligger høyt? 269	☐	☐
Får du mindre vondt når beinet ligger lavt, f.eks. om beinet henger utfor sengekanten? 270	☐	☐
Bedres smertene når du står opp og går litt? 271	☐	☐

MENSTRUASJON

Har du menstruasjon fremdeles?..... 272 Ja ☐ Nei ☐

Hvis «Nei»: **Hvor gammel var du da den sluttet?** 273 ☐☐ år

Er du gravid nå? ..... 275 Ja ☐ Nei ☐ Vet ikke ☐

Har du innsatt spiral nå? ..... 276 Ja ☐ Nei ☐

Når hadde du siste menstruasjon? ..... 277 Dag ☐☐ Måned ☐☐ År ☐☐☐☐
Husker du ikke dag, bare angi måned og år, husker du bare år, angi år.

Menstruasjonen din de siste 12 måneder:

Har du det siste året hatt regelmessige menstruasjoner?
At menstruasjonen har vart omtrent like lenge hver gang med omtrent like lange mellomrom ..... 283 Ja ☐ Nei ☐ Usikker ☐

Hvor mange dager hadde du blødning siste gang du hadde menstruasjon? ..... 284 Antall dager ☐☐

Hvor mange dager var du uten blødning mellom nest siste og siste menstruasjon? ... 286 Antall dager ☐☐

Har menstruasjonen din det siste året uteblitt i mer enn 3 måneder uten at du var gravid? 289 Ja ☐ Nei ☐

Hvis «Ja»: **Hvor mange måneder i trekk har du vært uten menstruasjonsblødninger?** ..... 290 Antall mndr. ☐☐

Hvis «Ja»: **Oppsøkte du lege?** ..... 292 Ja ☐ Nei ☐

Menstruasjonen tidligere (dvs. før de siste 12 månedene):

Har menstruasjonen din tidligere uteblitt uten at du var gravid? ..... 293 Ja ☐ Nei ☐

Hvis «Ja»: **Hvor lenge og hvor ofte var den borte sammenhengende?** *Sett kryss eventuelt flere steder*

	1 gang	*2 ganger*	*Oftere*
3–6 måneder..... 294	☐	☐	☐
6–12 måneder.....	☐	☐	☐
Over ett år..... 296	☐	☐	☐

OPERASJONER I UNDERLIVET

	Ja	Nei	Vet ikke
Har du noen gang blitt operert i underlivet? 297	☐	☐	☐

Hvis «Ja»: **Kryss av for hver operasjon:**

	Ja	Nei	Vet ikke
Fjernet deler av eller bare én eggstokk 298	☐	☐	☐
Fjernet begge eggstokkene (totalt) 299	☐	☐	☐

Hvis du har fjernet begge eggstokkene, hvor gammel var du da? 300 ____ år

	Ja	Nei	Vet ikke
Operert for endometriose 302	☐	☐	☐
Sterilisert	☐	☐	☐
Utskraping fra livmor (sykehus)	☐	☐	☐
Fjernet hele livmoren 305	☐	☐	☐

Hvis du har fjernet hele livmoren, hvor gammel var du da? 306 ____ år

P-PILLER

	Ja	Nei
Har du noen gang brukt p-piller, minipiller inkludert? 308	☐	☐

Hvis «Ja»: **Hvor gammel var du første gang du brukte p-piller?** 309 ____ år

Hvor lenge har du brukt p-piller i alt? 311 ____ år

Hvis under ett år, antall måneder 313 ____ mndr.

	Ja	Nei
Bruker du p-piller nå?	☐	☐

Hvilket merke bruker du? 316 ____

HORMONBEHANDLING

Utenom p-piller

Har du noen gang brukt medisiner som inneholder østrogen? Vanlige navn på slike medisiner er: Cyclabil, Estraderm, Kilogest, Ovesterin, Progynova, Trisekvens.

	Nå	Før	Aldri
Tabletter eller plaster 318	☐	☐	☐
Krem eller stikkpiller 319	☐	☐	☐

Hvis «Ja»: **Hvor gammel var du første gang du fikk østrogenmedisin, og omtrent hvor mange år brukte du slik medisin?**

	Din alder	Antall år
Tabletter eller plaster 320		
Krem eller stikkpiller 324		

Hvis du bruker østrogenmedisin nå, hvilket merke bruker du? 328 ____

PROBLEMER MED Å BLI GRAVID

	Ja	Nei
Har du noen gang prøvd i mer enn ett år å bli gravid? 329	☐	☐

Hvis «Ja»: **Hvor gammel var du første gang du hadde problemer med å bli gravid?** 330 ____ år

	Ja	Nei
Har du noen gang oppsøkt lege fordi du hadde problemer med å bli gravid? 332	☐	☐

GRAVIDITETER, FØDSLER OG AMMING

Hvor mange ganger har du vært gravid totalt?
*Regn med **alle** svangerskap, spontane eller selvbestemte aborter, så vel som fødsler (også dødfødsler)* 333 ____ ganger

Hvor mange barn har du født? 335 ____ barn

Fyll ut for hvert barn (de første 7) opplysninger om fødselsår og omtrent antall måneder du ammet hvert barn og antall måneder menstruasjonen din var borte etter fødselen (fylles ut også for dødfødte eller for barn som er døde senere i livet).

Barn	Fødselsår	Antall måneder med amming	Antall blødningsfrie måneder
1	336 19		
2	342 19		
3	348 19		
4	354 19		
5	360 19		
6	366 19		
7	372 19		

URINLEKKASJE

	Ja	Nei
Har du ufrivillig urinlekkasje? 378	☐	☐

Hvis «Nei»: Gå til KALK I KOSTEN ...

Hvor ofte har du urinlekkasje? 379
- sjeldnere enn en gang pr. måned ☐
- en eller flere ganger pr. måned ☐
- en eller flere ganger pr. uke ☐
- hver dag og/eller natt ☐

Hvor mye urin lekker du vanligvis hver gang? 380
dråper eller lite ☐ små skvetter ☐ større mengder ☐

	Ja	Nei
Har du lekkasje av urin i forbindelse med hosting, nysing, latter, tunge løft 381	☐	☐
Har du lekkasje av urin i forbindelse med plutselig og sterk vannlatingstrang? 382	☐	☐

Hvor lenge har du hatt urinlekkasje? 383
0-5 år ☐ 5-10 år ☐ Over 10 år ☐

	Ja	Nei
Har du søkt lege på grunn av urinlekkasje? 384	☐	☐

Hvordan opplever du lekkasjeplagene dine? 385 *Ett kryss*
- ikke noe problem ☐
- en liten plage ☐
- en del plaget ☐
- mye plaget ☐
- svært stort problem ☐

KALK I KOSTEN OG KOSTTILSKUDD

Hvor mange glass melk (alle sorter, også drikkeyoghurt) drikker du vanligvis daglig? *Bare ett kryss* 386
- Ingen ☐ 1
- Mindre enn ett ☐ 2
- 1–2 glass ☐ 3
- 3 eller mer ☐ 4

Hvor mange brødskiver med kvitost spiser du vanligvis daglig? *Bare ett kryss*
- Ingen ☐ 1
- Mindre enn en ☐ 2
- 1–2 skiver ☐ 3
- 3 eller mer ☐ 4

Bruker du vanligvis noen av disse kosttilskuddene?

	Ja	Nei
vitamin D-tilskudd 388	☐	☐
kalktabletter eller benmel	☐	☐

HUMØR OG TRIVSEL

Ett kryss på hver linje

Angi hvordan du har følt deg den siste måneden:	*Aldri*	*Noen ganger*	*Ganske ofte*	*For det meste*
i godt humør 390	☐	☐	☐	☐
i dårlig humør 391	☐	☐	☐	☐

Er du rask til å oppfatte et humoristisk poeng? 392	*Svært treg*	*Ganske treg*	*Ganske rask*	*Svært rask*
	☐	☐	☐	☐

Er du enig i at det er noe ansvarsløst over folk som stadig prøver å være morsomme? 393

Nei, slett ikke ☐1 Ganske enig ☐3
I noen grad ☐2 Ja, absolutt ☐4

Er du en munter person? 394

Nei, slett ikke ☐1 Ganske munter ☐3
I noen grad ☐2 Ja, absolutt ☐4

SINNE

Sett kryss på det svaret som best beskriver deg i forhold til de to påstandene nedenfor:

Jeg gir uttrykk for mitt sinne, og andre mennesker vet at jeg er sint 395

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

Jeg koker av sinne, men jeg viser det ikke til andre 396

Nesten aldri ☐1 Ganske ofte ☐3
Noen ganger ☐2 Nesten alltid ☐4

HVILE OG AVSLAPPING

Hvor mange timer tilbringer du *vanligvis* i *liggende* stilling i løpet av et døgn?
(nattesøvn, middagshvil) 397 — Antall timer: ☐

Hvor mange timer tilbringer du *vanligvis* i *sittende* stilling i løpet av et døgn?
(arbeid, måltider, TV, bil etc.) 399 — Antall timer: ☐

Hvor ofte er du plaget av søvnløshet? 401

Aldri, eller noen få ganger i året ☐1
1–2 ganger i måneden ☐2
Omtrent 1 gang i uka ☐3
Mer enn en gang i uka ☐4

Har du siste år vært plaget av søvnløshet slik at det har gått ut over arbeidsevnen? 402	*Ja*	*Nei*
	☐	☐

Har du i løpet av siste måned hatt innsovningsproblemer? *Bare ett kryss* 403

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned våknet for tidlig og ikke fått sove igjen? *Bare ett kryss* 404

Nesten hver natt ☐1 Av og til ☐3
Ofte ☐2 Aldri ☐4

Har du i løpet av siste måned vært plaget av nervøsitet (irritabel, urolig, anspent eller rastløs)? 405

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

HVORDAN DU HAR HATT DET

Har det noen gang i løpet av ditt liv vært *sammenhengende perioder på 2 uker eller mer* da du:	*Ja*	*Nei*
følte deg deprimert, trist og nedfor 406	☐	☐
hadde problemer med matlysten eller spiste alt for lite	☐	☐
var plaget av kraftløshet eller mangel på overskudd	☐	☐
virkelig bebreidet deg selv og følte deg verdiløs	☐	☐
hadde problemer med å konsentrere deg eller vanskelig for å ta beslutninger	☐	☐
hadde minst tre av de problemene som er nevnt ovenfor samtidig 411	☐	☐

HVORDAN DU SER PÅ DEG SELV

Folk ser på seg selv på ulike måter. Kryss av for hvert utsagn hvor enig eller uenig du er. *Ett kryss på hver linje*

	Svært enig	*Enig*	*Uenig*	*Svært uenig*
Jeg har en positiv holdning til meg selv 412	☐	☐	☐	☐
Jeg føler meg virkelig ubrukelig til tider 413	☐	☐	☐	☐
Jeg føler at jeg ikke har mye å være stolt av 414	☐	☐	☐	☐
Jeg føler at jeg er en verdifull person, i allefall på lik linje med andre 415	☐	☐	☐	☐

	Ja	*Nei*
Synes du at du har funnet et virkelig betydningsfullt innhold i livet ditt? 416	☐	☐
Føler du at du lever fullt ut? 417	☐	☐

HVORDAN DU FØLER DEG NÅ

*Sett kryss i den ruta utenfor det svaret som best beskriver dine følelser **den siste uka.** Bare ett kryss*

Er du vanligvis glad eller nedstemt? 418

Svært nedstemt ☐1
Nedstemt ☐2
Nokså nedstemt ☐3
Både – og ☐4
Nokså glad ☐5
Glad ☐6
Svært glad ☐7

Har du i det store og hele en rolig og god følelse inne i deg? 419

Nesten hele tida ☐1
Ofte ☐2
Av og til ☐3
Aldri ☐4

Føler du deg stort sett sterk og opplagt, eller trøtt og sliten? 420

Meget sterk og opplagt ☐1
Sterk og opplagt ☐2
Ganske sterk og opplagt ☐3
Både – og ☐4
Ganske trøtt og sliten ☐5
Trøtt og sliten ☐6
Svært trøtt og sliten ☐7

Legg det utfylte spørreskjemaet i den vedlagte svarkonvolutten og postlegg den så snart som mulig!
Porto er betalt.

Hjertelig takk for hjelpa!

Steinkjer Trykkeri AS – 74 16 30 00

L	10.10.08	Siste Word før feltapplikasjon			
K	06.11.2007	Muskel-skjelettsmerte Stj.dal revidert	SK		
J	06.11.2007	Kømodus: Redusert omfang ved kø	AL/SK		
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H	07.09.2006	Rev etter gjennomgang av feltapplik	SK		
G	05.05.2006	Endelig versjon temagrupper	AL		
F	24.01.2006	Forb spørreskjemagr			
E	03.01.2006	Til Datatilsyn/REK			
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Eier:		Tittel	Dokumentnummer		
HUNT 3 PROSJEKTET		**Intervju feltstasjon**	**HUNT 3-04-H02**		
Dette dokumentet tilhører HUNT 3 Prosjektet og kan ikke kopieres uten at det på forhånd er innhentet skriftlig tillatelse.					Antall sider: **7**

Oppvekst
I hvilket land bodde du da du fylte 1 år?
DEFAULT NORGE (men valgmulighet alle land)

Hvis Norge:
I hvilken kommune bodde du da du fylte 1 år?
(liste over kommuner i N_T med mulighet får å skrive inn andre)

Hvis alder ≤ 70 år:
Er du yrkesaktiv, student eller hjemmearbeidende?

1.	**yrkesaktiv**	Ja ☐ Nei ☐
2.	**student**	Ja ☐ Nei ☐
3.	**hjemmearbeidende (husmor/far)**	Ja ☐ Nei ☐

(Klassifiseringshjelp: Alle som har yrkesinntekt (lønn) skal klassifiseres som yrkesaktive.
Alle som har studier som hovedvirksomhet, skal klassifiseres som studenter.
De som mottar trygd (uføretrygd, attføring eller rehabilitering) skal registreres med det yrket de hadde tidligere, selv om de ikke lenger er i arbeid og ikke som hjemmeværende.
De som er hjemmeværende med omsorg for barn eller andre, og som ikke har inntekt, skal registreres som hjemmearbeidende (husmor/far)).

Hvis 1 er ja:
Arbeider du i en fulltidsstilling eller deltidsstilling i hovedyrket ditt?
Svar: 1. ☐ Fulltidsstilling (Default)
2. ☐ Deltidsstilling

Hvis 1: **Arbeider du vanligvis mer enn 40 timer i uka?**

Svar: 1. ☐ Nei(Default)
2. ☐ Ja

Hvis 2: **Hvor stor stillingsandel har du?**

Svar: ☐☐ %

Er du lønnsmottaker eller selvstendig næringsdrivende?

lønnsmottaker	1 ☐
selvstendig næringsdrivende	2 ☐
begge deler	3 ☐

Hvis > 70 år eller hvis nei på spørsmål om yrkesaktiv:

Har du tidligere hatt inntektsgivende arbeid? Ja ☐ Nei ☐

Hvis ja:
I hvilket år hadde du sist betalt arbeid? ☐☐☐☐

Dette feltet droppes ved kø på stasjonen (rød tekst)

Hvis nåværende eller tidligere inntektsgivende arbeid = ja:

I hvilken bransje arbeider/arbeidet du i ditt hovedyrke? Se på plakaten!

(PLAKAT MED SVARALTERNATIV) (Velg tallverdi) Alfabetisk

1. Jordbruk, skogbruk
2. Fiske, sjøfart
3. Bergverksdrift og utvinning
4. Industri
5. Olje og gassutvinning
6. Leverandør-industri til olje og gassutvinning
7. Kraft- og vannforsyning
8. Bygge- og anleggsvirksomhet
9. Varehandel, hotell- og restaurantvirksomhet
10. Landtransport og kommunikasjon
11. Bank-, forsikrings- og finansvirksomhet
12. Offentlig forvaltning
13. Undervisning
14. Helsearbeid
15. Personlige tjenester og annen tjenesteyting
16. Annet

Hvis < 66 år:
Har du helseattest for offshorearbeid? **Ja** **Nei**

Hvis yrkesaktiv eller tidligere inntektsgivende arbeid:

Hva er/var navnet på hovedyrket ditt (yrkestittel)? …….. (de som svarte ja på student og husmor/far, og ja på at de tidligere har hatt inntektsgivende arbeid spørres også)

Kan du kort beskrive dine arbeidsoppgaver i hovedyrke? ……..

Arbeidet du i en fulltidsstilling eller deltidsstilling i hovedyrket ditt?

Svar: 1. ☐ Fulltidsstilling (Default)
2. ☐ Deltidsstilling

Hvis 1: **Arbeider du vanligvis mer enn 40 timer i uka?**

Svar: 1. ☐ Nei(Default)
2. ☐ Ja

Hvis 2: **Hvor stor stillingsandel har du?**

Svar: ☐☐ %

Hvis yrkesaktiv:

Har du skiftarbeid, nattarbeid eller går vakter? **Ja** **Nei**

Har du i løpet av de siste 12 mnd hatt sykefravær?

Egenmelding	**Ja**	**Nei**
Sykmelding fra lege	**Ja**	**Nei**

Hvis ja;
Hvor lenge til sammen: **≤ 2 uker** **2-8 uker** **> 8 uker**

Har du noen gang fått luftveisplager i forbindelse med arbeidet ditt (hoste, oppspytt, tung pust eller pipelyder i brystet)? Ja ☐ Nei ☐ **INNVALG BONT**

Dette feltet droppes ved kø på stasjonen (rød tekst)

Så kommer noen spørsmål om din arbeidssituasjon (disse kunne vært spurt til alle som også tidl har arbeidet, men det droppes pga tidsbruk, kun yrkesaktive nå)

Har du tunge løft?
- ☐ Aldri, eller nesten aldri
- ☐ Ganske sjelden
- ☐ Ganske ofte
- ☐ Nesten alltid

Er du utsatt for støy?
- ☐ Aldri, eller nesten aldri
- ☐ Ganske sjelden
- ☐ Ganske ofte
- ☐ Nesten alltid

Er du utsatt for støv og røyk som f.eks. steinstøv, sveiserøyk og lignende?
- ☐ Aldri, eller nesten aldri
- ☐ Ganske sjelden
- ☐ Ganske ofte
- ☐ Nesten alltid

Er du utsatt for skadelige gasser?
- ☐ Aldri, eller nesten aldri
- ☐ Ganske sjelden
- ☐ Ganske ofte
- ☐ Nesten alltid

Er du utsatt for løsemidler?
- ☐ Aldri, eller nesten aldri
- ☐ Ganske sjelden

☐ Ganske ofte
☐ Nesten alltid

Alle ≤ 70 år:

Bor du eller arbeider du på gårdbruk? Ja ☐ Nei ☐

Hvis ja:

Brukes det sprøytemidler på gårdsbruket? Ja ☐ Nei ☐ Vet ikke ☐

Hvis "nei "

Kvinne: besvar kvinnespørsmål
Mann: Avslutt intervju, - men i Stjørdal tilleggsspørsmål

Hvis ja:

Utfører du selv sprøyting? Ja ☐ Nei ☐

Hvis ja:

TENK PÅ DE SISTE 10 ÅRENE:

Er det dyrket potet på bruket? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er det dyrket potet? ☐☐ ☐ vet ikke

Er det sprøytet med soppmidlet mankozeb på bruket
(i potet og /eller annen kultur)? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er mankozeb brukt? ☐☐ ☐ vet ikke

Er det sprøytet med andre soppmidler? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er dette brukt? ☐☐ ☐ vet ikke

Er det sprøytet med Roundup? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er dette brukt? ☐☐ ☐ vet ikke

Er det sprøytet med andre ugrasmidler? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er dette brukt? ☐☐ ☐ vet ikke

Er det sprøytet med stråforkortere/vekstregulerende stoffer? Ja ☐ Nei ☐

Hvis ja:
Hvor mange av de siste 10 år er dette brukt? ☐☐ ☐ vet ikke

Følgende spørsmål kommer opp dersom KJØNN = KVINNE

Innledning: Så har vi noen spørsmål som gjelder menstruasjon og fødsler.

Hvor gammel var du da du fikk menstruasjon første gang? ☐☐ ÅR
Har aldri hatt menstruasjon ☐

Hvis alder 19 – 55
Har du de siste 12 måneder hatt regelmessig menstruasjon? Nei ☐ Ja ☐

Hvis nei: hva mener du er grunnen til dette?
* sluttet av seg selv
* usikkert om menstruasjonen har sluttet
* sluttet etter operasjon, strålebehandling eller cellegift eller andre medisiner
* har ikke kommet tilbake etter svangerskap / er fortsatt uregelmessig etter svangerskap
* kan hos meg ha pauser på mer enn tre måneder
* kan hos meg være uregelmessig
* annet

Hvis nei eller ved alder > 55 år:

Hvor gammel var du da menstruasjonen sluttet? ☐☐ ÅR

Hvis ja: (regelmessig mens)

Hva er det vanlige intervallet mellom menstruasjonene -fra første dag i en menstruasjon til første dag i neste? ☐☐ dager

Omtrent hvilken dato startet din siste menstruasjon? _____

Alle:
Har du noen gang vært gravid? Ja☐ Nei☐
Hvis ja;
Hvor mange barn har du født? ☐☐
(hvis f.eks 3 barn, kommer det opp spørsmål om amming av barn 1-3)

Dette feltet droppes ved kø på stasjonen (rød tekst)
Hvis > 0: Hvor lenge ammet du? Barn 1 ? ___ mnd Barn 2? ___ mnd Barn 3? ___ mnd osv

Når var du gravid siste gang? Årstall
Hvis gravid i løpet av siste 3 år:
Ammer du nå? Nei /Ja
Hvis gravid nå:
Hvilken dato har du termin: dd/mm/åå ☐ vet ikke

Slutt på generelt intervju.

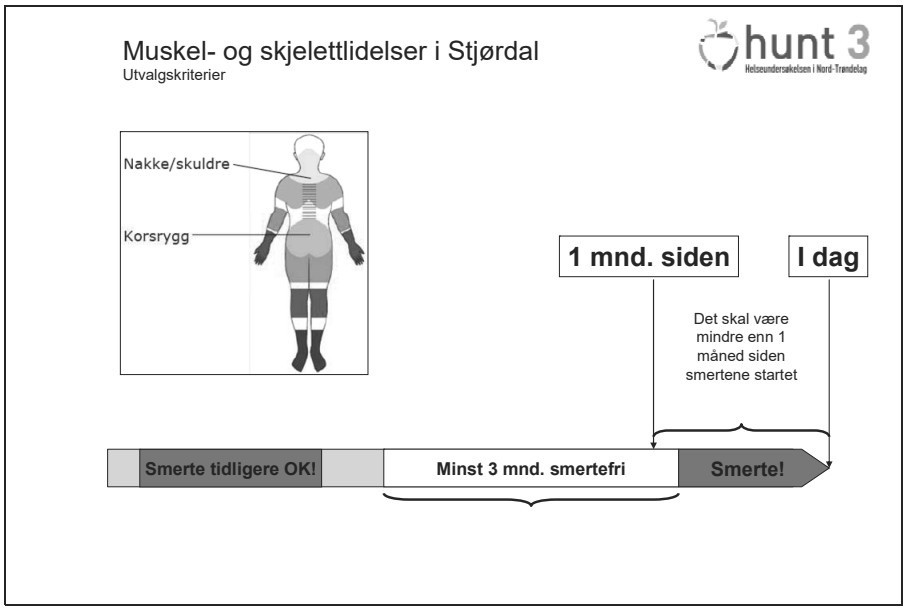
Tillegg Stjørdal (Muskel-skjelettlidelser prosjekt Ottar Vasseljen)

1. "Har du vondt i nakke/skuldre eller i korsryggen i dag?" Ja☐ Nei☐
   (Hold opp plakat og pek på figur)
   (Hvis nei, droppes spørsmål 2) Hvis ja:

2. "Er det mindre enn én måned siden disse smertene startet?" Ja☐ Nei☐
   (Hold opp plakat og pek på tidslinje ved behov)

   Hvis de tilfredsstiller kriteriene, kryss ja. **INNVALG Muskel-skjelettlidelser**

Plakat



Invitasjon til HUNT 3

Viktig
Enkelt
Gratis

Du inviteres herved til å delta i den tredje store Helseundersøkelsen i Nord-Trøndelag (HUNT 3). Ved å delta får du en enkel undersøkelse av din egen helse, og du gir samtidig et viktig bidrag til medisinsk forskning.

Hver deltaker er like viktig, enten du er ung eller gammel, frisk eller syk, er HUNT-veteran eller møter for første gang. Tilsvarende undersøkelse er tidligere gjennomført i 1984-86 (HUNT 1) og 1995-97 (HUNT 2 og Ung-HUNT). For å kunne studere årsaker til sykdom, er det viktig at også de som tidligere har deltatt møter fram.

Vennligst fyll ut spørreskjemaet, og ta det med når du møter til undersøkelse.

Undersøkelsen tar vanligvis ca 1/2 time. Du vil få brev med resultater fra dine prøver etter noen uker. Dersom noen av resultatene er utenom det normale, vil du bli anbefalt undersøkelse hos fastlegen din.

Du kan lese mer om HUNT 3 i den vedlagte brosjyren eller på www.hunt.ntnu.no. Har du spørsmål, kan du også ringe til HUNT forskningssenter, tlf 74075180.

Vel møtt til undersøkelsen!

Vennlig hilsen

Steinar Krokstad
Førsteamanuensis
Prosjektleder HUNT 3

Jostein Holmen
Professor, daglig leder
HUNT forskningssenter

Stig A. Slørdahl
Professor, dekanus
Det medisinske fakultet, NTNU

Tid og sted for oppmøte

Dersom det foreslåtte tidspunktet ikke passer for deg, behøver du ikke bestille ny time. Du kan møte når det passer deg innenfor åpningstiden, men det kan da bli noe ventetid. Du kan også møte i en annen kommune, hvis det skulle passe bedre. Takk for at du deltar!

Åpningstida:

hunt 3
Helseundersøkelsen i Nord-Trøndelag

NTNU
HUNT forskningssenter

En time for bedre folkehelse

VESTVIK REKLAME AS. FOTO: HARALD SÆTERØY OG JOHAN ARNT NESGÅRD.

Slik fyller du ut skjemaet

- Skjemaet vil bli lest maskinelt.
- Det er derfor viktig at du krysser av riktig: **Rett** ☒ **Galt** ☒ ☑
- Krysser du feil sted, retter du ved å fylle boksen slik: ■
- Skriv tydelige tall: 0 1 2 3 4 5 6 7 8 9
- Bruk bare svart eller blå penn. Ikke bruk blyant eller tusj.

HELSE OG DAGLIGLIV

1 Hvordan er helsa di nå?

☐ Dårlig ☐ Ikke helt god ☐ God ☐ Svært god

2 Har du noen langvarig (minst 1 år) sykdom, skade eller lidelse av fysisk eller psykisk art som nedsetter dine funksjoner i ditt daglige liv? Ja ☐ Nei ☐

Hvis ja:
Hvor mye vil du si at dine funksjoner er nedsatt?

	Litt nedsatt	Middels nedsatt	Mye nedsatt
Er bevegelseshemmet	☐	☐	☐
Har nedsatt syn	☐	☐	☐
Har nedsatt hørsel	☐	☐	☐
Hemmet pga. kroppslig sykdom	☐	☐	☐
Hemmet pga. psykisk sykdom	☐	☐	☐

3 Har du kroppslige smerter nå som har vart mer enn 6 måneder? Ja ☐ Nei ☐

4 Hvor sterke kroppslige smerter har du hatt i løpet av de siste 4 uker?

Ingen	Meget svake	Svake	Mode-rate	Sterke	Meget sterke
☐	☐	☐	☐	☐	☐

5 I hvilken grad har din fysiske helse eller følelses-messige problemer begrenset deg i din vanlige sosiale omgang med familie eller venner i løpet av de siste 4 uker?

Ikke i det hele tatt	En del	Litt	Mye	Kunne ikke ha sosial omgang
☐	☐	☐	☐	☐

HELSETJENESTER

6 Har du i løpet av de siste 12 måneder vært hos:

	Ja	Nei
Fastlege/allmennlege	☐	☐
Annen legespesialist utenfor sykehus	☐	☐
Konsultasjon uten innleggelse		
- ved psykiatrisk poliklinikk	☐	☐
- ved annen poliklinikk i sykehus	☐	☐
Kiropraktor	☐	☐
Homøopat, akupunktør, soneterapeut, hånds-pålegger eller annen alternativ behandler	☐	☐

7 Har du vært innlagt i sykehus i løpet av de siste 12 måneder? Ja ☐ Nei ☐

SYKDOMMER OG PLAGER

8 Har du hatt noe anfall med pipende eller tung pust de siste 12 måneder? Ja ☐ Nei ☐

9 Har du noen gang de siste 5 år brukt medisiner for astma, kronisk bronkitt, emfysem eller KOLS? Ja ☐ Nei ☐

10 Bruker du, eller har du brukt, medisin mot høyt blodtrykk? Ja ☐ Nei ☐

11 Har du, eller har du noen gang hatt, noen av disse sykdommene/plagene:
(Sett ett kryss pr. linje)

	Ja	Nei	Hvis ja, hvor gammel var du **første** gang?
Eksempel:			34 år gammel
Hjerteinfarkt	☐	☐	____ år gammel
Angina pectoris (hjertekrampe)	☐	☐	____ år gammel
Hjertesvikt	☐	☐	____ år gammel
Annen hjertesykdom	☐	☐	____ år gammel
Hjerneslag/hjerneblødning	☐	☐	____ år gammel
Nyresykdom	☐	☐	____ år gammel
Astma	☐	☐	____ år gammel
Kronisk bronkitt, emfysem, KOLS	☐	☐	____ år gammel
Diabetes (sukkersyke)	☐	☐	____ år gammel
Psoriasis	☐	☐	____ år gammel
Eksem på hendene	☐	☐	____ år gammel
Kreftsykdom	☐	☐	____ år gammel
Epilepsi	☐	☐	____ år gammel
Leddgikt (reumatoid artritt)	☐	☐	____ år gammel
Bechterews sykdom	☐	☐	____ år gammel
Sarkoidose	☐	☐	____ år gammel
Beinskjørhet (osteoporose)	☐	☐	____ år gammel
Fibromyalgi	☐	☐	____ år gammel
Slitasjegikt (artrose)	☐	☐	____ år gammel
Psykiske plager som du har søkt hjelp for	☐	☐	____ år gammel

12 Har du noen gang fått påvist for høyt blodsukker? Ja ☐ Nei ☐

Hvis ja: I hvilken situasjon første gang?

Ved helseundersøkelse ☐ Under sykdom ☐
Under svangerskap ☐ Annet ☐

SKADER

13 Har du noen gang hatt:

	Ja	Nei	Hvis ja, hvor gammel var du **første** gang?
			Eksempel: 3 4 *år gammel*
Lårhalsbrudd	☐	☐	*år gammel*
Brudd i handledd/underarm	☐	☐	*år gammel*
Brudd/sammenfall av ryggvirvler	☐	☐	*år gammel*
Nakkesleng (whiplash)	☐	☐	*år gammel*

14 Har du foreldre, søsken eller barn som har, eller har hatt, følgende sykdommer?
(Sett ett kryss pr. linje)

	Ja	Nei	Vet ikke
Hjerneslag eller hjerneblødning før 60 års alder	☐	☐	☐
Hjerteinfarkt før 60-års alder	☐	☐	☐
Astma	☐	☐	☐
Allergi/høysnue/neseallergi	☐	☐	☐
Kronisk bronkitt/emfysem/KOLS	☐	☐	☐
Kreftsykdom	☐	☐	☐
Psykiske plager	☐	☐	☐
Beinskjørhet (osteoporose)	☐	☐	☐
Nyresykdom (ikke nyresten, urinveisinfeksjon, urinlekkasje)	☐	☐	☐
Diabetes (sukkersyke)	☐	☐	☐

15 Har noen av dine besteforeldre, dine foreldres søsken eller dine søskenbarn fått diagnosen diabetes (type 1 eller type 2)?

Ja	Nei
☐	☐

HVORDAN FØLER DU DEG?

16 Har du de to siste uker følt deg:
(Sett ett kryss pr. linje)

	Nei	Litt	En god del	Svært mye
Trygg og rolig?	☐	☐	☐	☐
Glad og optimistisk?	☐	☐	☐	☐
Nervøs og urolig?	☐	☐	☐	☐
Plaget av angst?	☐	☐	☐	☐
Irritabel?	☐	☐	☐	☐
Nedfor/deprimert?	☐	☐	☐	☐
Ensom?	☐	☐	☐	☐

17 Har du noen gang i livet opplevd at noen over lengre tid har forsøkt å kue, fornedre eller ydmyke deg?

Ja	Nei
☐	☐

TOBAKK

18 Røykte noen av de voksne innendørs da du vokste opp?

Ja	Nei
☐	☐

19 Røykte mora di da du vokste opp?

Ja	Nei
☐	☐

20 Røyker du selv?

- **Nei**, jeg har aldri røykt ☐
  Hvis du aldri har røykt, hopp til spørsmål 22.
- **Nei**, jeg har sluttet å røyke ☐
- **Ja**, sigaretter av og til (fest/ferie, ikke daglig) ☐
- **Ja**, sigarer/sigarillos/pipe av og til ☐
- **Ja**, sigaretter daglig ☐
- **Ja**, sigarer/sigarillos/pipe daglig ☐

21 A Svar på dette hvis du nå røyker **daglig** eller tidligere har røykt **daglig**:

Hvor mange sigaretter røyker eller røykte du vanligvis daglig? *sigaretter pr. dag*

Hvor gammel var du da du begynte å røyke daglig? *år gammel*

Hvis du tidligere har røykt daglig, hvor gammel var du da du sluttet? *år gammel*

21 B Svar på dette hvis du røyker eller har røykt **av og til**, men ikke daglig:

Hvor mange sigaretter røyker eller røykte du vanligvis i måneden? *sigaretter pr. mnd*

Hvor gammel var du da du begynte å røyke av og til? *år gammel*

Hvis du tidligere har røykt av og til, hvor gammel var du da du sluttet? *år gammel*

22 Bruker du, eller har du brukt, snus?

Nei, aldri ☐ Ja, av og til ☐
Ja, men jeg har sluttet ☐ Ja, daglig ☐

Hvis du aldri har brukt snus, hopp til spørsmål 23.

Hvis ja:

Hvor gammel var du da du begynte med snus? *år gammel*

Hvor mange esker snus bruker/brukte du pr. måned? *esker snus pr. måned*

Hvis du bruker eller har brukt både sigaretter og snus, hva begynte du med først?

Snus ☐ Sigaretter ☐
Omtrent samtidig ☐ Husker ikke ☐
(innenfor 3 måneder)

Da du begynte å bruke snus, var det for å prøve å slutte å røyke eller for å redusere røykinga?

Nei ☐
Ja, for å slutte å røyke ☐
Ja, for å redusere røykinga ☐

MATVARER

23 Hvor ofte spiser du vanligvis disse matvarene?
(Sett ett kryss pr. linje)

	0-3 ganger pr. mnd	1-3 ganger pr. uke	4-6 ganger pr. uke	1 gang pr. dag	2 ggr el mer pr. dag
Frukt/bær	☐	☐	☐	☐	☐
Grønnsaker	☐	☐	☐	☐	☐
Sjokolade/smågodt	☐	☐	☐	☐	☐
Kokte poteter	☐	☐	☐	☐	☐
Pasta/ris	☐	☐	☐	☐	☐
Pølser/hamburgere	☐	☐	☐	☐	☐
Fet fisk (laks, ørret, sild, makrell, uer som pålegg/middag)	☐	☐	☐	☐	☐

24 Bruker du følgende kosttilskudd?
(Sett ett kryss for hvert kosttilskudd)

	Ja, daglig	Av og til	Nei
Tran	☐	☐	☐
Omega-3-kapsler	☐	☐	☐
Vitamin- og/eller mineraltilskudd	☐	☐	☐

25 Hvor mange glass drikker du vanligvis av følgende?
1/2 liter = 3 glass *(Sett ett kryss pr. linje)*

	Sjelden eller aldri	1-6 gl. pr uke	1 gl. pr. dag	2-3 gl. pr. dag	4 gl. eller mer pr. dag
Vann, farris o.l	☐	☐	☐	☐	☐
Helmelk (søt/sur)	☐	☐	☐	☐	☐
Annen melk (søt/sur)	☐	☐	☐	☐	☐
Brus/saft med sukker	☐	☐	☐	☐	☐
Brus/saft uten sukker	☐	☐	☐	☐	☐
Juice eller nektar	☐	☐	☐	☐	☐

26 Hvor mange kopper kaffe/te drikker du pr. døgn?
(Sett 0 dersom du ikke drikker kaffe/te daglig)

	Koke-kaffe	Annen kaffe	Te
Antall kopper			

27 Hvor mange kopper kaffe drikker du om kvelden (etter kl 18)?
Antall kopper

ALKOHOLBRUK

28 Omtrent hvor ofte har du i løpet av de siste 12 måneder drukket alkohol? *(Regn ikke med lettøl)*

4-7 ganger pr. uke ☐ Ca 1 gang pr. måned ☐
2-3 ganger pr. uke ☐ Noen få ganger pr. år ☐
ca 1 gang pr. uke ☐ Ingen ganger siste år ☐
2-3 ganger pr. måned ☐ Aldri drukket alkohol ☐

29 Har du drukket alkohol i løpet av de siste 4 uker? Ja ☐ Nei ☐

Hvis ja:
Har du drukket så mye at du har kjent deg sterkt beruset (full)?
Nei ☐
Ja, 1-2 ganger ☐
Ja, 3 ganger eller mer ☐

30 Hvor mange glass øl, vin eller brennevin drikker du vanligvis i løpet av 2 uker? *(Regn ikke med lettøl)*
(Sett 0 hvis du ikke drikker alkohol)

	Øl	Vin	Brenne-vin
Antall glass			

31 Hvor ofte drikker du 5 glass eller mer av øl, vin eller brennevin ved samme anledning?

Aldri ☐ Ukentlig ☐
Månedlig ☐ Daglig ☐

MOSJON/FYSISK AKTIVITET

Med mosjon mener vi at du f.eks går tur, går på ski, svømmer eller driver trening/idrett.

32 Hvor ofte driver du mosjon? *(Ta et gjennomsnitt)*

Aldri ☐
Sjeldnere enn en gang i uka ☐
En gang i uka ☐
2-3 ganger i uka ☐
Omtrent hver dag ☐

33 Dersom du driver slik mosjon, så ofte som en eller flere ganger i uka; hvor hardt mosjonerer du?
(Ta et gjennomsnitt)

Tar det rolig uten å bli andpusten eller svett ☐
Tar det så hardt at jeg blir andpusten og svett ☐
Tar meg nesten helt ut ☐

34 Hvor lenge holder du på hver gang?
(Ta et gjennomsnitt)

Mindre enn 15 minutter ☐ 30 minutter – 1 time ☐
15-29 minutter ☐ Mer enn 1 time ☐

35 Har du vanligvis minst 30 minutter fysisk aktivitet daglig på arbeid og/eller i fritida? Ja ☐ Nei ☐

36 Omtrent hvor mange timer sitter du i ro på en vanlig hverdag? *(Regn med både jobb og fritid)* Antall timer ☐

ARBEID

37 Hvis du er i lønnet eller ulønnet arbeid, hvordan vil du beskrive arbeidet ditt? *(Sett ett kryss)*

For det meste stillesittende arbeid *(f.eks skrivebordsarbeid, montering)* ☐

Arbeid som krever at du går mye *(f.eks ekspeditørarbeid, lett industriarb., undervisning)* ☐

Arbeid hvor du går og løfter mye *(f.eks postbud, pleier, bygningsarbeid)* ☐

Tungt kroppsarbeid *(f.eks skogsarbeid, tungt jordbruksarbeid, tungt bygningsarbeid)* ☐

HØYDE/VEKT

38 Omtrent hva var din høyde da du var 18 år?

☐ cm Husker ikke ☐

39 Omtrent hva var din kroppsvekt da du var 18 år?

☐ kg Husker ikke ☐

40 Er du fornøyd med vekta di nå?

Ja ☐ Nei, for lett ☐ Nei, for tung ☐

41 Har du forsøkt å slanke deg i løpet av de siste 10 år?

Nei ☐ Ja, noen ganger ☐ Ja, mange ganger ☐

42 Er din kroppsvekt minst 2 kg lavere nå enn for 1 år siden? Ja ☐ Nei ☐

Hvis ja:

Hva er grunnen til dette?

Slanking ☐ Sykdom/stress ☐ Vet ikke ☐

ALVORLIGE LIVSHENDELSER SISTE 12 MÅNEDER

43 Har det vært dødsfall i nær familie? *(barn, ektefelle/samboer, søsken eller foreldre)* Ja ☐ Nei ☐

44 Har du vært i overhengende livsfare pga. alvorlig ulykke, katastrofe, voldssituasjon eller krig? Ja ☐ Nei ☐

45 Har du hatt samlivsbrudd i ekteskap eller i lengre samboerforhold? Ja ☐ Nei ☐

46 Hvis du har svart ja på et eller flere av spm 43, 44 eller 45; i hvilken grad har du hatt reaksjoner på dette de siste 7 dager?

Ikke i det hele tatt ☐ I moderat grad ☐
Litt ☐ I høy grad ☐

OPPVEKST - DA DU VAR 0-18 ÅR

47 Hvem vokste du opp sammen med?

Mor ☐ Andre slektninger ☐
Far ☐ Adoptivforeldre ☐
Stemor/stefar ☐ Foster-/pleieforeldre ☐

48 Ble dine foreldre skilt, eller flyttet de fra hverandre, da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

49 Døde noen av dine foreldre da du var barn?

Nei ☐
Ja, før jeg var 7 år ☐
Ja, da jeg var 7-18 år ☐

50 Vokste du opp med kjæledyr?

Nei ☐
Ja, katt ☐ Ja, hund ☐
Ja, hest ☐ Ja, annet levende dyr ☐

51 Hvor mye melk eller yoghurt drakk du vanligvis?

Sjelden/ aldri	1-6 gl. pr. uke	1 glass pr. dag	2-3 gl. pr. dag	Mer enn 3 glass pr. dag
☐	☐	☐	☐	☐

52 Vokste du opp på gård med husdyr? Ja ☐ Nei ☐

53 Når du tenker på barndommen/oppveksten din, vil du beskrive den som:

Svært god ☐ Vanskelig ☐
God ☐ Svært vanskelig ☐
Middels ☐

ALT I ALT

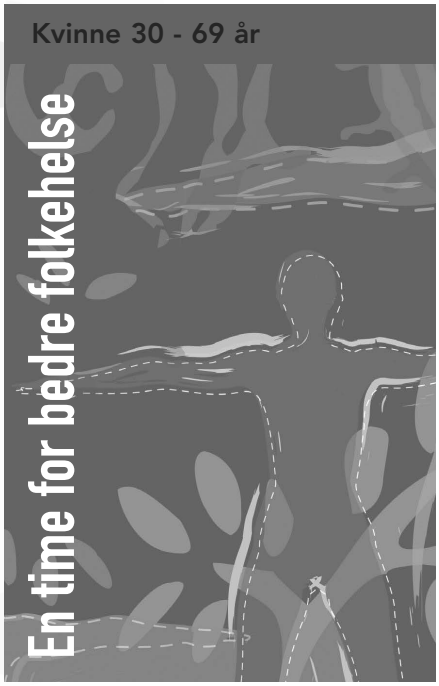
54 Når du tenker på hvordan du har det for tida, er du stort sett fornøyd med tilværelsen eller er du stort sett misfornøyd? *(Sett ett kryss)*

Svært fornøyd ☐ Nokså misfornøyd ☐
Meget fornøyd ☐ Meget misfornøyd ☐
Ganske fornøyd ☐ Svært misfornøyd ☐
Både/og ☐

hunt 3
Helseundersøkelsen i Nord-Trøndelag

Kjære HUNT-deltaker

Takk for at du møtte til Helseundersøkelsen. Vi vil også be deg om å fylle ut dette spørreskjemaet. Noen av spørsmålene likner de som du har svart på før, men det er viktig at du allikevel besvarer alt. Opplysningene blir brukt til forskning og forebyggende helsearbeid. Forskere vil kun ha tilgang til avidentifiserte data, det vil si at opplysningene ikke kan spores tilbake til en enkeltperson.



Slik fyller du ut skjemaet

- Skjemaet vil bli lest maskinelt.
- Det er derfor viktig at du krysser av riktig: **Rett** ☒ **Galt** ☐ ☒ ☑
- Krysser du feil sted, retter du ved å fylle boksen slik: ■
- Skriv tydelige tall: 0 1 2 3 4 5 6 7 8 9
- Bruk bare svart eller blå penn. Ikke bruk blyant eller tusj.

Dato for utfylling: ☐☐ / ☐☐ 20☐☐

Dag Måned År

Vennligst fyll ut skjemaet, og post det snarest mulig. Porto er betalt.

BOLIGFORHOLD OG VENNER

1 Hvem bor du sammen med?
(Sett ett eller flere kryss)

Ingen ☐ Andre personer over 18 år ☐
Foreldre ☐ Personer under 18 år ☐
Ektefelle/samboer ☐ Antall under 18 år ☐☐

2 Er det kjæledyr i boligen?

Nei ☐ Ja, katt ☐
Ja, hund ☐
Ja, andre pelsdyr/fugl ☐

3 Har du venner som kan gi deg hjelp når du trenger det? Ja ☐ Nei ☐

4 Har du venner som du kan snakke fortrolig med? Ja ☐ Nei ☐

DITT NÆRMILJØ, DVS. NABOLAGET/GRENDA

5 Jeg føler et sterkt fellesskap med de som bor her
(Sett ett kryss)

Helt enig	Delvis enig	Usikker	Delvis uenig	Helt uenig
☐	☐	☐	☐	☐

6 Man kan ikke stole på hverandre her *(Sett ett kryss)*

Helt enig	Delvis enig	Usikker	Delvis uenig	Helt uenig
☐	☐	☐	☐	☐

7 Folk trives godt her *(Sett ett kryss)*

Helt enig	Delvis enig	Usikker	Delvis uenig	Helt uenig
☐	☐	☐	☐	☐

AKTIVITET

8 Hvordan har din fysiske aktivitet i fritida vært det siste året? *(Tenk deg et ukentlig gjennomsnitt for året. Arbeidsvei regnes som fritid.)*

	Timer pr. uke			
	Ingen	Under 1	1-2	3 el. mer
Lett aktivitet *(ikke svett/andpusten)*	☐	☐	☐	☐
Hard fysisk aktivitet *(svett/andpusten)*	☐	☐	☐	☐

9 Hvor lang tid bruker du til sammen daglig foran dataskjerm? (*Sett 0 hvis du ikke bruker data)*

I arbeid ____ timer I fritid ____ timer

10 Hvor mange timer ser du på TV/video/DVD daglig?

Mindre enn 1 time ☐ 4-6 timer ☐
1-3 timer ☐ Mer enn 6 timer ☐

KULTUR/LIVSSYN

11 Hvor mange ganger har du i løpet av de siste 6 måneder vært på/i: *(Sett ett kryss pr. linje)*

	Mer enn 3g /mnd	1-3g /mnd	1-6g siste 6 mnd	Aldri
Museum, kunstutstilling	☐	☐	☐	☐
Konsert, teater, kino	☐	☐	☐	☐
Kirke, bedehus	☐	☐	☐	☐
Idrettsarrangement	☐	☐	☐	☐

12 Hvor mange ganger har du i løpet av de siste 6 måneder selv drevet med: *(Sett ett kryss pr. linje)*

	Mer enn 1g /uke	1g /uke	1-3g /mnd	1-5g siste 6 mnd	Ingen gang
Foreningsvirksomhet	☐	☐	☐	☐	☐
Musikk, sang, teater	☐	☐	☐	☐	☐
Menighetsarbeid	☐	☐	☐	☐	☐
Friluftsliv	☐	☐	☐	☐	☐
Dans	☐	☐	☐	☐	☐
Trening, idrett	☐	☐	☐	☐	☐

13 Hvilket livssyn vil du si ligger nærmest opp til ditt eget? *(Sett ett kryss)*

Kristent livssyn ☐ Ateistisk livssyn ☐
Humanetisk livssyn ☐ Annet livssyn ☐

14 Når det skjer vonde ting i livet mitt, tenker jeg: "det er ei mening med det".

Ja ☐ Nei ☐ Vet ikke ☐

15 Jeg søker hjelp hos Gud når jeg trenger styrke og trøst.

Aldri ☐ Av og til ☐ Ofte ☐

PERSONLIGHET

16 Beskriv deg selv slik du vanligvis er:

	Ja	Nei
Klarer du å få fart i et selskap?	☐	☐
Er du stort sett stille og tilbakeholden når du er sammen med andre?	☐	☐
Liker du å treffe nye mennesker?	☐	☐
Liker du å ha masse liv og røre rundt deg?	☐	☐
Er du forholdsvis livlig?	☐	☐
Tar du vanligvis selv initiativet for å få nye venner?	☐	☐
Er du ofte bekymret?	☐	☐
Blir dine følelser lett såret?	☐	☐
Hender det ofte at du "går trøtt"?	☐	☐
Plages du av "nerver"?	☐	☐
Har du ofte følt deg trøtt og likeglad uten grunn?	☐	☐
Bekymrer du deg for at fryktelige ting kan skje?	☐	☐

HODEPINE

17 Har du vært plaget av hodepine det siste året? *Hvis nei, gå til spørsmål 24.* Ja ☐ Nei ☐

Hvis ja:
Hva slags hodepine: Migrene ☐ Annen hodepine ☐

18 Omtrent antall dager pr. måned med hodepine:

Mindre enn 1 dag ☐ 7-14 dager ☐
1-6 dager ☐ Mer enn 14 dager ☐

19 Hvor sterk er hodepina vanligvis?

Mild *(hemmer ikke aktivitet)* ☐
Moderat *(hemmer aktivitet)* ☐
Sterk *(forhindrer aktivitet)* ☐

20 Hvor lenge varer hodepina vanligvis?

Mindre enn 4 timer ☐ 1-3 døgn ☐
4 timer – 1 døgn ☐ Mer enn 3 døgn ☐

21 Er hodepina vanligvis preget av eller ledsaget av: *(Sett ett kryss pr. linje)*

	Ja	Nei
Bankende/dunkende smerte?	☐	☐
Pressende smerte?	☐	☐
Ensidig smerte (høyre eller venstre)?	☐	☐
Forverring ved moderat fysisk aktivitet?	☐	☐
Kvalme og/eller oppkast?	☐	☐
Lys- og lydskyhet?	☐	☐

22 Før eller under hodepina; kan du ha forbigående: *(Sett ett kryss pr. linje)*

	Ja	Nei
Synsforstyrrelse? *(takkede linjer, flimring, tåkesyn, lysglimt)*	☐	☐
Nummenhet i halve ansiktet eller i handa?	☐	☐

23 Angi hvor mange dager du har vært borte fra arbeid eller skole siste måned på grunn av hodepine: ____ dager

LUFTVEIER

24 Hoster du daglig i perioder av året? Ja ☐ Nei ☐

Hvis ja:
Er hosten vanligvis ledsaget av oppspytt? Ja ☐ Nei ☐

Har du hatt hoste med oppspytt, i minst 3 måneder, sammenhengende i hvert av de to siste åra? Ja ☐ Nei ☐

25 Har du, eller har du hatt, høysnue eller neseallergi? Ja ☐ Nei ☐

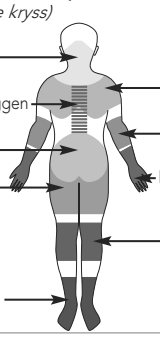
Hvis ja:
Har du hatt slike plager i løpet av de siste 12 måneder? Ja ☐ Nei ☐

26 Har du i løpet av de siste 12 måneder blitt vekket av anfall med tung pust? Ja ☐ Nei ☐

MUSKLER OG LEDD

27 Har du i løpet av det siste året vært plaget med smerter og/eller stivhet i muskler og ledd, som har vart i minst 3 måneder sammenhengende? Ja ☐ Nei ☐
Hvis nei, gå til spørsmål 30.

Hvis ja:
Hvor har du hatt disse plagene?
(Sett ett eller flere kryss)



☐ Nakke
☐ Øvre del av ryggen
☐ Korsryggen
☐ Hofter
☐ Ankler/føtter
☐ Skuldre (aksler)
☐ Albuer
☐ Handledd/hender
☐ Knær

28 Har du vært plaget både i høyre og venstre kroppshalvdel? Ja ☐ Nei ☐

29 Har plagene hindret deg i å utføre daglige aktiviteter?

	Ja	Nei
I arbeid	☐	☐
I fritid	☐	☐

30 Er du operert for ryggplager? Ja ☐ Nei ☐

Hvis ja: Hvilken type operasjon?

Prolaps/ischias-operasjon ☐ Annet ☐
Avstivning ☐

STOFFSKIFTE

31 Har du noen gang fått påvist for lavt stoffskifte (hypotyreose)? Ja ☐ Nei ☐

Hvis ja, hvor gammel var du **første** gang?
Eksempel: 34 *år gammel*
_____ *år gammel*

32 Har du noen gang fått påvist for høyt stoffskifte (hypertyreose)? Ja ☐ Nei ☐

Hvis ja, hvor gammel var du **første** gang?
Eksempel: 34 *år gammel*
_____ *år gammel*

Hvis ja:
Har du brukt Neo-Mercazole? ☐ ☐ _____ *år gammel*
Har du fått radiojodbehandling? ☐ ☐ _____ *år gammel*

MAGE OG TARM

33 Har du vært plaget med smerter eller ubehag fra magen de siste 12 måneder?

Ja, mye ... ☐ Ja, litt.. ☐ Nei, aldri .. ☐
Hvis nei, gå til spørsmål 34.

Hvis ja:	Ja	Nei
Er disse lokalisert øverst i magen?	☐	☐
Har du de siste 3 måneder hatt disse plagene så ofte som 1 dag i uka i minst 3 uker?	☐	☐
Blir smertene eller ubehaget bedre etter at du har hatt avføring?	☐	☐
Har smertene eller ubehaget noen sammenheng med hyppigere eller sjeldnere avføring enn vanlig?	☐	☐
Har smertene eller ubehaget noen sammenheng med at avføringen blir løsere eller fastere enn vanlig?	☐	☐
Kommer smertene eller ubehaget etter måltid?	☐	☐

34 I hvilken grad har du hatt følgende plager i de siste 12 måneder?

	Aldri	Litt	Mye
Kvalme	☐	☐	☐
Halsbrann/sure oppstøt	☐	☐	☐
Diaré	☐	☐	☐
Treg mage	☐	☐	☐
Vekslende treg mage og diaré	☐	☐	☐
Oppblåsthet	☐	☐	☐

HVORDAN FØLER DU DEG

Her kommer noen utsagn om hvordan du føler deg. For hvert spørsmål setter du kryss for ett av de fire svarene som best beskriver dine følelser den siste uken. Ikke tenk for lenge på svaret – de spontane svarene er best.

35 Jeg føler meg nervøs og urolig

Nei ☐ En god del ☐
Litt ☐ Svært mye ☐

36 Jeg gleder meg fortsatt over ting slik jeg pleide før

Avgjort like mye ☐ Bare lite grann ☐
Ikke fullt så mye ☐ Ikke i det hele tatt ☐

37 Jeg har en urofølelse som om noe forferdelig vil skje

Ja, og noe svært ille ☐ Litt, bekymrer meg lite ☐
Ja, ikke så veldig ille ☐ Ikke i det hele tatt ☐

38 Jeg kan le og se det morsomme i situasjoner

Like mye nå som før ☐ Avgjort ikke som før ☐
Ikke like mye nå som før. ☐ Ikke i det hele tatt ☐

39 Jeg har hodet fullt av bekymringer

Veldig ofte ☐ Av og til ☐
Ganske ofte ☐ En gang i blant ☐

40 Jeg er i godt humør

Aldri ☐ Ganske ofte ☐
Noen ganger ☐ For det meste ☐

41 Jeg kan sitte i fred og ro og kjenne meg avslappet

Ja, helt klart ☐ Ikke så ofte ☐
Vanligvis ☐ Ikke i det hele tatt ☐

42 Jeg føler meg som om alt går langsommere

Nesten hele tiden ☐ Fra tid til annen ☐
Svært ofte ☐ Ikke i det hele tatt ☐

43 Jeg føler meg urolig som om jeg har sommerfugler i magen

Ikke i det hele tatt ☐ Ganske ofte ☐
Fra tid til annen ☐ Svært ofte ☐

44 Jeg bryr meg ikke lenger om hvordan jeg ser ut

Ja, har sluttet å bry meg ☐ Kan hende ikke nok ☐
Ikke som jeg burde ☐ Bryr meg som før ☐

45 Jeg er rastløs som om jeg stadig må være aktiv

Uten tvil svært mye ☐ Ikke så veldig mye ☐
Ganske mye ☐ Ikke i det hele tatt ☐

46 Jeg ser med glede fram til hendelser og ting

Like mye som før ☐ Avgjort mindre enn før ☐
Heller mindre enn før ☐ Nesten ikke i hele tatt. ☐

47 Jeg kan plutselig få en følelse av panikk

Uten tvil svært ofte ☐ Ikke så veldig ofte ☐
Ganske ofte ☐ Ikke i det hele tatt ☐

48 Jeg kan glede meg over gode bøker, radio/TV

Ofte ☐ Ikke så ofte ☐
Fra tid til annen ☐ Svært sjelden ☐

SØVN

49 Hvor ofte har det hendt i løpet av de siste 3 måneder at du:

	Aldri/ sjelden	Av og til	Flere ggr/ uka
Snorker høyt og sjenerende?	☐	☐	☐
Får pustestopp når du sover?	☐	☐	☐
Har vanskelig for å sovne om kvelden?	☐	☐	☐
Våkner gjentatte ganger om natta?	☐	☐	☐
Våkner for tidlig og får ikke sove igjen?	☐	☐	☐
Kjenner deg søvnig om dagen?	☐	☐	☐
Har plagsom nattesvette?	☐	☐	☐
Våkner med hodepine?	☐	☐	☐
Får ubehag, kribling eller mauring i bein?	☐	☐	☐

ALKOHOL

Hvis du ikke drikker alkohol, gå til spørsmål 54.

	Ja	Nei
50 Har du noen gang følt at du burde redusere alkoholforbruket ditt?	☐	☐
51 Har andre noen gang kritisert alkoholbruken din?	☐	☐
52 Har du noen gang følt ubehag eller skyldfølelse pga. alkoholbruken din?	☐	☐
53 Har det å ta en drink noen gang vært det første du har gjort om morgenen for å roe nervene, kurere bakrus eller som en oppkvikker?	☐	☐

KOSTHOLD

54 Hvor mange skiver brød spiser du vanligvis?
(Sett ett kryss for hver type brød)

	0-4 /uke	5-7 /uke	2-3 /dag	4-5 /dag	6 el flere /dag
Loff/fint brød	☐	☐	☐	☐	☐
Kneipp/mellomgrovt	☐	☐	☐	☐	☐
Grovt brød	☐	☐	☐	☐	☐

55 Hvor ofte spiser du vanligvis disse måltidene?
(Sett ett kryss pr. måltid)

	Sjelden /aldri	1-2 g /uke	3-4 g /uke	5-6 g /uke	Hver dag
Frokost	☐	☐	☐	☐	☐
Formiddagsmat	☐	☐	☐	☐	☐
Varm middag	☐	☐	☐	☐	☐
Kveldsmat	☐	☐	☐	☐	☐
Annet måltid	☐	☐	☐	☐	☐
Nattmat (kl 24-06)	☐	☐	☐	☐	☐

56 Hva slags fett bruker du oftest?
(Sett ett kryss pr. linje)

		Margarin			
	Meieri-smør	Hard	Myk /lett	Oljer	Bruker ikke
På brød	☐	☐	☐	☐	☐
I matlaging	☐	☐	☐	☐	☐

TANNHELSE

57 Har du de siste 12 måneder vært hos tannlege/tannhelsetjeneste? Ja ☐ Nei ☐

58 Hvordan vurderer du tannhelsa di?

Meget dårlig ☐ God ☐
Dårlig ☐ Meget god ☐
Verken god eller dårlig ☐

59 Hva betyr god tannhelse for helsa di ellers?

Svært mye ☐ Lite ☐
Mye ☐ Svært lite ☐
Både og ☐

BRUK AV RESEPTFRIE MEDISINER

60 Hvor ofte har du brukt reseptfrie medisiner mot følgende plager i løpet av den siste måneden?
(Sett ett kryss pr. linje)

	Sjelden /aldri	1-3 g /uke	4-6 g /uke	Dag-lig
Halsbrann/sure oppstøt	☐	☐	☐	☐
Treg mage	☐	☐	☐	☐
Hodepine	☐	☐	☐	☐
Smerter i muskler/ledd	☐	☐	☐	☐

61 Har du brukt noen av disse reseptfrie medisinene minst en gang i uka i løpet av den siste måneden?

	Ja	Nei
Paracetamol, Paracet, Panodil, Pamol, Pinex, Perfalgan	☐	☐
Albyl E (500 mg), Aspirin, Globoid, Dispril	☐	☐
Ibuprofen, Ibux, Ibuprox, Ibumetin, Brufen	☐	☐
Naproxen, Naprosyn, Ledox	☐	☐
Andre	☐	☐

HVORDAN FØLER DU DEG NÅ

62 Føler du deg stort sett sterk og opplagt, eller trøtt og sliten?

Meget sterk og opplagt ☐
Sterk og opplagt ☐
Ganske sterk og opplagt ☐
Både – og ☐
Ganske trøtt og sliten ☐
Trøtt og sliten ☐
Svært trøtt og sliten ☐

SVANGERSKAP OG PREVENSJON

63 Når du ser bort fra svangerskap og barselperiode, har du noen gang vært blødningsfri i minst 6 måneder før overgangsalder? Ja ☐ Nei ☐

Hvis ja: Hvor mange ganger? ____ ganger

64 Hvor mange ganger har du i alt vært gravid? ____ ganger

65 Har du noen gang prøvd i mer enn ett år å bli gravid? Ja ☐ Nei ☐

Hvis ja:
Hvor gammel var du første gang du hadde problemer med å bli gravid? ____ år gammel

66 Har du noen gang fått hormonbehandling for å bli gravid? Ja ☐ Nei ☐

Hvis ja: Har du fått slik behandling *siste 3 måneder?* ☐ ☐

67 Bruker du, eller har du brukt:
(Sett ett kryss pr. linje)

	Nå	Før, ikke nå	Aldri
P-piller?	☐	☐	☐
P-plaster?	☐	☐	☐
Annen hormonprevensjon? *(P-sprøyte, P-ring, P-implantat, hormonspiral)*	☐	☐	☐

68 Hvis du har brukt P-piller:
Hvor gammel var du første gang du begynte med dette? ____ år gammel

Hvor mange år har du i alt brukt P-piller?

Mindre enn 1 år ☐ 4-10 år ☐
1-3 år ☐ Over 10 år ☐

OVERGANGSALDER

Hvis ikke kommet i overgangsalder, hopp til spm. 75.

69 Merker/merket du hetetokter i forbindelse med overgangsalder?

Om dagen ☐ Begge deler ☐
Om natten ☐ Merket ikke ☐

Hvis du merket hetetokter, hvordan vil du beskrive plagene?

Store ☐ Middels ☐ Små ☐

Oppsøkte du lege i forbindelse med plagene? Ja ☐ Nei ☐

70 Har du noen gang brukt medisiner som inneholder østrogen?

	Nå	Før	Aldri
Tabletter eller plaster (på resept fra lege)	☐	☐	☐
Krem eller stikkpiller	☐	☐	☐

71 Hvis du har brukt reseptpliktig østrogen, hvor gammel var du da du begynte? ____ år gammel

72 Hvis du bruker eller har brukt reseptpliktig østrogen, hvor gammel er/var du siste gang du brukte dette? ____ år gammel

73 Hvis du bruker eller har brukt østrogentabletter eller -plaster, hvorfor begynte du?

Lindre plager i overgangsalder ☐
Forebygge beinskjørhet ☐ Annet ☐

74 Hvis du tidligere har brukt østrogentabletter eller -plaster, hvorfor sluttet du?

Er/var kvitt plagene ☐ Redd for bivirkninger ☐
Fikk plagsomme bivirkninger ☐ Annet ☐

OPERASJONER/STRÅLEBEHANDLING I UNDERLIVET

	Ja	Nei	Vet ikke
75 Har du noen gang blitt operert for nedsunken livmor eller skjedevegg?	☐	☐	☐

Hvis ja:
Hvor gammel var du da? ____ år gammel

	Ja	Nei	Vet ikke
76 Har du ved operasjon fått fjernet begge eggstokkene (totalt)?	☐	☐	☐

Hvis ja:
Hvor gammel var du da? ____ år gammel

	Ja	Nei	Vet ikke
77 Har du ved operasjon fått fjernet hele livmoren?	☐	☐	☐

Hvis ja:
Hvor gammel var du da? ____ år gammel

	Ja	Nei	Vet ikke
78 Har du noen gang hatt stråle-behandling mot underlivet?	☐	☐	☐

Hvis ja:
Hvor gammel var du da? ____ år gammel

URINVEIER

79 Hvor ofte later du vanligvis vannet om dagen?

1-4 ganger ☐ 8-11 ganger ☐
5-7 ganger ☐ Over 11 ganger ☐

80 Hvor mange ganger må du opp om natta for å late vannet?

Ingen	1 gang	2 ganger	3 ganger	4 ganger	5 ganger eller mer
☐	☐	☐	☐	☐	☐

81 Hvis du må opp om natta for å late vannet, hvordan opplever du dette?

Ikke noe problem ☐ Mye plaget ☐
Litt plaget ☐ Svært stort problem ☐

82 Opplever du plutselig og/eller sterk vannlatings-trang som er vanskelig å holde tilbake?

Aldri ☐ Flere ganger i uka ☐
Månedlig ☐ Daglig ☐

	Ja	Nei
83 Har du ufrivillig urinlekkasje? *(Hvis nei, gå til spm. 84)*	☐	☐

Hvis ja:

Hvor ofte har du urinlekkasje?

Mindre enn 1 gang/mnd ☐ En el. flere ganger /uke ☐
En eller flere ganger/mnd ☐ Hver dag og/eller natt ☐

Hvor mye urin lekker du vanligvis hver gang?

Dråper ☐ Større mengder ☐
Små skvetter ☐

	Ja	Nei
Har du lekkasje av urin i forbindelse med hosting, nysing, latter, tunge løft?	☐	☐
Har du lekkasje av urin i forbindelse med plutselig og sterk vannlatingstrang?	☐	☐

Hvordan opplever du lekkasjeplagene dine?

Ikke noe problem ☐ Mye plaget ☐
En liten plage ☐ Svært stort problem ☐
En del plaget ☐

Hvor gammel var du da du fikk urinlekkasje? ____ år gammel

	Ja	Nei
84 Har du søkt lege for urinlekkasje?	☐	☐

85 Har du noengang fått behandling for ufrivillig urinlekkasje?

Nei, jeg har aldri hatt urinlekkasje ☐
Nei, jeg hadde urinlekkasje, men ble bra av meg selv ☐
Ja ☐

Hvis ja: ***Hvilken behandling?***
(Du kan sette flere kryss)

Operasjon ☐ Medisiner ☐
Bekkenbunnstrening ☐ Annet ☐

AVFØRING

	Aldri/ sjelden	Hver uke	Hver dag
86 Har du hatt ukontrollert lekkasje av luft fra tarmen i løpet av den siste måneden?	☐	☐	☐
87 Har du hatt lekkasje av avføring fra tarmen i løpet av den siste måneden?	☐	☐	☐
88 Hvis ja på spm 86 eller 87; har plagene med lekkasje fra endetarmen innvirkning på ditt hverdagsliv?	☐	☐	☐

	Ja	Nei
89 Har du evne til å holde igjen avføring og utsette toalettbesøk i 15 minutter etter første følelse av trang?	☐	☐

VURDERING AV DIN ARBEIDSPLASS

Besvares hvis du er eller har vært i arbeid. Ta stilling til følgende påstander/spørsmål om arbeidsplassen din og arbeidet ditt.

90 Det er et godt samhold på arbeidsplassen
- Stemmer helt ☐ Stemmer ikke særlig ☐
- Stemmer ganske bra ☐ Stemmer slett ikke ☐

91 Mine kolleger stiller opp for meg (gir meg støtte)
- Stemmer helt ☐ Stemmer ikke særlig ☐
- Stemmer ganske bra ☐ Stemmer slett ikke ☐

92 Jeg trives godt med mine arbeidskamerater
- Stemmer helt ☐ Stemmer ikke særlig ☐
- Stemmer ganske bra ☐ Stemmer slett ikke ☐

93 Er du blitt mobbet/trakassert på din arbeidsplass
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

94 Krever arbeidet ditt at du må arbeide veldig hurtig?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

95 Krever arbeidet ditt at du må arbeide svært hardt?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

96 Krever arbeidet ditt for stor arbeidsinnsats?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

97 Krever arbeidet ditt oppfinnsomhet?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

98 Har du mulighet til selv å bestemme hvordan arbeidet skal utføres?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

99 Har du mulighet til selv å bestemme hva som skal gjøres i arbeidet ditt?
- Ja, ofte ☐ Nei, sjelden ☐
- Ja, iblant ☐ Nei, så godt som aldri ☐

100 Er arbeidet ditt så fysisk anstrengende at du ofte er sliten i kroppen etter en arbeidsdag?
- Ja, nesten alltid ☐ Ganske sjelden ☐
- Ja, ganske ofte ☐ Aldri eller nesten aldri. ☐

SMERTER I BEINA

	Ja	Nei
101 Har du sår på tå, fot eller ankel som ikke vil gro?	☐	☐
102 Har du smerter i det ene eller i begge beina når du går?	☐	☐

Hvis ja:

Hvor gjør det mest vondt?
- Fot ☐
- Legg ☐
- Lår ☐
- Hofte ☐

	Ja	Nei
Forsvinner smertene når du står stille en stund?	☐	☐
103 Har du smerter i beina når du er i ro?	☐	☐

Hvis ja:

	Ja	Nei
Er smertene verst når du ligger i senga?	☐	☐
Får du mindre vondt når beinet ligger lavt, f.eks. om beinet henger utfor sengekanten?	☐	☐
Har du hatt smertene i beina sammenhengende i mer enn 14 dager?	☐	☐
104 Har du brukt smertestillende medisin pga. smerter i beina?	☐	☐

SYN

105 Har du noen av disse øyesykdommene?	Ja	Nei
Katarakt *(grå stær)*	☐	☐
Glaukom *(grønn stær, høyt trykk i øyet)*	☐	☐
Aldersrelatert makuladegenerasjon *(forkalkning på netthinna)*	☐	☐

HUKOMMELSE

106 Har du problemer med hukommelsen?

Nei ..... ☐ Ja, noe .... ☐ Ja, store ..... ☐

107 Har hukommelsen endret seg siden du var yngre?

Nei ..... ☐ Ja, noe .... ☐ Ja, mye ..... ☐

108 Har du problemer med å huske:

	Aldri	Av og til	Ofte
Hendelser for få minutter siden?	☐	☐	☐
Navn på andre mennesker?	☐	☐	☐
Datoer?	☐	☐	☐
Å gjøre det du har planlagt?	☐	☐	☐
Hendelser som skjedde for noen dager siden?	☐	☐	☐
Hendelser som skjedde for år siden?	☐	☐	☐
Å holde tråden i samtaler?	☐	☐	☐

SPISEFORSTYRRELSER

Sett en ring rundt det tallet som best beskriver dine spisevaner, slik du synes det har vært <u>den siste måneden</u>.

109 Hvor fornøyd har du vært med dine spisevaner?

Svært fornøyd 1 2 3 4 5 6 7 Svært misfornøyd

110 Har du trøstespist eller spist ekstra på grunn av at du har vært nedstemt eller følt deg utilfreds?

Ikke i det hele tatt 1 2 3 4 5 6 7 Hver dag

111 Har du hatt skyldfølelse i forbindelse med spising?

Ikke i det hele tatt 1 2 3 4 5 6 7 Hver dag

112 Har du følt at det er nødvendig for deg å følge strenge dietter eller andre matritualer for å holde kontroll med hvor mye du spiser?

Ikke i det hele tatt 1 2 3 4 5 6 7 Hver dag

113 Har du følt at du er for tykk?

Ikke i det hele tatt 1 2 3 4 5 6 7 Hver dag

NB!

Det utfylte skjemaet returneres i den vedlagte svarkonvolutten.
Porto er betalt.

Takk for hjelpa!

STATENS HELSETILSYN
Postboks 8128 Dep.
0032 OSLO

Medisinsk registrering av fødsel

Sendes 9. dag etter fødselen til fylkeslegen (stadsfysikus) i det fylket der moren er bosatt.

Merk: Det skal fylles ut blankett for hvert barn (foster). Dør barnet etter fødselen, skal det også fylles ut legeerklæring om dødsfall, og/eller dødsfallet meldes til skifteretten (lensmannen).

Barnet

Barnet var: 1 ☐ Levende født 2 ☐ Dødfødt foster | Født dag, mnd., år | Klokkeslett | Personnr. | Skriv ikke her

1 ☐ Enkel 2 ☐ Tvilling 3 ☐ Trilling 4 ☐ Firling | Kjønn: 1 ☐ Gutt 2 ☐ Pike

Etternavn, alle fornavn (bare for levendefødte)

Fødested. Navn og adresse på sykehuset/fødehjemmet | Kommune

Faren

Etternavn, alle fornavn | Født dag, mnd., år | Bostedskommune

Moren

Etternavn, alle fornavn. Pikenavn | Født dag, mnd., år

Bosted. Adresse | Kommune

Ekteskapelig status: 1 ☐ Ugift 6 ☐ Samboende 2 ☐ Gift 3 ☐ Enke 4 ☐ Separert 5 ☐ Skilt | Ekteskapsår (gifte)

Antall tidligere fødte (før denne fødselen) | Levende fødte | Av disse i live | Dødfødte

Er moren i slekt med faren? 1 ☐ Nei 2 ☐ Ja. Hvilket slektskapsforhold:

Morens helse før svangerskapet

1 ☐ Normal 2 ☐ Sykdom (spesifiser):

Siste menstruasjons første blødningsdag

Morens helse under svangerskapet

1 ☐ Normal 2 ☐ Komplikasjoner (spesifiser):

Ble fødselen provosert

1 ☐ Nei 2 ☐ Ja

Inngrep under fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Inngrepet utført av: 1 ☐ Lege 2 ☐ Jordmor

Komplikasjoner i forbindelse med fødselen

1 ☐ Nei 2 ☐ Ja (spesifiser):

Fostervann, placenta og navlesnor

1 ☐ Normalt 2 ☐ Patologisk (spesifiser):

Barnets tilstand

Bare for levende fødte. Tegn på asfyksi? 1 ☐ Nei 2 ☐ Ja | Apgarscore etter 1 min. | etter 5 min.

For levende fødte og dødfødte. Tegn på medfødt anomali, på skade eller sykdom? 1 ☐ Nei 2 ☐ Ja. Hvilke:

Lengde (i cm) | Hode-omkr. (i cm) | Vekt (i g) | For døde innen 24 timer Livet varte i | Timer | Min

For dødfødte. Døden inntrådte 1 ☐ Før fødselen 2 ☐ Under fødselen
Dødsårsak:

Seksjon? 1 ☐ Nei 2 ☐ Ja

Alvorlige arvelige lidelser i slekten

1 ☐ Nei 2 ☐ Ja Sykdommens art og hos hvilke slektninger:

Sted (sykehusets stempel) | Dato | Jordmor | Lege

IK - 1002.

50 000. 5.96. SFM GRAFISK

Melding om avsluttet svangerskap etter 12. uke – Fødsel, dødfødsel, spontanabort

Se utfyllingsinstruks for blanketten på baksiden

MFR

Sosial- og helsedirektoratet

A – Sivile opplysninger

Institusjonsnr: | Institusjonsnavn

Fødsel utenfor institusjon: ☐ Hjemme, planlagt ☐ Hjemme, ikke planlagt ☐ Under transport ☐ Annet sted

Mors fulle navn og adresse

Pikenavn (etternavn):

Mors sivilstatus ☐ Gift ☐ Ugift/enslig ☐ Annet ☐ Samboer ☐ Skilt/separert/enke

Slektskap mellom barnets foreldre? ☐ Nei ☐ Ja Hvis ja, hvorledes:

Mors bokommune

Fars fødselsdato | Fars fulle navn | **Mors fødselsnr:**

B – Om svangerskap og mors helse

Siste menstr. 1. blødn.dag ☐ Sikker ☐ Usikker

Mors tidligere svangerskap/fødte Levende-fødte | Dødfødte (24. uke og over) | Spontanabort/Død-fødte (12.–23. uke) | Spontanaborter (under 12. uke)

Ultralyd utført? ☐ Nei ☐ Ja UL termin:

Annen prenatal diagnostikk? ☐ Nei ☐ Ja, angi type:

Patologiske funn ved prenatal diagnostikk? ☐ Nei ☐ Ja, hvis bekreftet – spesifiser

Spesielle forhold før svangerskapet:
☐ Intet spesielt
☐ Astma ☐ Allergi ☐ Tidligere sectio ☐ Res. urinveisinfeksjon ☐ Kronisk nyresykdom ☐ Kronisk hypertensjon ☐ Reumatoid artritt ☐ Hjertesykom ☐ Epilepsi ☐ Diabetes type 1 ☐ Diabetes type 2 ☐ Annet, spesifiser i «B»

Regelmessig kosttilskudd: ☐ Nei Før sv.sk. I sv.sk.
Multivitaminer ☐ ☐
Folat/Folsyre ☐ ☐

Spesifikasjon av forhold før eller under svangerskapet: B

Spesielle forhold under svangerskapet:
☐ Intet spesielt
☐ Blødning < 13 uke ☐ Blødning 13–28 uke ☐ Blødning > 28 uke ☐ Glukosuri ☐ Svangerskapsdiabetes ☐ Hypertensjon alene ☐ Preeklampsi lett ☐ Preeklampsi alvorlig ☐ Preeklampsi før 34. uke ☐ HELLP syndrom ☐ Eklampsi ☐ Hb < 9.0 g/dl ☐ Hb > 13.5 g/dl ☐ Trombose, beh. ☐ Infeksjon, spes. i «B»

☐ Annet, spesifiser i «B»

Legemidler i svangerskapet:
☐ Nei
☐ Ja – spesifiser i «B»

Røyking og yrke
Forutsetter mors samtykke – se rettledning på baksiden

Røykte mor ved sv.sk. begynnelse? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

- ved sv.sk. avslutning? ☐ Nei ☐ Daglig ☐ Av og til Ant. sig. dagl.:

☐ Skriftlig orientering gitt til mor
☐ Samtykker ikke for røykeoppl.

Mors yrke ☐ Samtykker ikke for yrkesoppl. ☐ Ikke yrkesaktiv ☐ Yrkesaktiv heltid ☐ Yrkesaktiv deltid

Mors yrke

Bransje:

C – Om fødselen

Leie/presentasjon:
☐ Normal bakhode
☐ Sete ☐ Tverrleie ☐ Avvikende hodefødsel ☐ Annet, spesifiser i «C»

Fødselstart:
☐ Spontan ☐ Indusert ☐ Sectio

Ev. induksjons-metode:
☐ Prostaglandin ☐ Oxytocin ☐ Amniotomi ☐ Annet, spesifiser i «C»

Indikasjon for inngrep og/eller induksjon
☐ Komplikasjoner som beskrevet nedenfor ☐ Fostermisdannelser ☐ Overtid ☐ Annet, spesifiser i «C»

Inngrep/tiltak
☐ Ingen
☐ Utskj. tang, hodeleie ☐ Annen tang, hodeleie ☐ Vakuumekstraktor ☐ Episitomi

Fremhj. ved setefødsel:
☐ Vanlig fremhjelp ☐ Uttrekning ☐ Tang på etterk. hode

Sectio:
Var sectio planlagt før fødsel? ☐ Nei ☐ Ja
☐ Utført som elektiv sectio ☐ Utført som akutt sectio

Spesifikasjon av forhold ved fødselen/andre komplikasjoner C

Komplikasjoner
☐ Ingen
☐ Vannavg. 12–24 timer ☐ Vannavg. > 24 timer ☐ Mekaniske misforhold ☐ Vanskelig skulderforløsning ☐ Placenta previa ☐ Abruptio placentae ☐ Perinealruptur (grad 1-2) ☐ Sphincterruptur (gr. 3-4) ☐ Blødn.> 1500 ml, transf. ☐ Blødning 500–1500 ml ☐ Eklampsi under fødsel ☐ Navlesnorfremfall ☐ Truende intrauterin asfyksi ☐ Risvekkelse, stimulert ☐ Langsom fremgang ☐ Uterus atoni ☐ Annet:

Anestesi/analgesi:
☐ Ingen
☐ Lystgass ☐ Petidin ☐ Epidural ☐ Spinal ☐ Pudendal ☐ Infiltrasjon ☐ Paracervical blokk ☐ Narkose ☐ Annet:

Placenta:
☐ Normal ☐ Hinnerester ☐ Ufullstendig ☐ Infarkter
☐ Koagler ☐ Utskrapning ☐ Manuell uthenting
Placenta-vekt

Navlesnor
☐ Normal ☐ Velamentøst feste ☐ Marginalt feste ☐ Karanomalier
☐ Omslyng rundt hals ☐ Annet omslyng ☐ Ekte knute
Navlesnor-lengde:

Fostervann
☐ Normal ☐ Polyhydramnion ☐ Oligohydramnion ☐ Misfarget ☐ Stinkende, infisert ☐ Blodtilblandet

Komplikasjoner hos mor etter fødsel
☐ Intet spesielt ☐ Feber > 38.5° ☐ Trombose ☐ Eklampsi post partum ☐ Mor overflyttet ☐ Mor intensivbeh. ☐ Sepsis ☐ Annet, spesifiser

D – Om barnet

Fødselsdato | **Klokken**

Pluralitet ☐ Enkeltfødsel ☐ Flerfødsel For flerfødsel: Nr. | Av totalt

Kjønn ☐ Gutt ☐ Pike Barnets vekt:

Ved tvil spesifiser i «D»
For dødfødte: ☐ Usikkert kjønn Hode-omkrets:

Total lengde:

Eventuelt sete–issemål:

Apgar score: 1 min | 5 min

Barnet var:
☐ Levendefødt
☐ Dødfødt/sp.abort Oppgi dødsårsak i «D»

For dødfødte:
☐ Død før fødsel ☐ Død under fødselen ☐ Ukjent dødstidspunkt

For dødfødte, oppgi også
☐ Død før innkomst ☐ Død etter innkomst

Levendefødt, død innen 24 timer
Livet varte: Timer Min.

Død senere (dato): | **Klokken**

Overfl. barneavd. ☐ Nei ☐ Ja Dato: | Overfl. til

Indikasjon for overflytting: ☐ Respirasjonsproblem ☐ Prematur ☐ Medfødte misd. ☐ Perinatale infeksjoner ☐ Annet, spesifiser

Neonatale diagn.: (Fylles ut av lege/pediater)
☐ Intet spesielt
☐ Hypoglyk. (< 2 mmol/l) ☐ Medf. anemi (Hb < 13.5 g/dl) ☐ Hofteleddsdyspl. beh. m/pute ☐ Transit. tachypnoe ☐ Resp. distress syndr. ☐ Aspirasjonssyndrom ☐ Intrakraniell blødning ☐ Cerebral irritasjon ☐ Cerebral depresjon ☐ Abstinens ☐ Neonatale kramper ☐ Konjunktivitt beh. ☐ Navle./hudinf. beh. ☐ Perinat. inf. bakterielle ☐ Perinat. inf. andre ☐ Fract. claviculae ☐ Annen fraktur ☐ Facialisparese ☐ Plexusskade

Behandlingskoder:
☐ Systemisk antibiotika ☐ Respiratorbeh. ☐ CPAP beh.

Icterus behandlet:
☐ Lysbehandlet ☐ Utskifting

Årsak:
☐ AB0 uforlik. ☐ RH immunisering ☐ Fysiologisk ☐ Annen årsak

Tegn til medfødte misdannelser: ☐ Nei ☐ Ja

D Spesifikasjon av skader, neonatale diagnoser og medfødte misdannelser – utfylles av lege

☐ **Kryss av hvis skjema er oppfølgingsskjema**

Jordmor v/fødsel:

Jordmor v/utskrivning:

Utskrivningsdato
Mor:
Barn:

Protokollnr.: /

Lege:

Lege barsel/barneavd:

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