ELHAM KHARAZMI

Reproduction, Hysterectomy and Risk of Cardiovascular Disease

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ACADEMIC DISSERTATION
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This dissertation is based on the following original publications, referred to in the text by Roman numerals:

I Elham Kharazmi, Leena Moilanen, Mahdi Fallah, Risto Kaaja, Anna Kattainen, Mika Kähönen, Antti Jula, Antero Kesäniemi, Riitta Luoto. Reproductive history and carotid intima-media thickness. Acta Obstetricia et Gynecologica Scandinavica. 2007;86(8):995–1002.

II Riitta Luoto, Elham Kharazmi, Elise Whitley, Jani Raitanen, Mika Gissler, Elina Hemminki. Systolic hypertension in pregnancy and cardiovascular mortality: a 44-year follow-up study. Hypertension in Pregnancy. 2008; 27(1):87–94.

III Elham Kharazmi, Risto Kaaja, Mahdi Fallah, Riitta Luoto. Pregnancy-related factors and the risk of isolated systolic hypertension. Blood Pressure. 2007;16(1):50–5.

IV Elham Kharazmi, Mahdi Fallah, Riitta Luoto. Cardiovascular disease attributable to hysterectomy: a population-based study. Acta Obstetricia et Gynecologica Scandinavica. 2007;86(12):1476–83.

Abbreviations

AF	Attributable fraction
BMI	Body mass index
BP	Blood pressure
CHD	Coronary heart disease
CI	Confidence interval
CVD	Cardiovascular disease
ECG	Electrocardiogram
HDL	High-density lipoprotein
HR	Hazard ratio
HT	(Postmenopausal) hormone therapy
ID	Personal identification
IHD	Ischemic heart disease
IMT	Intima-media thickness
ISH	Isolated systolic hypertension
KTL	National Public Health Institute of Finland
LDL	Low-density lipoprotein
MI	Myocardial infarction
OC	Oral contraceptive use
OR	Odds ratio
P	Statistical significance
SD	Standard deviation

Abstract

Background: Cardiovascular disease (CVD), the most common cause of death in most developed countries, has gender-specific characteristics. The protective effect of endogenous estrogen for CVD is acknowledged. In older ages, women have similar rates of CVD, and even a higher prevalence of hypertension than men. Although CVD is considered a "man's disease", CVD kills more women. Most of our knowledge about management guidelines for CVD in women arises from studies conducted mostly in men. The increasing number of women with CVD shows the substantial need to identify those specific variables relevant to cardiovascular health in women. Whether pregnancy-related factors and hysterectomy would reveal some of these variables and risk for CVD is still uncertain.

Objective: To further elucidate the associations between reproduction, hysterectomy, and risk of CVD in women.

Materials and methods: Data were obtained from the Health 2000 Study, a cross-sectional comprehensive study carried out in 2000-1 in Finland, except for Study II. Study I comprised 746 Finnish women aged 45–74, in which associations of reproductive history (assessed by questionnaire) and measures of subclinical atherosclerosis (by ultrasonographic detection) were studied. In Study III, associations between pregnancy-related factors and isolated systolic hypertension (ISH) were assessed in 3,937 Finnish women aged 30–99. In Study IV, data of 2,514 Finnish women aged 30–99 were used to investigate associations between hysterectomy and CVD.

A total of 4,090 Finnish women who delivered in the period 1954–1963 were followed up for an average of 44 years in Study II. Mortality data were obtained from the Finnish cause-of-death registry.

Logistic, linear regression and Cox-proportional hazard models were used for the analyses.

Results: Women with a history of stillbirth tended to have higher IMT than other women. A history of stillbirth was associated with an increased age-adjusted risk of plaque [Odds ratio (OR): 3.43, 95% CI: 1.07–11.05] but in

the fully-adjusted model it lost its statistical significance (OR: 2.73, 95% CI: 0.55–13.55). Cardiovascular mortality was significantly higher among women with systolic hypertension in early or late pregnancy than in normotensive subjects. Younger age at first delivery predicted a higher risk of ISH (OR after adjustment for age, height, weight diastolic blood pressure (BP), fasting blood glucose, low-density lipoprotein and total cholesterol, education, smoking, and physical activity: 1.04, 95 % CI: 1.01–1.06). Age at first and last delivery was significantly associated with age, education, and marital status; age at first delivery was also associated with toxemia in any pregnancy, weight and BMI. Hysterectomy was significantly associated with hypertension, angina pectoris, stroke, age, education, oral contraceptive use, postmenopausal hormone therapy, BMI, fasting blood glucose, and cholesterol. The fully-adjusted ORs for associations between CVD and hysterectomy were dramatically lower than the crude ORs and remained significant only for medication for hypertension.

Conclusion: Hypertension in pregnancy and earlier age at first delivery may predict higher risk of CVD in later life. The adverse effect of child-bearing and hysterectomy, as the most common non-obstetric surgery, on cardiovascular systems seems to be mediated by more adverse common known risk factors, rather than these factors per se. Pregnancy acts as an important screening opportunity for CVD. Further studies are needed to show whether the risk of later CVD morbidity or mortality decreases with early intervention and precise control of common known risk factors of CVD in women who delivered at a younger age or who had experienced pregnancy complications such as systolic hypertension.

1. Introduction

CVD as the most common cause of death in most developed countries has gender-specific characteristics. In young to middle-aged population, hypertension and CVD are more common in men than in women (Kannel and Wilson 1995). In both sexes, CVD risk increases with age. However, this increase is sharper in women, so that in old age, women have similar rates of CVD, and even a higher prevalence of hypertension than that of men (Sjoberg *et al.* 2004). Prevalence of coronary heart disease (CHD) changed in Finland from a disease of middle-aged men in the late 1970s, to a disease of elderly women in the 2000s. In 1980, the major CHD group was of men aged 45 to 64, whereas in 2000, women aged 75 or over comprised the largest CHD group among Finns (Kattainen *et al.* 2006). CVD is responsible for more deaths in women each year than from all other causes combined (Jneid and Thacker 2001). Although CVD is considered a "man's disease" (American Heart Association 2006) CVD kills more women (Mosca *et al.* 1997).

Although we are aware of gender-related differences and effects of sex hormones on CVD (Gorodeski 2002), most of our knowledge about the pathophysiology of CVD and management guidelines in women arise from studies conducted mostly on men (Mieres *et al.* 2005). The increasing prevalence of cardiovascular pathology in women shows the substantial need for identification of those variables specifically relevant to cardiovascular health in women. Women differ considerably in the clinical manifestations and symptoms. Physiological and pathological changes of pregnancy, such as insulin resistance, thrombophilia, immunosuppression, and hypervolemia, and exaggerated responses reflective of the metabolic syndrome in pre-eclampsia and gestational diabetes may predict the development of disease in later life (Kaaja and Greer 2005). Pregnancy is therefore an important screening opportunity for cardiovascular and metabolic disease risk factors, with the possibility of early intervention (Kaaja and Greer 2005). Whether pregnancy

has a direct effect or just plays a role in changing the known risk factors of CVD is uncertain. In addition, checking reproductive history among other predictors of CVD is simple but can be of high predictive value. If endpoints of CVD (morbidity or mortality) can thus be predicted many years before manifestation of its clinical symptoms by checking the reproductive history, then it is worth investigating reproductive history as one of the predictors of CVD, which is the aim of this study.

2. Review of the literature

The protective effect of endogenous estrogen for CVD is well acknowledged. Whether reproduction, which affects endogenous estrogen levels during a woman's life, affects CVD risk as well, is still uncertain. Associations between some of pregnancy-related factors and CVD have already been studied as this issue has a great deal of biological plausibility. However, investigating these associations between these variables and CVD is difficult due to the long lag time between childbirth and the occurrence of CVD in women, as well as low incidence of CVD in them in reproductive ages. Hysterectomy as the most common non-obstetric surgery in women also shows contradictory results in this issue. In the following sections, the factors studied in this dissertation more thoroughly as an exposure or outcome will be reviewed.

2.1. Reproduction, hysterectomy and cardiovascular disease risk

2.1.1. Parity

Parity is defined as the number of offspring a female has borne. It is contrasted with gravidity, which refers to the number of pregnancies, regardless of outcome (National Library of Medicine, USA 2008a).

Beside structural and functional alterations of cardiovascular system (Sadaniantz *et al.* 1996; Clapp and Capeless 1997) pregnancy induces substantial changes in metabolism as well as in endocrine regulation. It alters blood lipoprotein levels (Fahraeus *et al.* 1985; Lewis *et al.* 1996), increase insulin concentrations (Kritz-Silverstein *et al.* 1989) and also increases generation of reactive oxygen species (Toescu *et al.* 2002). Parity shows the effect on long-term CVD risk and mortality (Colditz *et al.* 1987b; Green *et al.*

1988; Ness *et al.* 1993; Steenland *et al.* 1996; Qureshi *et al.* 1997; Lawlor *et al.* 2003). In a prospective cohort study in Northern Finland, high parity was associated with an up to twofold risk of mortality from vascular complications, but after adjustment for all background factors, this significance disappeared. Mortality from hemorrhagic stroke was four times higher among the women with >=10 births compared with those who had 2–4 births (Koski-Rahikkala *et al.* 2006). By contrast, Steenland describes no association between higher parity and CVD (Steenland *et al.* 1996) and another study even found opposite effects with nulliparity or lower parity rates related to higher CVD risk (Colditz *et al.* 1987b). Nulliparity and greater numbers of children show an association with increased carotid intima-media thickness (IMT) as a predictor of CVD (Wolff *et al.* 2005). Lifestyle risk factors associated with child-rearing lead to obesity and result in increased CHD in both sexes; biological responses of pregnancy may have additional adverse effects in women (Lawlor *et al.* 2003). Hardy suggests that any association between number of children and CHD risk factors is a result of lifestyle and behaviors associated with family life rather than a result of the biological impact of pregnancy in women (Hardy *et al.* 2007). Thus, the association between parity and risk of CVD remains uncertain as there are many contradictory results in this field.

2.1.2. Age at first/last delivery

A large retrospective cohort study found no significant association between age at first delivery and CHD (Colditz *et al.* 1987b). Some other studies found that the women who had their first delivery before age 25 appeared to be at higher risk of CHD (Beard *et al.* 1984; La Vecchia *et al.* 1987) and ischemic heart disease (IHD) (Guo *et al.* 1992).

2.1.3. Multiple pregnancy

Multiple pregnancy, which is the condition of bearing two or more fetuses simultaneously, appears to be associated with higher risk of gestational hypertension (Santema *et al.* 1995; Senat *et al.* 1998; Sibai *et al.* 2000) as a major maternal complication. Women with multiple gestations also show

higher risk of eclampsia and pre-eclampsia (Long and Oats 1987; Coonrod *et al.* 1995; Conde-Agudelo *et al.* 2000). These associations increase with plurality (four quads more than triplets and triplets more than twins) (Seoud *et al.* 1992; Franco 1994; Skupski *et al.* 1996).

2.1.4. Hypertensive disorders in pregnancy

Hypertensive disorders are seen in about 7–10% of pregnant women (Sibai 2002). But pre-eclampsia, which manifests with new-onset of hypertension and proteinuria during pregnancy, is estimated to complicate 3–5% of all deliveries (Roberts and Cooper 2001). Uniformity in diagnosis and classification of hypertension in pregnancy are important for management, comparing investigative reports, as well as for future prognosis; generally it is diagnosed by diastolic BP $\geq$ 90 mmHg, and/or systolic $\geq$ 140 mmHg (Hibbard 2002). Whether pre-eclampsia has a long-term sequel remains controversial because it is difficult to distinguish pre-eclampsia from contributing conditions (van Pampus and Aarnoudse 2005). However, women with pre-eclampsia have an increased risk of later IHD and cardiovascular death, especially if preterm deliveries occur (Jonsdottir *et al.* 1995; Irgens *et al.* 2001; Smith *et al.* 2001).

An increased risk of CVD mortality among parous women with pregnancy hypertension has been reported earlier (Jonsdottir *et al.* 1995).

2.1.5. Stillbirth

Stillbirth is defined as the event of a fetus being born dead or stillborn (National Library of Medicine, USA 2008b). Some sources reserve the term "stillbirth" for a fetus which has died after reaching mid-second trimester to full term gestational age. For example, in the United Kingdom, "stillbirth" is used to describe an infant delivered without life after 24 weeks' gestation (Dimond 2004). Maternal high BP has been considered to be one of the possible causes of stillbirth. Mothers with hypertensive disorders during pregnancy have higher risk of stillbirth (Page and Christianson 1976; Ananth *et al.* 1995; Gupta *et al.* 1996; Yadav *et al.* 1997). Stillbirth is associated with an increased risk of death from CHD (Calderon-Margalit *et al.* 2007).

2.1.6. Hysterectomy

Hysterectomy was the most common non-obstetric surgical procedure performed on women between 1994 through 1999 in the United States (Keshavarz *et al.* 2002), yet the procedure remains common in many countries. For example, there were approximately 617,000 hysterectomies performed in the United States in 2004 (Centers for Disease Control and Prevention, National Center for Health Statistics 2006). From 1987 to 1992 the hysterectomy rate increased by 22%, from 340 to 414 per 100,000 females in Finland (Vuorma *et al.* 1998). Around 20% of women in the United Kingdom have a hysterectomy by age 55 (Vessey *et al.* 1992). Therefore, although hysterectomy is an appropriate therapeutic option for some conditions (Scialli 1998), any long term effect of hysterectomy is important as several new technologies reduce the need for hysterectomy (Bongers *et al.* 2004). For instance, the levonorgestrel-releasing intrauterine system (IUS) is a cost-effective alternative to hysterectomy in treatment of menorrhagia (Hurskainen *et al.* 2001).

The association of hysterectomy with increased CVD risk is still controversial. A number of studies have shown hysterectomy with ovarian preservation to be associated with risk of CVD (Luoto *et al.* 1995; Howard *et al.* 2005), and some others showed this effect only for hysterectomy with bilateral oophorectomy (Rosenberg *et al.* 1981; Hsia *et al.* 2003; Kannel and Levy 2004; Boynton-Jarrett *et al.* 2005) and some studies did not find any association between hysterectomy and CVD (Falkeborn *et al.* 2000; Iversen *et al.* 2005). The large observational study of the Women's Health Initiative (Howard *et al.* 2005) suggested that higher cardiovascular risk in hysterectomized women may be due to the more adverse initial risk profile of women who had undergone hysterectomy rather than to the operation per se.

These findings add support to the hypothesis of a link between various aspects of the reproductive history of women and CVD.

2.2. Surrogate markers of cardiovascular disease

2.2.1. Intima-media thickness

Investigations of the putative link of reproductive history with CVD are hampered by a low incidence of cardiovascular endpoints among young childbearing women. However, markers of subclinical atherosclerosis such as carotid IMT, which have a predictive value of subsequent myocardial infarction (MI) and stroke (Touboul *et al.* 2000), may offer an alternative. A change in carotid IMT has been validated as a vascular marker of the progression of atherosclerosis (Bots and Grobbee 2002). Carotid B-mode ultrasonography, which measures the IMT of carotid arteries non-invasively, provides an independent approximation of coronary atherosclerosis. Carotid IMT carries independent predictive power for development of CHD (Smith *et al.* 2000).

2.2.2. Isolated systolic hypertension

Isolated systolic hypertension (ISH) is defined as systolic BP ≥ 140 mm Hg and diastolic BP <90 mm Hg (European Society of Hypertension-European Society of Cardiology Guidelines, Committee 2003). The prevalence of ISH is 26% in population aged 55 and older (Langille *et al.* 1999). ISH is a strong predictor of cerebrovascular, stroke (Paultre and Mosca 2005) and cardiac events (Antikainen *et al.* 1998).

The superior predictive power of systolic BP compared with diastolic BP with respect to all complications attributed to hypertension was already shown three decades ago in the Framingham Heart Study (Kannel *et al.* 1971). Data from the Framingham Study show that isolated ISH was associated not only with increased mortality but also cardiovascular morbidity. During recent decades the importance of perceiving ISH in cardiovascular pathophysiology has been changed from a benign condition to the major cardiovascular risk factor (Kocemba *et al.* 1998). Elevated systolic BP has consistently been shown to be a better predictor of cardiovascular events, including stroke and MI (Mann 1992). ISH increases the risk of overall mortality, cardiovascular mortality, and congestive heart failures (Anonymous1991; Petrovitch *et al.*

1992; O'Donnell *et al.* 1997; Potter 1997; Staessen *et al.* 1997; Himmelmann *et al.* 1998; Black 2004; Martin *et al.* 2005).

The incidence of cerebrovascular and cardiac events in women of all ages is lower than in men, but increases disproportionately in women after menopause (Thrift *et al.* 2000). Furthermore, elderly women have a greater incidence of ISH than elderly men (Langille *et al.* 1999; Martins *et al.* 2001). During the reproductive years, women have a less stiff arterial system than men, but this difference is no longer evident after menopause (Waddell *et al.* 2001). Large-artery stiffening is a principal determinant of systolic BP (Stella *et al.* 1998) There is preliminary evidence that healthy older women may actually have stiffer large arteries than elderly men (Liang *et al.* 1997).

Many studies investigated the relation between the reproductive history of women and morbidity and mortality from CVD and have found some controversial results (de Kleijn *et al.* 1999). However, there are no published studies on the association between pregnancy related factors and ISH. Thus, it may be plausible that ISH has some connections to pregnancy and parity related issues.

3. Aims of the study

The objective of this study was to find out the associations between some pregnancy-related factors, hysterectomy and risk of CVD in women. To achieve this aim, several specific aims were followed:

To further elucidate the association between:

- Multiple aspects of reproductive history and measures of subclinical atherosclerosis, carotid IMT and presence of plaque (Study I)
- Systolic hypertension during pregnancy and long-term mortality from all-cause and CVD (Study II)
- Pregnancy-related factors (parity, timing of deliveries, multiple pregnancy, miscarriage, stillbirth) and isolated systolic hypertension (Study III)
- Hysterectomy and cardiovascular outcomes, in particular to estimate the excess risk of CVD attributable to hysterectomy (Study IV)

4. Materials and methods

4.1. Health 2000 Study

Health 2000 was a health interview and examination study carried out in Finland from fall 2000 to spring 2001 (Aromaa and Koskinen 2004). The main aim of the Health 2000 Study was to provide an up-to-date comprehensive picture of health and functional capacity in Finland. It was of major importance for the planning and development of Finnish health policy, health care and social security in general. KTL (the National Public Health Institute) had the main responsibility for the study. Other Finnish social and health care organizations also participated. The people selected for the study were first interviewed at home. After one to six weeks they received an invitation to attend a health examination.

The two-stage stratified cluster sampling design was planned by Statistics Finland. The sampling frame comprised adults aged 30 and over living in mainland Finland (Aromaa and Koskinen 2004). This frame was regionally stratified according to the five university hospital regions, each containing roughly one million inhabitants. From each university hospital region 16 health care districts were sampled as clusters (altogether 80 health care districts in the whole country, including 160 municipalities). Ethical permission for the Health 2000 Study was received from the Uusimaa Hospital District.

The first phase was the health interview conducted by more than 160 members of the Statistics Finland interview staff. Few weeks later a health examination carried out by five KTL field units comprising nurses, dentists and physicians. Each unit had a staff of 16 to 17.

4.1.1. Health interview

The interview was used to gather basic background and sociodemographic data, information about health and illnesses as well as use of medicines, use of

health services, living habits, environment, functional capacity, work and work capacity as well as need for help and rehabilitation (Appendix 1); the detailed forms are available on KTL website at www.ktl.fi/health2000.

4.1.2. Health examination

The health examination comprised nine phases (Appendix 2). The Symptom Interview was usually carried out in the first part of the examination: this covered respiratory and cardiovascular symptoms, atopy and allergies and musculoskeletal symptoms (Appendix 3). At this stage the examinees received an information leaflet and an informed consent form for signing. Information on systolic and diastolic BP, fasting blood glucose and cholesterol, and height and weight were obtained from direct physical examinations and laboratory tests.

In brief, of the nationally representative sample involving 8,028 Finns aged 30 or over, 88% were interviewed and 80% attended a comprehensive health examination in the Health 2000 Study carried out in 2000–2001. The implementation of the study is described in detail elsewhere (Aromaa and Koskinen 2004). The most essential information on health and functional capacity was obtained from more than 93% of the subjects. Health 2000 data were used in this dissertation except for Study II.

4.1.3. Information on reproductive factors

The subjects responded to an extensive interviewer-administered questionnaire. Regarding pregnancy related factors, they were asked about parity, gravidity, age at deliveries, multiple pregnancy, miscarriage and stillbirth (Appendix 3). They were asked about current and ever use of oral contraceptive (OC) and postmenopausal hormone therapy (HT) and some other reproductive history factors which were not included in studies of this dissertation. Hysterectomy status was determined by asking: Have you ever been operated on for hysterectomy? (Yes/No). Oophorectomy status was determined by asking the next question: What was removed or extirpated: The uterus and both ovaries, the uterus and one ovary, or only the uterus?

4.1.4. Information on CVD and CVD risk factors

The information on CVD which was used in Study IV was based upon replies to the interview questions, "Have you ever been diagnosed with hypertension/ myocardial infarction/ angina pectoris/ heart failure/ arrhythmia/ stroke?" These responses were also available for subjects who took part in the health examination proper by clinical diagnoses made by the field physicians. The CVD variables used in Study IV were from the interview information since it was available on the largest group of participants.

Blood pressure (BP) was measured by a nurse with a conventional, calibrated, mercury sphygmomanometer from the sitting individuals' right arm after a 10-min rest. BP was measured using a cuff size 15 × 43 cm; a larger cuff was used where necessary. Diastolic pressure was recorded at the fifth phase of the Korotkoff sounds (Reunanen *et al.* 2004b). The means of two measurements performed at a 2-min interval were used in Studies I, III and IV.

Weight was measured as part of the bioimpedance examination with a spring scale (Biospace, Inbody 3.0). The machine automatically calculated the body mass index (BMI; kg/m^2) after measured height was entered. In subjects examined at home, BMI was calculated on the basis of measured height and the weight measured on a portable spring scale (Reunanen *et al.* 2004b).

Serum total cholesterol and triglycerides were determined by commercial automated enzymatic methods (Olympus System Reagent, Germany). Direct enzymatic methods were used for LDL and HDL cholesterol determinations (Roche Diagnostics, Mannheim, Germany). The analyses were performed on an Olympus AU400 (Germany) clinical chemistry autoanalyzer. (Reunanen *et al.* 2004b).

4.2. Supplementary study to Health 2000

To study cardiovascular disease and diabetes more thoroughly, a supplementary study was carried out (sample size, 1867; participation rate, 82%). The subjects, a subpopulation of the Health 2000 Study, in the supplementary study were 45 years and older, and the study was executed in the catchment areas

of the five Finnish university hospitals because specialized equipment was required (Sipila *et al.* 2007). The carotid ultrasound substudy was performed from October 2001 to August 2002.

Ultrasound measurement

High-resolution B-mode carotid ultrasound examination of the right carotid artery was performed according to a standardized protocol using a 7.5 MHz linear array transducer. The examinations were performed by centrally trained and certified sonographers at five study locations around Finland. IMT measurements were performed off-line with automated imaging processing software. One reader was responsible for reading all ultrasound images. Details of the IMT measurements were described in Study I.

4.3. Historical cohort (1954–2005)

To further elucidate the association of systolic hypertension during pregnancy and long-term mortality from all-cause and CVD (Study II), the data from a Finnish cohort of women were used, the details of which have been reported previously (Hemminki *et al.* 1999a; Hemminki *et al.* 1999b). The information on exposure and confounding factors were collected from patient records in maternity centers in Helsinki and that on long-term outcomes was collected from mortality registers through record linkage.

4.3.1. Subjects and exposure assessment

Since 1944, municipalities in Finland have offered free prenatal care. By 1960, 85% of Helsinki women who gave birth were registered in maternity centers. In the 1950s and 1960s, care was given mainly by midwives supported by gynecologists. A duplicate standard maternity card was used to record all visits a woman made to health care providers because of her pregnancy; one copy of the card was given to the mother. All drugs prescribed were to be noted on this card, including those prescribed by physicians outside the maternity center. If the maternity card indicated that the mother had been sent to a hospital during

pregnancy for pregnancy-related reasons (18% of the mothers), her records were studied in the hospital archives.

A systematic sample of half (233 of 470) of the boxes containing the maternity cards (in Helsinki municipality archives) was searched to identify all mothers who had given birth between 1954 and 1963 and who were prescribed estrogen and progestin drugs. For each exposed mother the next mother in the file who had given birth during the same year and who was not prescribed hormones was chosen as the control.

Data on systolic or diastolic BP and proteinuria were abstracted from two periods during pregnancy; the first around the beginning of the second trimester [median (inter-quartile range) at gestational age 14 (range 11–17) weeks] and secondly, close to term [median gestational age: 38 (range 37–40) weeks]. Any diagnosis of pre-eclampsia or eclampsia given at a hospital or at a prenatal care center was also considered. Additional data were available in maternity cards on age, height, marital status and whether the woman consulted a private doctor (as a proxy for socioeconomic status).

4.3.2. Outcome assessment

Follow-up was done with the help of life-long personal identification (ID) numbers given to all Finns between 1964 and 1967. Because our cohort was formed of people born before 1964, ID numbers for the mothers were sought from the Central Population Register, supplemented by data from local church records and death certificates. An ID number was found for 99% of the mothers;

Women were followed up for an average of 43.5 (range 5–52) years, until death, emigration or the year 2005. After linkage to the causes of deaths we found 867 deaths of which 275 were from CVD. Data on deaths and their causes were obtained from the cause-of-death register kept by Statistics Finland. The linkage key used for this record linkage study was the unique Finnish personal identity number.

4.4. Reproductive history and carotid intima-media thickness

To further elucidate the association of reproductive history and cardiovascular health in women, we investigated in a cross-sectional study the relation between some aspects of reproductive history and measures of subclinical atherosclerosis, carotid IMT and presence of plaque (Study I). Of the Health 2000 supplementary study subjects, 746 were women and they have been included in this study. Information on pregnancy-related factors, hysterectomy and potential confounders were obtained from the Health 2000 Study.

4.5. Systolic hypertension during pregnancy and long-term cardiovascular mortality

In Study II all mothers (exposed to drug or controls) involved in historical cohort described (1954–2005) and had ID number available were included. In brief, 4,090 women who gave birth to live-born singletons in Helsinki between 1954 and 1963 were included in a study to further elucidate the association of systolic hypertension during pregnancy and long-term mortality from all-cause and CVD.

4.6. Reproduction and isolated systolic hypertension

In a population-based cross-sectional study involving 3,937 Finnish women aged 30–99 years (Health 2000 Study), associations between pregnancy-related factors (assessed by questionnaire) and measures of ISH (by physical examination) were studied (Study III).

We used ISH as our outcome variable. The definition which we used for ISH was systolic BP $\geq$ 140 mm Hg and diastolic BP < 90 mm Hg (European Society of Hypertension-European Society of Cardiology Guidelines, Committee 2003).

4.7. Hysterectomy and cardiovascular disease

From the Health 2000 database, those women with available information on hysterectomy status (n = 2,514) were included in Study IV, to further elucidate the association of hysterectomy and cardiovascular outcomes and find out the excess risk of CVD attributable to hysterectomy.

4.8. Statistical methods

IMT, systolic and diastolic BP, systolic and diastolic BP during early/late pregnancy, parity, gravidity, age at first/last delivery, age at menopause, age at hysterectomy, height and weight, BMI, fasting blood glucose, total and low-density lipoprotein cholesterol were used as continuous variables unless otherwise stated. Plaque, ISH, hypertension, current use of antihypertensive drugs, angina pectoris, stroke, MI, cardiac arrhythmia, heart failure, cardiovascular/all cause mortality, menopause, hysterectomy, oophorectomy, abortion, miscarriage, stillbirth, extrauterine pregnancy, multiple pregnancy, post-menopausal hormone therapy (HT) and oral contraceptive (OC) use were used as binomial variables (yes/no). Hysterectomy was also categorized into no hysterectomy, with/without unilateral oophorectomy and with bilateral oophorectomy. Age at the time of the study was considered as a continuous variable in the analyses; age-group as a categorical variable was only used to show subjects' baseline characteristics. We also used education on three levels (basic, middle and high), marital status (married, living with partner, divorced or separated, widowed or single) and physical activity (ideal, sufficient, uncertain, and insufficient) and smoking (non-smoker, past smoker, occasional smoker, and daily smoker) as categorical variables.

Statistical significance (P=0.05) by the χ^2 test were assessed. Linear regression analysis was used for continuous outcome variable (Study I) and logistic regression was performed for binary outcome variables to estimate the odds ratios (Studies I, III and IV). In Study II the Cox-proportional hazards model was used to explore the relation between raised BP or pre-eclampsia in pregnancy and all-cause and cardiovascular mortality (ICD-9 codes

389–459 and ICD-10 codes I00–I99). Analyses were first adjusted for maternal age at delivery and baby's birth year and additionally for hormone drug use, height, marital status and visit to a private doctor in Study II. In three other studies, age, systolic and diastolic BP, fasting blood glucose, total and low-density lipoprotein cholesterol, smoking, BMI, physical activity and education (as a proxy of socioeconomic status) were considered as covariates in the multivariable analyses unless otherwise stated in the tables.

By considering hysterectomy as an indicator for the risk of CVD rather than the cause of the CVD based on our primary results, the attributable fraction (AF) was calculated for conditions associated with hysterectomy. AF is the proportion of CVD among hysterectomized women which would be prevented if none of these women had been hysterectomized. Attributable fractions (excess fraction %) were calculated by using this formula: "$100 \times (OR_{adj} - 1) / OR_{adj}$", where OR_{adj} is fully-adjusted odds ratio (dos Santos Silva 1999).

Weighting (survey analysis) was used to obtain results from the random sample that would be more generalizable to the source population. This applies to almost all the results presented in Study III and IV, either descriptive or regression analyses. All analyses were done using STATA statistical software 8th version.

5. Results

5.1. Pregnancy related factors and cardiovascular disease (Health 2000 Study)

Out of 3,840 women who answered the question "How many pregnancies have you had?" (gravidity), 13.4% never had any pregnancy. Among those with history of pregnancy, 16.5% had had abortion, 24.1% miscarriage, 2.8% stillbirth, 4.2% extrauterine pregnancy, 4.4% multiple pregnancy, and 5.3% toxemia. Out of those answering the question "How many deliveries have you had?" (parity), 16.5% were nulliparous. Among parous women, mean number of deliveries was 2.5 (range 1–16). Mean age at first delivery was 24.7 (range 15–46), whereas mean age at last delivery was 30.6 (range 15–48). Mean age at menopause was 48.5 and 90.5% of women over age 50 were menopausal. 22.4% of those who were menopausal had ever used postmenopausal hormone therapy. 56.4% of women had ever used oral contraceptives.

Out of 3,920 women, 3.2% answered affirmatively the question regarding MI; 7.1% had experience of angina pectoris, 6.7% reported heart failure/ cardiac insufficiency, 16.3% arrhythmia, 31.4% hypertension and 65.8% of this group were current users of medication for hypertension. Three percent reported stroke. The field physician's clinical examination showed lower prevalence of past MI, heart failure and arrhythmia than the self-report results, but angina pectoris and stroke were more common according to the physician's report (Reunanen *et al.* 2004a). Further rechecking by available source of information (physician's examination, hospital discharge, drug reimbursement registers and ECG) for CVD diagnosis for all subjects in Health 2000 showed angina pectoris was 3.2% higher than self-report. 0.4% of self-reported angina pectoris could not be confirmed by other sources. According to the above mentioned additional sources, false positive for self-reported MI was 1.1% and false negative was 0.6% compared to self-reported results.

5.2. Reproductive history and carotid intima-media thickness

The mean age of subjects in the IMT sub-sample (746 subjects) was 56.7 (SD: 8.2). After age-adjustment, no significant relation between IMT and reproductive history was observed (Table 1). Women with a history of stillbirth had higher IMT than other women, but the association was not statistically significant (Study I).

Table 1. Mean carotid IMT (mm) by parity, age at first/last delivery, miscarriage, stillbirth, oral contraceptive (OC) ever use, hysterectomy, age at hysterectomy and postmenopausal hormone therapy (HT) ever use

			P-value			Adjusted* coefficient
	Number	Mean IMT	Crude	Age-adjusted	Adjusted*	
Parity						
0	110	0.893	0.92	0.92	0.67	-0.011
1**	169	0.891				
2–3	392	0.895	0.83	0.92	0.66	-0.008
≥ 4	72	0.955	0.03	0.97	0.52	-0.019
Age at first delivery						
	633	0.900	0.15	0.42	0.74	-0.001
Age at last delivery						
	633	0.900	0.76	0.74	0.67	-0.001
Miscarriage						
No**	583	0.902				
Yes	159	0.891	0.58	0.67	0.68	-0.008
Stillbirth						
No**	706	0.899				
Yes	15	0.984	0.12	0.20	0.30	0.065
Oral contraceptive use ever						
No**	280	0.958				
Yes	463	0.864	0.00	0.48	0.28	0.019
Hysterectomy						
No**	342	0.820				
Yes	111	0.912	0.00	0.58	0.34	0.022
Age at hysterectomy						
	93	0.926	0.76	0.06	0.34	0.022
Postmenopausal hormone therapy use ever						
No**	356	0.885				
Yes	387	0.912	0.08	0.76	0.40	0.013

* Adjusted for age, systolic and diastolic blood pressure, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity and BMI (all in the model)

** Reference group

The presence of plaque in any of the three images of the carotid bulb was used as a single variable in the logistic regression analysis to ascertain its association with some of reproductive history variables (Table 2). History of stillbirth was associated with an increased age-adjusted risk of plaque (OR: 3.43, 95% confidence interval (CI): 1.07–11.05); after adjustment for age, BMI, systolic and diastolic BP, fasting blood glucose, low-density lipoprotein and total cholesterol, education, smoking, and physical activity, it lost its statistical significance (OR: 2.73, 95% CI: 0.55–13.55; Figure 1). When gravidity was included in the model, the odds ratio decreased to 2.11 (95% CI: 0.41–10.95).

Table 2. Plaque by some reproduction factors and hysterectomy

	Plaque		Crude			Age-adjusted			Adjusted*		
	No	Yes	OR	95% CI		OR	95% CI		OR	95% CI	
Parity											
0	81	15	1.28	0.61	2.65	1.17	0.54	2.51	1.29	0.51	3.28
1	131	19	1.00**			1.00			1.00		
2–3	315	42	0.92	0.52	1.64	0.91	0.50	1.65	0.96	0.47	1.96
≥ 4	47	18	2.64	1.28	5.46	1.84	0.86	3.94	1.76	0.69	4.46
Age at first delivery											
	493	79	0.96	0.91	1.01	0.96	0.91	1.02	0.97	0.90	1.05
Age at last delivery											
	493	79	1.01	0.97	1.06	1.02	0.97	1.06	1.03	0.98	1.09
Miscarriage											
No	453	70	1.00**	1.29	0.00	1.00			1.00		
Yes	120	24	1.29			1.34	0.79	2.28	1.42	0.75	2.66
Stillbirth											
No	553	86	1.00**			1.00			1.00		
Yes	9	5	3.57	1.17	10.91	3.43	1.07	11.05	2.73	0.55	13.55
Oral contraceptive use ever											
No	206	51	1.00**			1.00			1.00		
Yes	368	43	0.47	0.30	0.73	1.07	0.63	1.81	1.38	0.73	2.62
Hysterectomy											
No	280	30	1.00**			1.00			1.00		
Yes	88	11	1.17	0.56	2.42	0.35	0.14	0.87	0.40	0.14	1.18
Age at hysterectomy											
	75	9	1.09	1.00	1.18	1.04	0.96	1.13	1.04	0.88	1.23
Postmenopausal hormone therapy use ever											
No	281	45	1.00**			1.00			1.00		
Yes	293	49	1.04	0.67	1.62	0.94	0.60	1.49	1.11	0.63	1.95

* Adjusted for age, systolic and diastolic blood pressure, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity and BMI (all in the model)

** Reference group

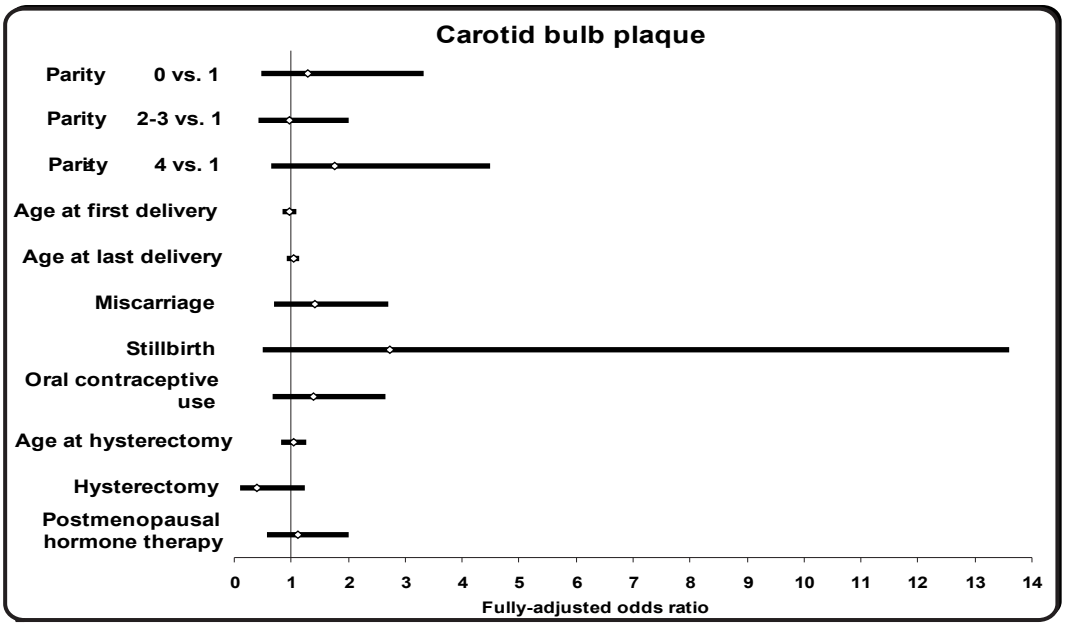

Figure 1. Some reproductive factors, hysterectomy and carotid bulb plaque (adjusted for, age, systolic and diastolic blood pressure, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity, and BMI)

5.3. Hypertension in pregnancy and long term mortality

Cardiovascular mortality was significantly higher among women with systolic hypertension in early or late pregnancy. There was an approximate 20% increase in cardiovascular mortality for every 13 mmHg (one standard deviation) rise in systolic BP in early pregnancy (Table 3 and Figure 2) and a 14% increase in cardiovascular mortality for rises of one standard deviation in late pregnancy. When stratified by proteinuria, the odds ratio increased for women with proteinuria in late pregnancy.

Table 3. Hazard ratio* (95% CI) for all cause and cardiovascular disease (CVD) mortality associated with an SD† increase in blood pressure of early pregnancy

	All cause mortality	CVD mortality		
	All women	All women	Women with no proteinuria	Women with proteinuria
Early pregnancy	(858 events)	(272 events)	(267 events)	(2 events)
Systolic blood pressure	1.09 (1.01, 1.16)	1.18 (1.05, 1.33)	1.18 (1.05, 1.34)	Too few cases (14)
p value	*0.020*	*0.008*	*0.006*	*included in analysis*
Diastolic blood pressure	1.03 (0.96, 1.11)	1.06 (0.93, 1.20)	1.06 (0.93, 1.21)	Too few cases (14)
p value	*0.404*	*0.394*	*0.363*	*included in analysis*
Late pregnancy	(800 events)	(249 events)	(232 events)	(12 events)
Systolic blood pressure	1.07 (1.00, 1.14)	1.14 (1.02, 1.28)	1.14 (1.00, 1.28)	1.77 (1.02, 3.06)
p value	*0.053*	*0.025*	*0.043*	*0.042*
Diastolic blood pressure	1.00 (0.93, 1.07)	1.03 (0.91, 1.18)	0.99 (0.87, 1.14)	1.92 (1.03, 3.58)
p value	*0.979*	*0.607*	*0.936*	*0.041*

* Adjusted for hormone use, age, height, marital status, and visit to private doctor
† Standard deviation for the first and second measurements: systolic 13.0; diastolic 11.0
‡ Interaction between blood pressure and presence or absence of protein

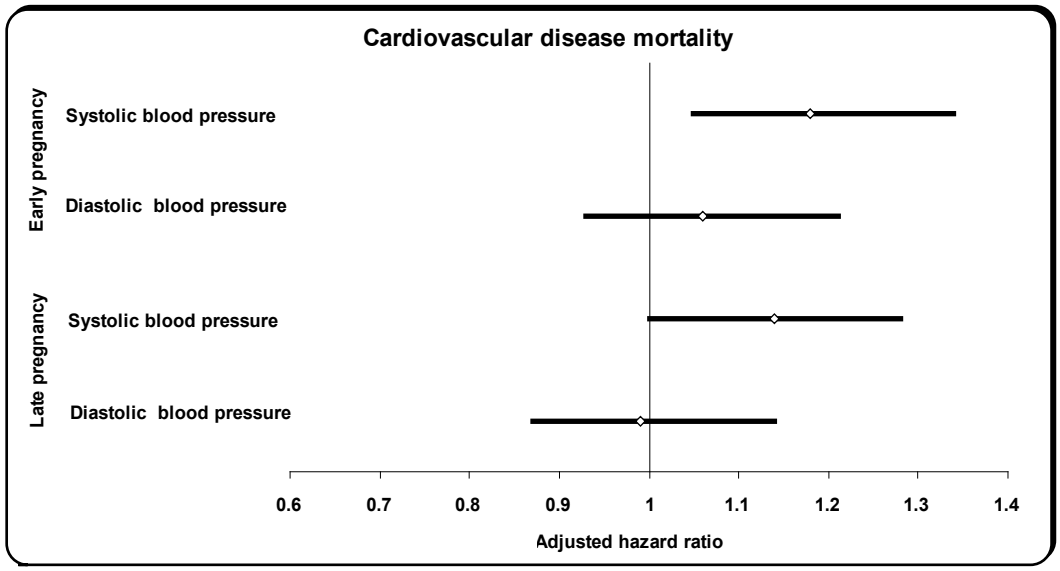

Figure 2. Hazard ratio and 95% confidence interval for cardiovascular disease mortality associated with one standard deviation increase in blood pressure in women with no proteinuria adjusted for hormone use, age, height, marital status, and visit to private doctor

When stratified by parity, only primiparas with systolic hypertension and proteinuria in late pregnancy had a higher risk of cardiovascular death than normotensive controls (Table 4 and Figure 3). Adjustment for available factors did not substantially change the results. When stratified by parity the association between diastolic hypertension and cardiovascular mortality did not reach statistical significance.

Table 4. Cardiovascular mortality among women with systolic blood pressure (BP) ≥ 140 or diastolic BP ≥ 90 with (+ prot) or without (- prot) proteinuria by parity (HR = Hazard Ratio)

	CVD deaths		Age-adjusted HR		Adjusted* HR	
	+ prot (N)	- prot (N)	+ prot 95% CI	- prot 95% CI	+ prot 95% CI	- prot 95% CI
Systolic						
Primiparous women	27	39	1.46 (1.10, 1.92)	0.87 (0.61, 1.25)	1.42 (1.06, 1.90)	0.90 (0.62, 1.30)
Parous women	45	98	1.14 (0.90, 1.44)	1.18 (0.99, 1.40)	1.11 (0.87, 1.43)	1.17 (0.98, 1.41)
Diastolic						
Primiparous women	27	39	1.33 (0.97, 1.82)	0.84 (0.60, 1.18)	1.31 (0.95, 1.79)	0.85 (0.60, 1.20)
Parous women	45	98	1.11 (0.82, 1.49)	1.01 (0.82, 1.24)	1.16 (0.85, 1.58)	1.02 (0.82, 1.27)

* Adjusted for hormone use, age, height, marital status, and visit to private doctor.

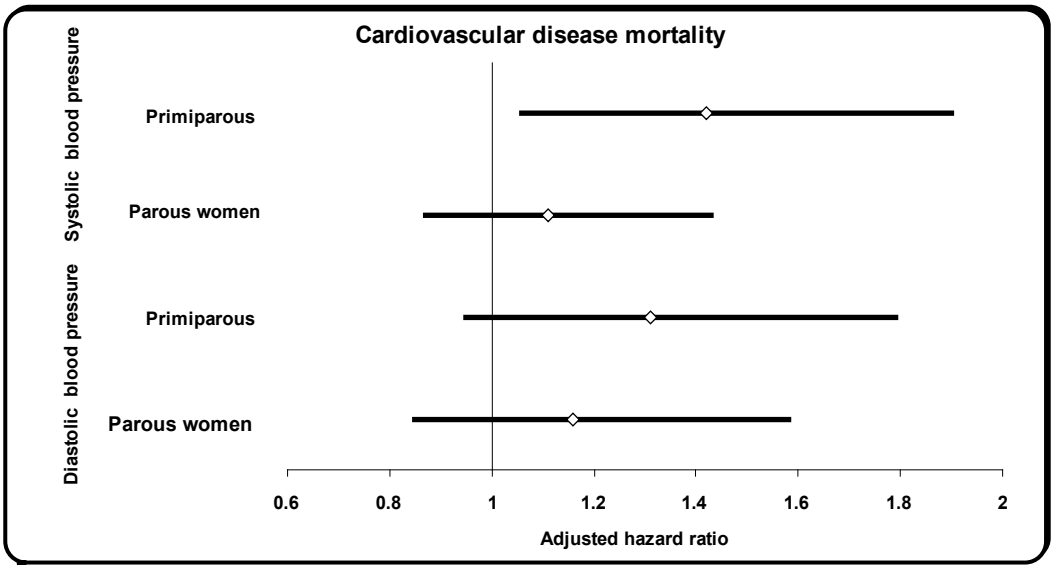

Figure 3. Cardiovascular mortality among women with systolic blood pressure ≥ 140 or diastolic blood pressure ≥ 90 and proteinuria by parity adjusted for hormone use, age, height, marital status, and visit to private doctor

5.4. Reproduction and isolated systolic hypertension

Out of 3,470 subjects whose BP data was available, 26% had ISH (Study III). Age at first and last delivery was significantly associated with age, height, education, marital status, and use at any time of HT; age at first delivery was also associated with toxemia in any pregnancy, weight and BMI (Table 5). In the univariable analyses ISH was significantly associated with age, height, weight, BMI, education, marital status, OC use past or present. The association of ISH and age was independent of educational status. However, the effect of education lost its statistical significance when age was added into the model. Logistic regression analyses were performed to find out the associations between ISH and pregnancy related variables (Table 6 and Figure 4). ISH was positively associated with parity, gravidity, earlier age at first delivery. Younger age at first delivery predicted a higher risk of ISH after considering age, weight, height, diastolic blood pressure, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, and physical activity in the fully-adjusted model (OR: 0.97; 95% CI: 0.94–0.99). Among subjects in whom no ISH was detected, 18% were using antihypertensive drugs. After adding use of antihypertensive medication in multivariable analysis, the association of ISH and early age at first delivery did not change substantially.

Table 5. Distribution of isolated systolic hypertension (ISH), age at first/last delivery by age group, height, weight, BMI, education, marital status, OC ever use, HT ever use, and toxemia

	ISH			Age at first delivery			Age at last delivery			
	No (n)	Yes (n)	P value	< 25 (%)	≥ 25	P value	≤ 30 (%)	> 30	P value	Total (N)*
Age group			<0.01			0.000			<0.01	
30–49	1499	67		43.6	56.4		43.6	56.4		1326
50–69	916	313		58.1	41.9		58.1	41.9		1124
70+	305	370		50.4	49.6		50.4	49.6		744
Height (cm)**	162.7	158.8	<0.01	161.1	162.1	<0.01	162.1	161.1	<0.01	3129
Weight (kg)**	70.0	70.7	0.025	70.8	69.2	<0.01	70.2	69.7	0.76	3136
BMI (kg/m^2)**	26.5	28.0	<0.01	27.4	26.4	<0.01	26.8	26.9	0.35	3122
Education			<0.01			<0.01			<0.01	
Basic level	933	476		64.9	35.1		53.5	46.5		1431
Middle level	798	146		51.9	48.1		54	46		846
High level	982	122		27.8	72.2		42.8	57.2		911
Marital status			<0.01			<0.01			<0.01	
Married	1541	349		48.9	51.1		50.3	49.7		1840
Living with partner	308	29		49.4	50.6		59.1	40.9		262
Divorced or separated	322	66		55.9	44.1		57.7	42.3		397
Widowed	262	239		55	45		40.2	59.8		614
Single	281	65		35.8	64.2		56.8	43.2		81
OC use ever			<0.01			0.34			<0.01	
No	891	491		51.6	48.4		46.5	53.5		1322
Yes	1808	248		49.7	50.3		53.1	46.9		1844
HT use ever			<0.01			0.040			0.04	
No	1895	469		48.2	51.8		47.5	52.5		2201
Yes	333	117		53.6	46.4		52.6	47.4		414
Toxemia in any pregnancy			0.16			0.05			0.13	
No	2337	497		94.0	6.1	1346	95.3	4.7		1403
Yes	101	30		95.5	4.5	1307	94.0	6.0		1250

* Total number for age at first/last delivery

** Mean value in each group of ISH (yes vs. no) was used.

Table 6. Isolated systolic hypertension (ISH) by some reproductive history variables

	Isolated systolic hypertension								
	Crude			Age-adjusted			Fully-adjusted***		
	OR	95% CI		OR	95% CI		OR	95% CI	
Parity*	1.20	1.13	1.27	1.02	0.96	1.08	1.02	0.96	1.08
Parous vs. nulliparous	1.14	0.88	1.47	0.98	0.74	1.30	0.97	0.73	1.30
Gravidity*	1.11	1.06	1.16	1.01	0.96	1.06	1.00	0.95	1.06
Abortion**	0.62	0.46	0.84	0.96	0.70	1.34	0.92	0.65	1.29
Miscarriage**	0.89	0.72	1.09	0.85	0.67	1.07	0.82	0.64	1.05
Stillbirth**	1.59	0.97	2.57	0.77	0.42	1.42	0.87	0.46	1.65
Age at first delivery*	0.96	0.95	0.98	0.96	0.94	0.98	0.97	0.94	0.99
Age at last delivery*	1.03	1.01	1.05	0.98	0.97	1.01	0.99	0.97	1.01
Multiple pregnancy**	1.33	0.90	1.99	1.06	0.65	1.74	0.97	0.58	1.63

* Used as continuous variable

** Used as binary variable (Yes / No)

*** Adjusted for age, weight, height, diastolic blood pressure, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity

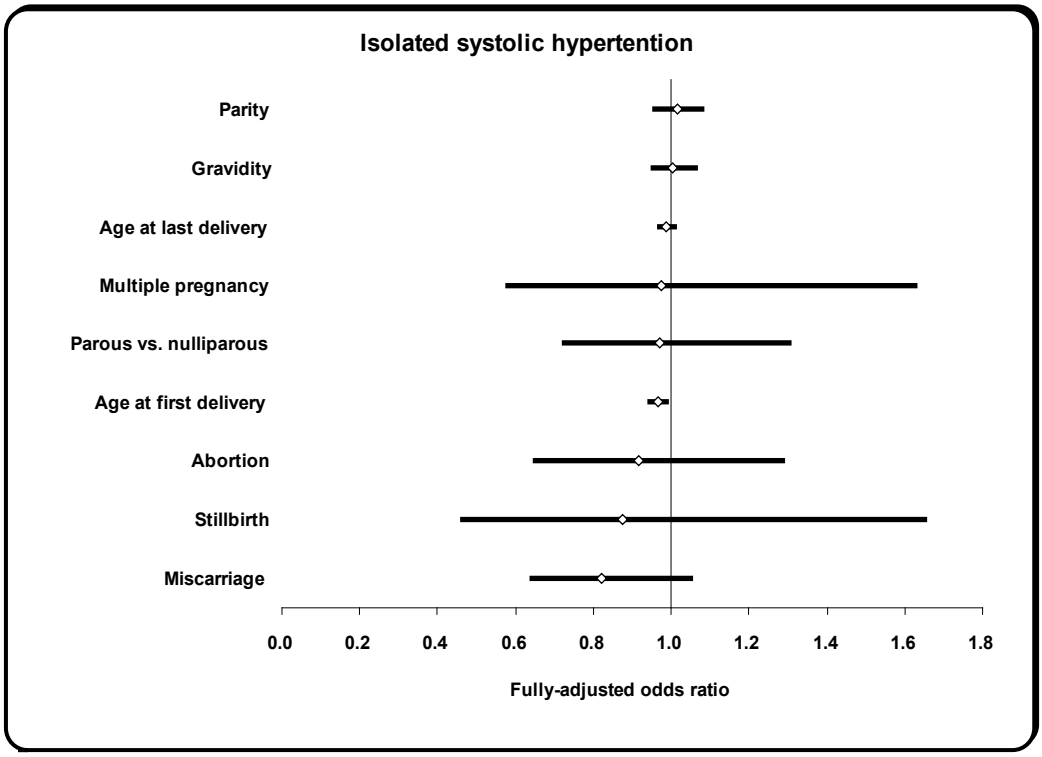

Figure 4. Isolated systolic hypertension by reproductive factors

5.5. Hysterectomy and cardiovascular disease

Thirty three percent of women aged 50 or older had undergone hysterectomy (Study IV). Out of all hysterectomized women 119 cases had hysterectomy and bilateral oophorectomy and in 246 cases uterus alone or uterus with one ovary had been removed.

Hysterectomy, hypertension, medication for hypertension, angina pectoris and stroke were significantly associated with age, education, OC use, HT use and BMI (Table 7). Only the association of medication for hypertension and stroke with HT use was not statistically significant. Hysterectomy was most common among the age group 50 to 69 and among women with basic level education. Hysterectomized women also had higher mean fasting blood glucose, cholesterol, and BMI compared to other women.

Hypertension, current use of medication for hypertension, angina pectoris, MI, stroke, heart failure and arrhythmia were positively associated with hysterectomy (regardless of type of categorization) in the univariable analysis. After adjustment for age, hysterectomized women (yes vs. no) still had a significantly increased risk of hypertension, current use of medication for hypertension and angina pectoris (Table 8). These associations were attenuated except for heart failure when we included fasting blood glucose, low-density lipoprotein and total cholesterol, education, smoking, BMI, physical activity and HT use in the multivariable model as our potential confounders (Figure 5).

Table 7. Baseline characteristics

	Hysterectomy					Hypertension			Current use of medication for hypertension			Angina pectoris			Stroke		
	No Hysterectomy	With/without unilateral oophorectomy	With bilateral oophorectomy	Total	P value**	Yes	Total	P value	Yes	Total	P Value	Yes	Total	P value	Yes	Total	P value
	(%*)	(%*)	(%*)	(N)		(%*)	(N)		(%*)	(N)		(%*)	(N)		(%*)	(N)	
Age group					< 0.01			< 0.01			< 0.01			< 0.01			< 0.01
30-49	95.7	3.9	0.4	1,623		16.1	1,662		5.7	1,658		0.1	1,663		0.4	1,662	
50-69	70.3	19.9	9.8	654		39.7	1,291		26.4	1,290		5.8	1,291		2.1	1,291	
70+	57.4	22.4	20.3	237		46.5	964		38.0	945		20.9	965		9.0	967	
Education					< 0.01			< 0.01			< 0.01			< 0.01			< 0.01
Basic level	74.3	16.8	9.0	781		41.9	1,708		30.7	1,694		12.2	1,706		5.3	1,711	
Middle level	88.8	9.1	2.1	748		26.7	1,028		15.0	1,022		5.0	1,028		1.8	1,027	
High level	91.9	4.8	3.4	982		20.1	1,169		10.0	1,165		1.5	1,170		1.0	1,169	
OC use ever					< 0.01			< 0.01			< 0.01			< 0.01			< 0.01
No	75.6	15.1	9.3	688		41.4	1,657		31.5	1,653		13.7	1,655		5.6	1,657	
Yes	89.7	7.5	2.8	1,791		23.7	2,146		12.3	2,146		1.6	2,146		0.8	2,146	
HT use ever					< 0.01			< 0.01			0.06			0.02			0.24
No	91.5	5.9	2.6	1,821		29.3	2,684		19.4	2,681		6.7	2,683		3.1	2,684	
Yes	77.9	16.1	6.0	267		36.0	475		23.2	474		9.7	475		2.1	475	
Body mass index					< 0.01			< 0.01			< 0.01			< 0.01			< 0.01
BMI < 18.5	96.3	3.7	0.0	27		13.7	51		3.9	51		10.0	50		2.0	51	
18.5 ≤ BMI < 25	90.0	6.7	3.2	1,145		18.8	1,539		10.8	1,531		4.2	1,539		3.0	1,540	
25 ≤ BMI < 30	83.6	10.8	5.6	803		34.7	1,320		21.9	1,309		8.2	1,319		2.1	1,319	
BMI ≥ 30	78.1	15.0	6.9	539		47.0	1,007		33.8	1,002		9.9	1,011		4.7	1,010	

* Row percentage
** Chi-square test

Table 8. Hysterectomy by cardiovascular disease

	Hypertension										Current use of medication for hypertension									
	No*	Yes	Crude		Age-adjusted		Adjusted**				No*	Yes	Crude		Age-adjusted		Adjusted**			
	n	n	OR	95% CI	OR	95% CI	OR	95% CI			n	n	OR	95% CI	OR	95% CI	OR	95% CI		
No hysterectomy*	1,707	442									1940	205								
With/without unilateral oophorectomy	147	99	2.55	1.95	3.33	1.45	1.09	1.94	1.17	0.75	1.84	173	72	3.92	2.92	5.26	1.92	1.37	2.68	1.90	1.10	3.28
With bilateral oophorectomy	69	50	2.72	1.83	4.06	1.26	0.82	1.94	0.87	0.40	1.89	74	45	5.66	3.67	8.75	2.14	1.32	3.48	1.71	0.74	3.93
Hysterectomy any type	216	149	2.60	2.06	3.29	1.39	1.08	1.79	1.10	0.71	1.68	247	117	4.43	3.41	5.75	1.98	1.48	2.67	1.85	1.12	3.05
	Angina pectoris										Myocardial infarction									
No hysterectomy*	2,122	26									2129	19								
With/without unilateral oophorectomy	229	17	5.35	2.69	10.64	1.85	0.85	4.02	2.09	0.57	7.70	238	8	3.77	1.63	8.70	1.37	0.57	3.27	0.16	0.02	1.26
With bilateral oophorectomy	106	13	9.85	4.52	21.46	2.36	0.99	5.61	1.09	0.21	5.69	116	3	2.90	0.84	9.94	0.64	0.18	2.28	NC	NC	NC
Hysterectomy any type	335	30	6.74	3.66	12.42	2.04	1.02	4.08	1.69	0.52	5.52	354	11	3.04	1.26	7.31	0.87	0.34	2.21	0.11	0.01	1.09
	Heart failure										Stroke									
No hysterectomy*	2,110	37									2129	20								
With/without unilateral oophorectomy	230	16	4.84	2.71	8.64	1.65	0.85	3.20	2.26	0.83	6.14	234	12	4.80	2.35	9.77	1.84	0.90	3.77	1.23	0.37	4.07
With bilateral oophorectomy	109	10	5.56	2.58	11.98	1.23	0.53	2.85	2.28	0.74	7.00	111	8	7.70	3.07	19.30	2.13	0.79	5.76	1.72	0.37	7.93
Hysterectomy any type	339	26	5.07	3.07	8.37	1.48	0.85	2.60	2.27	0.96	5.36	345	20	5.71	2.99	10.89	1.95	0.99	3.83	1.40	0.51	3.80

* Reference group

** Adjusted for age, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, body mass index, postmenopausal hormone therapy, physical activity for all and systolic and diastolic blood pressure in addition only for angina pectoris and stroke

*** NC=Not calculable

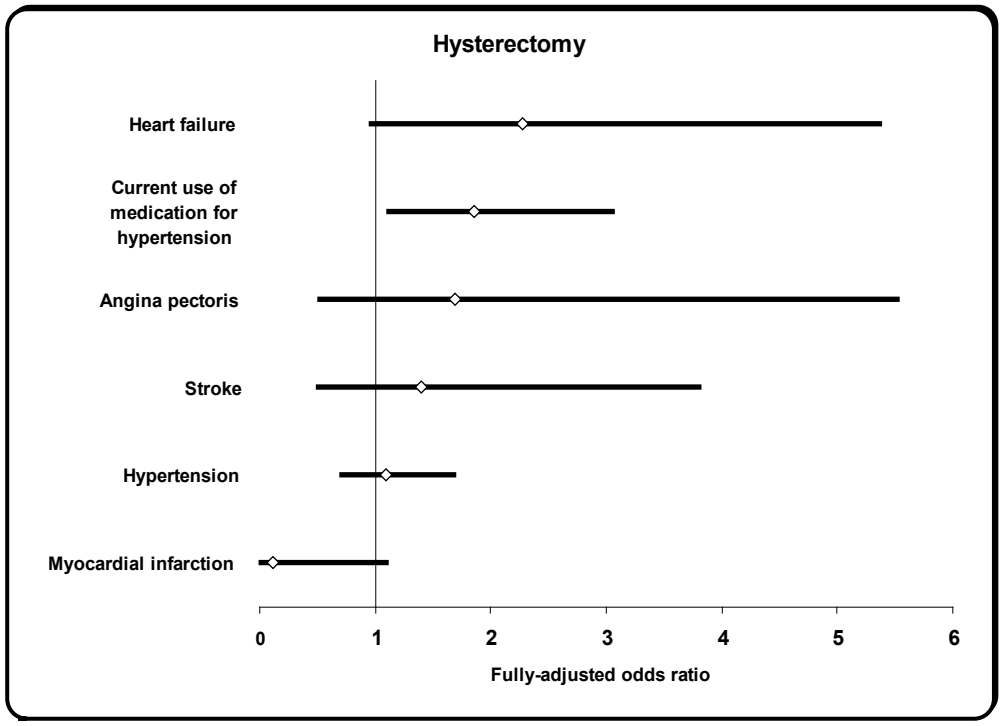

Figure 5. Hysterectomy (yes vs. no) and cardiovascular disease (ORs adjusted for age, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, body mass index, postmenopausal hormone therapy, and physical activity for all and also systolic and diastolic blood pressure except for hypertension and current use of medication for hypertension)

We also conducted another analysis using the variables available in our dataset for year of hysterectomy and year of first diagnosis of hypertension to assess the temporality of hysterectomy as our adopted exposure and hypertension as its assumed outcome. In 63% of hysterectomized women who also had hypertension, hysterectomy was done before diagnosis of hypertension and in the remaining 37% diagnosis for hypertension was prior to hysterectomy.

To further elucidate the effect of hysterectomy with and without preservation of ovaries, we made a three-stage categorical variable for status of hysterectomy (no hysterectomy, hysterectomy alone/hysterectomy with unilateral oophorectomy, and hysterectomy with bilateral oophorectomy). In the multinomial logistic regression analyses with this categorical variable,

we found the increased risk of hypertension (OR: 1.45, 95% CI: 1.09–1.94) and medication for hypertension (OR: 1.92, 95% CI: 1.37–2.68) for hysterectomized women with preservation of at least one ovary compared to not hysterectomized women after adjustment for age as a main potential confounder. After further adjustment for fasting blood glucose, low-density lipoprotein and total cholesterol, smoking, BMI, physical activity, education, and HT use as potential confounders, odds ratios remained significant only for current user of antihypertensive medication (OR: 1.90, 95% CI: 1.10–3.28). Hysterectomized women with bilateral oophorectomy were more likely to be current users of antihypertensive medication (age-adjusted OR: 2.14, 95% CI: 1.32–3.48) compared to women with intact uterus.

By considering hysterectomy as an indicator for the risk of CVD rather than as the cause of the CVD based on our results, the AF were calculated for conditions associated with hysterectomy. The proportion of hypertension among hysterectomized women which would be prevented if none of them had been hysterectomized (AF) was 8.7%. For current use of medication the AF was 46.0%. AF of hysterectomy for stroke was 28.5%.

6. Discussion

Women with a history of stillbirth tended to have higher IMT than other women. A history of stillbirth was associated with an increased age-adjusted risk of plaque but in the fully-adjusted model it lost its statistical significance (fully-adjusted OR: 2.73; 95% CI: 0.55–13.55). Cardiovascular mortality was significantly higher among women with systolic hypertension in early (adjusted HR: 1.18; 95% CI: 1.05–1.34) or late pregnancy (adjusted HR: 1.14; 95% CI: 1.00, 1.28). Younger age at first delivery predicted a higher risk of ISH (fully-adjusted OR: 0.97; 95% CI: 0.94–0.99). Age at first and last delivery was significantly associated with age, education and marital status; age at first delivery was also associated with toxemia in any pregnancy, weight and BMI. Hysterectomy was significantly associated with hypertension, medication for hypertension, angina pectoris, stroke, age, education, postmenopausal hormone therapy, BMI, fasting blood glucose and cholesterol. The fully-adjusted ORs for an association between CVD and hysterectomy were dramatically lower than the crude ORs and remained statistically significant only for medication for hypertension (fully-adjusted OR: 1.85; 95% CI: 1.12–3.05). Whether reproduction, which is associated with a variety of hormonal and metabolic changes, affects cardiovascular system as well, is still uncertain. Association between hysterectomy, as the most common non-obstetric surgery in women, and CVD is as yet another debatable issue. In the following sections main results of Studies I, II, III and IV are discussed, particularly in relation to earlier studies.

6.1. Parity

Mean carotid IMT was not significantly associated with parity after adjustment for age although women with higher parity tended to have higher IMT.

Therefore, the effect might have been due to the fact that those women with high parity number are usually older and age was strongly associated with IMT (Study I). Further adjustment for BP, fasting blood glucose, low-density lipoprotein and cholesterol, education, smoking, BMI, and physical activity did not substantially change the result. Nulliparous women (fully-adjusted OR: 1.29; 95% CI: 0.51–3.28) and those with more than 3 deliveries (fully-adjusted OR: 1.76; 95% CI: 0.69–4.46) tended to have higher risk of plaque compared to those with 1 delivery, but the associations were not statistitically significant (Study I). Parity was not significantly associated with higher risk of ISH (fully-adjusted OR: 1.02; 95% CI: 0.96–1.08; Study III)

The hypothesis of a relation between the pregnancy experience of women and cardiovascular risk has a great deal of biological plausibility. Several studies have investigated this issue, yet produced conflicting results. Some investigations reported slightly higher mortality (Green *et al.* 1988; Ness *et al.* 1993) and a higher incidence of CHD (Lawlor *et al.* 2003) and ischemic stroke (Qureshi *et al.* 1997) with increasing number of births. But others reported no association (Steenland *et al.* 1996) or even found opposite effects with nulliparity or lower parity rates related to higher cardiovascular risk (Colditz *et al.* 1987b). Another study showed that nulliparity and higher numbers of children are associated with increased carotid IMT as a predictor of CVD (Wolff *et al.* 2005).

In the study by Green, the mortality for all circulatory diseases and specific conditions such as hypertensive disease, IHD, increased with parity, but the trends were not significant and the relative increase in mortality according to number of children was small. Moreover, they had considered only age and socioeconomic status of husband in their analyses and not other known risk factors of CVD. The findings of two large studies showed that women with six or more pregnancies had a small but consistent increase in the risk for coronary artery disease (Ness *et al.* 1993) and cerebrovascular disease (Qureshi *et al.* 1997). In both studies, an adjustment for a variety of cardiovascular risk factors had little effect on the estimates of rate ratios. Because the strength of the observed association was slight, it is not clear whether parity itself or some other unmeasured factor was actually responsible for that elevated risk.

In the Lawlor study number of children was positively associated with BMI and waist-hip ratio in both sexes. Number of children was inversely associated with high-density lipoprotein (HDL) cholesterol and was positively associated with triglycerides and diabetes (Lawlor *et al.* 2003).

Parity is known to be strongly related to education (Strand *et al.* 2005). Women with lower education are also known to have higher parity, which may be one factor related to other health behaviors and reproductive profile. One reason for an increased risk of heart disease associated with parity may be the small sustained drop in HDL cholesterol found after pregnancy, along with a positive association between parity and adiposity, particularly abdominal fat (Kaye *et al.* 1990). Hankinson et al. measured plasma estrogen levels in a sample of 216 subjects and found that plasma estrogen levels were lower among women with high parity and those with young age at first birth, after controlling for BMI, alcohol consumption and age. The lower endogenous estrogen level is consistent with a lower HDL cholesterol level and with heart disease (Hankinson *et al.* 1995). It therefore seems the positive association between parity and CVD found in some earlier studies were mediated by known risk factor of cardiovascular disease or some other unmeasured risk factors.

6.2. Age at first/last delivery

Younger age at first delivery showed higher risk of ISH (odds ratio after adjustment for age, height, weight diastolic BP, fasting blood glucose, low-density lipoprotein and total cholesterol, education, smoking, and physical activity: 0.97; 95% CI: 0.94–0.99; Study III). The women with first delivery before age 25 had a significantly higher risk of ISH than those with first delivery after this age (odds ratio after adjustment for age, education, BMI, and smoking: 1.57, 95% CI: 1.12–2.20). A similar association was found for women with last delivery before age 30 (adjusted OR 1.46, 95% CI: 1.04–2.03).

Some conditions which change the estrogen level, such as pregnancy and childbirth, are accompanied by substantial changes in metabolism as well as in

endocrine regulation and activity. Not only do these alterations concern altered blood lipoprotein levels (Fahraeus *et al.* 1985; Lewis *et al.* 1996), but also structural and functional changes of cardiovascular regulation (Sadaniantz *et al.* 1996; Clapp and Capeless 1997).

A large retrospective cohort study found no significant association between age at first delivery and CHD (Colditz *et al.* 1987b). Some other studies found that the women who had their first delivery before age 25 appeared to be at higher risk of CHD (Beard *et al.* 1984; La Vecchia *et al.* 1987; Palmer *et al.* 1992) and IHD (Guo *et al.* 1992).

Age at first delivery is known to be closely related to education (Strand *et al.* 2005). The trend in the population is to postpone the first delivery. Women with less education are known to be younger at first delivery. Serum sialic acid has attracted attention as a possible cardiovascular risk factor as well as a potential marker. Serum sialic acid is elevated during pregnancy and post-partum (Crook *et al.* 1997). Hypertensive disorders of pregnancy have been reported to be more common in younger mothers (Scholl *et al.* 1994) who have a known risk of long-term CVD (Hannaford *et al.* 1997; Gifford 2000; Wilson *et al.* 2003; Arnadottir *et al.* 2005). Further studies are needed to explain the mechanisms behind the increasing risk of CVD with earlier age at first delivery.

6.3. Multiple pregnancy

The association between multiple pregnancies and ISH was not significant in Study III (age-adjusted OR: 0.97, 95% CI: 0.58–1.63). Multiple pregnancy shows an association with hypertension as a major maternal complication (Senat *et al.* 1998). Women with multiple gestations showed higher risk of eclampsia and pre-eclampsia (Conde-Agudelo *et al.* 2000). The higher incidence of pre-eclampsia has been related to a larger placenta in multiple gestations, which exposes the mother to more paternal antigen. Multiple gestations are happening increasingly in nulliparous and older mothers, so it is not surprising that the incidence of gestational hypertension and pre-eclampsia among these women is significantly increased compared with singleton

pregnancies (Smith-Levitin and Vohra 2005). The clinical manifestations of pre-eclampsia are usually earlier in its onset, more severe and often atypical in patients with twins and higher order multiples (Smith-Levitin and Vohra 2005). On the other hand, early-onset and severe pre-eclampsia predict an excess risk of subsequent cardiovascular morbidity and mortality (Arnadottir *et al.* 2005). Study III could not show any significant association between multiple pregnancy and ISH, possibly due to the small number of events in the data (168 out of 3,840).

6.4. Hypertension in pregnancy

In the 44-year follow-up (Study II), women with systolic BP ≥ 140 mmHg in early or late pregnancy had a significantly increased risk of cardiovascular death. This supports the theory that BP and metabolic responses occurring during pregnancy may be important and as yet unrecognized predictors of a special risk of several distinct cardiovascular conditions later in life (Hannaford et al. 1997). Irgens et al. showed that primiparas who had pre-eclampsia and preterm deliveries had an eightfold risk of death from CVD (95% CI: 4.3–15.3) (Irgens et al. 2001). Immunologic or an immunogenetic event early in pregnancy is one of the theories proposed as an etiology for pre-eclampsia (Smith-Levitin and Vohra 2005). From an Icelandic long follow-up study it emerged that there is an increased risk of death from IHD and cerebrovascular events in women suffering from hypertension in pregnancy compared with normotensive controls (Arnadottir et al. 2005). Likewise, a working group in the United States concluded that increased future health risks are heralded by recurrent hypertension in pregnancy, pre-eclampsia in a multipara, or early-onset disease in any pregnancy (Gifford 2000). Hypertensive diseases of pregnancy seem to be associated in later life with diseases related to hypertension such as stroke and IHD (Wilson et al. 2003; Kaaja and Greer 2005).

Systolic hypertension in pregnancy with proteinuria might suggest a 46% increased risk of cardiovascular mortality among primiparous women in Study II. This finding was in line with earlier studies showing an increased risk of

CVD mortality among pre-eclamptic women. If greater awareness of these associations leads to earlier diagnosis and improved management, there may be a potential to reduce the proportion of morbidity and mortality from such diseases. In addition, the paradigm has shifted from diastolic BP to systolic BP, since large trials among non-pregnant women have shown that treatment of ISH has lowered the rates of CVD and even all-cause mortality (Black 2004). Correspondingly, clinical attention also needs to be focused on systolic hypertension in pregnancy.

6.5. Stillbirth

There was a significant relation between having plaque and the number of stillbirths as a continuous variable (Study I). After adjustment for age and potential life style-related confounding factors such as smoking, BMI, and length of education, the result was of borderline significance. After adjustment for age, systolic and diastolic BP, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity and BMI, the association was not statistically significant (OR: 2.73; 95% CI: 0.55–13.55). As there were a few subjects with stillbirth higher than one in our dataset, we made a binary variable for stillbirth (yes/no) to increase the interpretability of the results. Using stillbirth as a binary variable showed the same positive association with plaque even after age adjustment. ISH and stillbirth showed no significant association (after adjustment for age, weight, height, diastolic BP, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, and physical activity, OR:0.87; 95% CI: 0.46–1.65; Study III). As our studies were cross-sectional, the direction of the relationship that we found is not obvious. Therefore, it seems that stillbirth is an outcome due to the effect of CVD (for instance, hypertension) in mothers rather than a causative risk factor for atherosclerosis. This theory is in line with earlier findings that show mothers with hypertensive disorders during pregnancy have a higher risk of stillbirth (Page and Christianson 1976; Plouin *et al.* 1986; Ananth *et al.* 1995; Gupta *et al.* 1996; Yadav *et al.* 1997; Simpson 2002; Vintzileos *et al.* 2002; Fretts 2005). Hypertension and diabetes have been shown to be responsible

for a significant proportion of fetal deaths. The most prevalent risk factor for stillbirth after late maternal age and low socioeconomic status is prepregnancy obesity (Fretts 2005). On the other hand, maternal obesity is associated with hyperlipidemia and clinically significant atherosclerosis (Mokdad *et al.* 2003). It seems more rational that stillbirth is an outcome due to the effect of CVD although our studies with cross-sectional design cannot provide evidence for this issue.

6.6. Hysterectomy

Study I did not show any significant association between hysterectomy and plaque after considering age, systolic and diastolic BP, fasting blood glucose and cholesterol, low-density lipoprotein, education, smoking, physical activity, and BMI in the multivariable model. Some studies have shown hysterectomy with ovarian preservation to be associated with risk of CVD (Luoto et al. 1995; Howard et al. 2005), and others showed this effect only for hysterectomy with bilateral oophorectomy (Rosenberg et al. 1981; Hsia et al. 2003; Kannel and Levy 2004; Boynton-Jarrett et al. 2005), whereas some other studies found no association between hysterectomy and CVD (Falkeborn et al. 2000; Iversen et al. 2005).

In a nationally representative sample we assessed the association of hysterectomy and CVD (Study IV). The association was significantly positive for hypertension, current use of medication for hypertension and angina pectoris for hysterectomized women compared to subjects who had not undergone this procedure. Hysterectomized women also had higher mean fasting blood glucose and cholesterol, and BMI, which are known risk factors of CVD. The fully-adjusted ORs for association between CVD and hysterectomy were dramatically lower than the crude ORs and remained significant only for medication for hypertension. These results were in line with the large observational study of the Women's Health Initiative (Howard *et al.* 2005) that higher cardiovascular risk in hysterectomized women may be due to the more adverse initial risk profile of women who had undergone hysterectomy rather than to the operation per se.

We found a significant positive association between hysterectomy and hypertension and use of medication for hypertension after age adjustment, which is in line with several earlier studies (Koepsell *et al.* 1980; Rosenberg *et al.* 1981; Luoto *et al.* 1995; Settnes and Jorgensen 1999; Kannel and Levy 2004; Boynton-Jarrett *et al.* 2005; Settnes *et al.* 2005). We also found this association of hysterectomy with angina pectoris.

In our population-based dataset, 63% of hysterectomized women who also had hypertension, hysterectomy had been done prior to diagnosis of hypertension and in the remaining 37% diagnosis for hypertension preceded hysterectomy. However, the onset of hypertension may occur years before the year of clinical diagnosis. On the other hand, as these 37% subjects with hypertension went through indication for hysterectomy, the most frequent reason for recommending it being myoma, these findings may confirm the results from some earlier studies suggesting a parallel pathogenesis for hypertension and myoma (Luoto *et al.* 1995) or which have found hypertension to be associated with uterine leiomyomata risk (Koepsell *et al.* 1980; Luoto *et al.* 1995; Faerstein *et al.* 2001; Luoto *et al.* 2001; Aboyeji and Ijaiya 2002; Luoto 2002; Boynton-Jarrett *et al.* 2005). A large prospective cohort study showed that every 10 mmHg increase in BP led respectively to an 8 percent and 9 percent increase in risk for hysterectomy-confirmed fibroids among women untreated and treated with antihypertensive medications respectively (Boynton-Jarrett *et al.* 2005).

We found the increased risk of hypertension (OR: 1.45, 95% CI: 1.09–1.94) and medication for hypertension (OR: 1.92, 95% CI: 1.37–2.68) for hysterectomized women with preservation of at least one ovary compared to not hysterectomized after adjustment for age to be a main potential confounder. Removal of one ovary or of the uterus could increase the risk of developing CHD (Punnonen *et al.* 1987; Luoto *et al.* 1995) by reducing the estrogen level or being associated with other endocrine changes (Centerwall 1981). Alternatively, conditions leading to surgery such as benign leiomyoma inducing menorrhagia may involve a hormonal imbalance (Rein *et al.* 1995).

After considering potential cardiovascular risk factors in multivariable models, we found no significant association between hysterectomy and some

other CVD such as arrhythmia, MI, and heart failure, consistent with some earlier studies (Luoto *et al.* 1995; Iversen *et al.* 2005).

By considering hysterectomy as an indicator for the risk of CVD rather than as the cause of the CVD in light of our results, the AF were calculated for conditions associated with hysterectomy. However, 3–14% of CVD in the whole female population could be attributed to conditions associated with hysterectomy. These measures of population impact suffer from a number of limitations. First, the assumption behind the formula of AF is the causality association, so it has been assumed that hysterectomy is causally associated with CVD. The fact that the adjusted ORs were dramatically lower than the crude ORs is a strong indicator that it is other CVD risk factors rather than hysterectomy itself which are responsible for the association between hysterectomy and the CVD endpoints. Our interpretation includes that hysterectomized women had more adverse risk profile of CVD and moreover hysterectomy may be a marker of cardiovascular risk, the original reason being benign leiomyomas. The possibility that hysterectomy increases the risk of CVD through loss of protecting factors in the endometrium remains unresolved. Second, it has been assumed that there is no residual confounding or bias in the calculated odds ratios.

A large prospective cohort study demonstrated a strong and independent association between BP and fibroid risk. Uterine fibroids are the most common gynecological tumor and the second largest indication for hysterectomies annually (Boynton-Jarrett *et al.* 2005). The other common indications for hysterectomy are abnormal uterine bleeding, endometriosis, pelvic pain, and pelvic organ prolapse. Although hysterectomy is an appropriate therapeutic option for some women with these conditions, several new technologies reduce the need for hysterectomy (Bongers *et al.* 2004), so in many instances less radical alternatives may be offered.

6.7. Strengths and limitations of the study

The random sample with high response rate in the Health 2000 Study and using weighting in the analysis can be considered as indicators of the high

external validity of our results from the Health 2000 Study. The fact that this was a representative sample of Finnish women and the access to all the important confounders was the strength of the study. Although people in Finland, as elsewhere, have been less keen to participate in survey studies over the past few decades, the results of Health 2000 are close to those achieved 20 years ago in the Mini-Finland Health Survey. Indeed, the participation was markedly higher than in any other recent Finnish survey. High participation is crucially important in that it reduces the major biases otherwise caused by non-response. Participation in Health 2000 was exceptionally good: counted on the basis of all persons for whom at least part of the information was obtained, the rate of participation was 93% (Aromaa and Koskinen 2004). However, the cross-sectional design of our studies caused some limitations. Especially in the case of longer-lasting diseases, such as CVD, any risk factor that results in death will be under-represented among those with the disease. The survey was carried out at one time point and gives no indication of the sequence of events, whether exposure occurred before, after or during the onset of the disease outcome. This being so, it is impossible to infer causality from the results of these cross-sectional studies. A further limitation of these studies may be due to errors in recall of the exposure and possibly outcome. CVD status and all pregnancy-related factors and hysterectomy variables were self-reported. However, reasonable validity for self-report of hysterectomy was reported (Colditz *et al.* 1987a). The field physician's clinical examination showed lower prevalence of past MI, heart failure and arrhythmia than the self-report results but angina pectoris and stroke were more common according to the physician's report (Reunanen *et al.* 2004a). Further rechecking by sources of information available (physician's examination, hospital discharge, drug reimbursement registers and ECG) for CVD diagnosis for these subjects showed angina pectoris was 3.2% more common than in self-report. On the other hand, only 0.4% of self-reported angina pectoris could not be confirmed by other sources. According to the above-mentioned additional sources, false positive for self-reported MI was 1.1% and false negative was 0.6% compared to self report. Information on systolic and diastolic BP, fasting blood glucose and cholesterol, and BMI were obtained from direct physical examinations and

laboratory tests in studies using the Health 2000 Study. There were no missing values for age, education, BMI and smoking in these studies, although we had some missing values in other variables, particularly in reproductive factors. However, the magnitude of the missing values was not large and did not have a major effect on the results.

The best study design for investigating associations between reproductive history and CVD is cohort study, which has its own limitations, such as long lag time between child bearing and occurrence of CVD in women. Research of this kind needs more financial resources and is time consuming. A future prospective section of the Health 2000 Study can also give more useful information on this topic.

Record linkage in a setting with the existence of a unique national identification number can be considered as the best possible quick method for evaluation of long-term complications of exposures. The Finnish cause-of-death registry is also a highly valid source for mortality as an outcome variable, because information on death and its cause(s) covers all the Finnish population and these items are precisely recorded there. In Study II (a 44-year follow-up), the collected data from another study were used which were originally intended to assess exposure to female hormone drugs during pregnancy and its effect on malformations and cancer. For this purpose, a systematic sample of half of the boxes containing the maternity cards (in Helsinki municipality archives) was searched to identify all mothers who had given birth in a specified period of time and who were prescribed estrogen and progestin drugs. For each exposed mother the next mother in the file who had given birth during the same year and who was not prescribed hormones was chosen as the control. Our outcome of interest (mortality from all causes and CVD) was assessed with in all these cases and controls as the same cohorts. Thus, in fact the subjects in Study II were not representative of all Finnish women. There may be potential residual confounding factors, such as smoking and BMI, on which no information was available in that data. Despite the relatively large sample size, it was not adequate to detect differences in sub-groups, nor to determine whether hypertension in pregnancy could have been due to an undetected problem existing prior to the hypertensive disorder in pregnancy.

6.8. Unanswered questions and future research

Other than known risk factors of CVD, genetic factors such as role of fetal genes which may modulate the risk for problems related to maternal dyslipidemia (Descamps *et al.* 2005), family history of CVD, environmental factors such as passive smoker condition, body fat distribution indices other than BMI, and role of insulin resistance are other topics of interest in this issue which may explain the mechanism by which the associations between our findings and cardiovascular risk may be mediated. High parity may be a marker for increased life span (McArdle *et al.* 2006) and larger, more supportive social networks of friends and relatives reduce cardiovascular mortality in women (Broadhead *et al.* 1983) which may indeed be explained by the relation between CVD and emotions, another interesting topic in risk/ preventive factors of CVD in women.

6.9. Conclusion

Hypertension in pregnancy and earlier age at first delivery may predict more risk of CVD in later life. The adverse effect of child-bearing and hysterectomy, as the most common non-obstetric surgery, on cardiovascular systems seems to be mediated by advanced age and more adverse common known risk factors rather than these factors per se. Pregnancy acts as an important screening opportunity for CVD. Further studies are needed to show whether risk of later CVD morbidity or mortality decreases with early intervention and precise control of common known risk factors of CVD in women who delivered at a younger age or who had experienced pregnancy complications such as systolic hypertension.

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Appendices

Appendix 1. Contents of the health interview

A. Background information

Mother tongue, marital status and relationship
Household and children
Education
Main activity, occupation
Present/previous occupation (main job), employer
Working hours
Secondary job
Unemployment
Information about spouse
Income

B. State of health and illnesses

Perceived health and chronic illness
Specific diseases, accidents and injuries
Treatment of illnesses
Hospital care
Surgical operations
Menstruation, pregnancies and deliveries
Fertility, infertility and treatment for infertility
Contraception, postmenopausal hormone therapy

C. Questions concerning parents and siblings

Illnesses of parents and siblings
Living conditions in childhood

D. Health services

Availability and accessibility of services
Ambulatory visits due to illnesses and symptoms
Mental health services
Health examinations and preventive health services
Physiotherapy and alternative treatments
Medicines

E. Oral health

Oral health status
Self-care of the mouth
Use of services
A customer of dental care

F. Living habits
Eating habits
Smoking

G. Living environment
Residential history
Housing
Services in the neighborhood

H. Functional capacity
Usual activities
Mobility and moving capacity
Sensory functions
Need and receipt of assistance and help, aids
Cognitive capacity

I. Work and work ability
Working conditions
Working capacity
Working skills
Pension attitudes
Working history

J. Rehabilitation
Use of services
Need for rehabilitation

K. Interviewer's assessments

Appendix 2. Phases of data collection and field personnel in the Health 2000 Study

AT HOME:

90 mlnutes **INTERVIEW** (by Statistics Finland's interview organisation)

30 minutes **FILLING IN QUESTIONNAIRE 1**

AT HEALTH CENTRE ETC.:

15 minutes **1 RECEPTION** (observer 1)
- information, informed consent, Symptom Interview
- handing Questionnaire 2 and the urine sample container

15 mlnutes **2 MEASUREMENTS: height, body circumference, ecg, blood pressure** (observer 2)

15 minutes **3 MEASUREMENTS: spirometry, bioimpedance, heel bone density** (observer 3)

15 mlnutes **4 LABORATORY** (observers 4 and 5)
- drawing blood samples (100 ml), handling of samples

15 minutes **5 ORAL EXAMINATION** (observers 6 and 7)
- cllnlcal oral examination, orthopantomography

15 minutes **SNACK, FILLING IN QUESTIONNAIRE 2**

30 minutes **6a FUNCTIONAL CAPACITY TESTS** (observer 8) **6b FUNCTIONAL CAPACITY TESTS** (observer 9)
- physical and cognitive capacity, vision and hearing

30 minutes **7a CLINICAL EXAMINATION** (observer 10) **7b CLINiCAL EXAMINATION** (observer 11)

30 minutes **8a MENTAL HEALTH INTERVIEW** (observer 12) **8b MENTAL HEALTH INTERVIEW** (observer 13)

15 minutes **9 FINAL INTERVIEW**
(observer 14)
- checking that all examinations and questionnaires have been completed
- handing Questionnaire 3 and Dietary Questionnaire
- information about the prevlous and posslble further examinatlons

altogether about 3 hours and 15 minutes

AT HOME:

(100 minutes) **(HEALTH EXAMINATION FOR THOSE NOT ATTENDING THE HEALTH EXAMINATION PROPER AT THE HEALTH CENTRE ETC.)**
(observers 15 and 16)

40 minutes **FILLING IN QUESTIONNAIRE 3 AND DIETARY QUESTIONNAIRE**

AT UNIVERSITY HOSPITALS AND RESEARCH INSTITUTES:
FURTHER EXAMINATIONS FOR SUBSAMPLES

FROM REGISTERS:
REGISTER DATA

Appendix 3. Contents of questionnaires in the Health 2000 Study

Questionnaire 1

Functional capacity and quality of life (e.g. Euroqol)
Income and sickness expenditure
Usual symptoms (e.g. SCL-90)
Weight and height
Time use and hobbies
Computer use
Retrieving information on health and illnesses
Exercise; leisure time, work, on the way to work, daily exercise (IPAQ)
Use of alcohol, treatment of drinking problems
Eating or drinking sweets or sweetened drinks
Health promotion
Environment
Social environment
Psychological experiences (e.g. GHQ 12)
Mood and feelings (BDI)
Job perception and job strain
Working conditions

Questionnaire 2

Gastrointestinal diseases
Respiratory diseases
Vaccinations

Questionnaire 3

Sleep and sleeping
Disadvantages in housing conditions
Pets and domestic animals
Attitudes regarding health
Oral health and quality of life (OHIP)
Experiencing every-day life (Antonovsky, sense of coherence)
Seasonal variations
Health related quality of life (15 D)
Experiences of the influence of alcohol
Emotions and feelings
Infections and diseases in the genital area
Driving

Symptom Interview

Respiratory and cardiovascular symptoms (Rose, Fletcher)
Cough and chronic bronchitis
Dyspnea
Chest pain in exercise
Myocardial infarction (possible)
Arterial diseases of lower extremities
Atopy and allergies
Hand eczema
Musculoskeletal symptoms
Back
Neck and shoulders
Joints in extremities
Symptoms of the hands
General handicap caused by musculoskeletal symptoms
Balance problems

Dietary Questionnaire

Milk products
Cereal products
Fat spread
Vegetables
Potatoes, rice and pasta
Meat dishes
Fish dishes
Poultry and eggs
Fruit and berries
Desserts
Snacks and confectionery
Beverages

Home interview: Questions for health and illnesses in women

Pregnancies and deliveries

< BD07 under 55 years and in BB15 NO code 61 (no hysterectomy)>

BD07. **Are you pregnant at the moment?**
1 yes
2 no

ALL WOMEN

BD08a. **How many pregnancies have you had? _____** IF BD08a=0 ->BD22
INSTRUCTION: INCLUDE ALL PREGNANCIES REGARDLESS OF WHETHER THEY HAVE ENDED IN A DELIVERY, A MISCARRIAGE OR AN ABORTION.

BD08b. **Was any of these pregnancies a multiple pregnancy (i.e. several babies)?**
1 yes
2 no -> BD08d

BD08c_1. **Which pregnancies? _____**
INSTRUCTION: MARK THE NUMBER INDICATING THE ORDER.
BD08C_2 **c_2**. _____
BD08C_3 **c_3**. _____
. .
. .
BD08C_10 **c_10**. _____

BD08d. **How many deliveries have you had? _____** if BD08d=0 → BD19
INSTRUCTION: INCLUDE ALL DELIVERIES ALSO CAESAREAN SECTIONS.

<BD09 is asked for as many deliveries as mentioned in BD08d (max. 20)>

BD09. INSTRUCTION: YEAR (YYYY)
BD09A **a. Which year was your first delivery? _____**
BD09B **b. Which year was your second delivery? _____**
BD09C **c. Which year was your third delivery? _____**
BD09D **d. Which year was your fourth delivery? _____**
BD09E **e. Which year was your fifth delivery? _____**
BD09F **f. Which year was your sixth delivery? _____**
BD09G **g. Which year was your seventh delivery? _____**
.
.
.
BD09T **t. Which year was your 20th delivery? _____**

BD11. **How many children have you delivered? _____**
INSTRUCTION: INCLUDE STILLBORN.

BD12a. **How many were born alive? _____**

<BD13-BD17 is asked from under 75 years old >

BD13. **Have you during any pregnancy had:**

BD13A **a. Toxaemia**
1 yes → BD13a_1
2 no

ALL WOMEN

BD19. **How many miscarriages have you had? _____**
INSTRUCTION: DO NOT INCLUDE ABORTION

BD20. **(How many) extra uterine pregnancies have you had? _____**

BD21. **(How many) abortions have you had? _____**