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EXPOSURES IN UTERO AND CHRONIC DISEASE

An alternative methodological approach

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SUMMARY

The aims of this thesis were to evaluate maternal and birth characteristics as risk factors for breast cancer and cardiovascular disease later in life, and to assess maternal serum concentrations of insulin-like growth factors in pregnancies complicated by preeclampsia.

Birth characteristics and risks of breast cancer were studied in a case-control study nested within the population-based Swedish Twin Register (Paper I). Female same-sexed twin pairs discordant for breast cancer (i.e., only one twin of the pair has the disease) were identified by record linkage between the Swedish Twin Register and the Cancer Register. Birth characteristics of 96 discordant twin pairs and 86 individual (i.e., not related) twins were obtained from birth records. In comparisons between breast cancer cases and age-matched external twin controls an increased risk of breast cancer was found among twins with gestational age of more than 40 weeks, compared to twins with gestational age less than 33 weeks. In within-pair comparisons between breast cancer cases and co-twin controls mean birth weight and ponderal index were higher in cases compared to co-twin controls. The risk of breast cancer also increased with increasing birth weight. Our results suggest an effect of growth and/or hormonal factors in utero, reflected by birth characteristics, on risk of breast cancer later in life.

To investigate birth characteristics as risk factors for acute myocardial infarction (Paper II), a similar study design was used as in Paper I. Same-sexed twin pairs discordant for acute myocardial infarction were identified by record linkage between the Swedish Twin Register, the Cause of Death Register, and the Hospital Discharge Register. In all, birth characteristics of 132 discordant twin pairs and 118 individual twins were obtained from birth records. In comparisons between cases and sex and age-matched external (i.e., not related) twin controls, cases had significantly lower birth weight, birth length, and head circumference than external twin controls. In within-pair comparisons, no significant differences in birth characteristics were found between cases and co-twin controls. These results suggest that genetic and/or early environmental factors could influence the association between birth characteristics and risk of acute myocardial infarction in adulthood.

To assess the association between birth weight and angina pectoris, we conducted a study using self-reported data of 4594 same-sexed twins participating in a complete screening of the Twin Register, of whom 381 individuals reported angina pectoris (Paper III). Low birth weight (<2.0 kg) was associated with increased risk of angina pectoris in the twin cohort, when data were adjusted for potential confounders the risk decreased and did not reach significance. Dizygotic (n=55) and monozygotic (n=37) twin pairs discordant for angina pectoris were analysed separately. Low birth weight was significantly associated with an adjusted increased risk of angina pectoris within dizygotic twin pairs, but not within monozygotic twin pairs. These results indicate that there are genetic factors associated with both fetal growth and risk of angina pectoris, yet the results of the within-pair comparisons are based on small numbers.

History of preeclamptic pregnancy reduces the risk of breast cancer both in the mother and the female offspring, and it has been suggested that lower levels of insulin-like growth factors (IGF) and higher levels of insulin-like growth factor binding proteins (IGFBP) play an important role. To evaluate the possible role of these factors in the aetiology of preeclampsia, we measured maternal serum concentrations of IGF-I, IGF-II, and IGFBP-3 in week 17 and 33 of gestation in 30 preeclamptic and 128 non-preeclamptic women (Paper IV). Results showed no significant differences in serum concentrations of IGF-I and IGFBP-3 neither in week 17 nor in week 33. Preeclamptic women had significantly higher serum levels of IGF-II in week 33, but there was no difference in week 17. We found no evidence for lower levels of IGF-I and IGF-II, or higher levels of IGFBP-3 in pregnancies complicated by preeclampsia before clinical signs of disease.

CONTENTS

LIST OF ARTICLES

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

I. Hübinette A, Lichtenstein P, Ekbom A, Cnattingius S.
Birth characteristics and breast cancer risk: a study among like-sexed twins.
Int J Cancer 2001; 91:248-51.

II. Hübinette A, Cnattingius S, Ekbom A, de Faire U, Kramer M, Lichtenstein P.
Birth weight, early environment, and genetics: a study of twins discordant for acute myocardial infarction.
Lancet 2001; 357:1997-2001.

III. Hübinette A, Cnattingius S, Johansson A L V, Henriksson C, Lichtenstein P.
Birth weight and risk of angina pectoris: analysis in Swedish twins.
Submitted for publication.

IV. Hübinette A, Lichtenstein P, Brismar K, Ekbom A, Vatten L, Jacobsen G, Cnattingius S.
Serum insulin-like growth factors in normal pregnancy and in pregnancies complicated by preeclampsia.
Acta Obstet Gynecol Scand; In press.

INTRODUCTION

Breast cancer and exposures in utero

The evidence for an association between intrauterine exposures and subsequent risk of cancer has come from subjects exposed to the atomic bombing of Hiroshima and Nagasaki, and from women exposed to diethylstilbestrol in utero. Subjects exposed to ionising radiation of more than 0.30 Gy in utero have elevated risk of cancer compared to non-exposed persons (Kato, *et al.*, 1989). Intrauterine hormonal exposure to diethylstilbestrol is associated with increased risk of clear cell adenocarcinoma of the vagina (Herbst, *et al.*, 1971). Prenatal factors may also play a role in mammary carcinogenesis (Le Marchand, *et al.*, 1988). In 1990, Trichopoulos (Trichopoulos, 1990) suggested that intrauterine exposure to high levels of endogenous estrogens might increase the risk of breast cancer.

Malnutrition in utero and cardiovascular disease

In 1977, Forsdahl (Forsdahl, 1977) reported that geographical variations in current death rates from arteriosclerotic heart disease in Norway showed a positive association with geographical variations in past infant mortality. Similarly, Williams et al. (Williams, *et al.*, 1979) reported that geographical variations in death rates from ischaemic heart disease in England and Wales were positively correlated with geographical variations in both current and past infant mortality rates. Barker et al. (Barker and Osmond, 1986) further showed that geographical variations of mortality from cardiovascular disease were associated with both neonatal and maternal mortality earlier in the century, and suggested that the association resulted from malnutrition in utero.

BACKGROUND

Breast cancer

Trends in breast cancer

Breast cancer is the most common cancer and the leading cause of cancer death among all women worldwide (Parkin, *et al.*, 2001a). Since the 1960s (Lacey, *et al.*, 2002, Ursin, *et al.*, 1994), incidence rates have increased for most countries. However, mortality rates have remained relatively constant (Coleman, *et al.*, 1993), and have declined during the last decade in the United States, Canada, and Western Europe (Howe, *et al.*, 2001, Levi, *et al.*, 2001, Peto, *et al.*, 2000).

The geographical distribution of breast cancer is characterised by wide international variations. High incidence rates are observed in Europe, North America, Australia, New Zealand, and in the south of South America. Contrastingly, low rates are found in Asia and Africa (Parkin, *et al.*, 2001b). Geographic variations also appear within many countries, but are generally considerably smaller than international differences (Parkin, *et al.*, 1997).

First-generation immigrants from low incidence countries migrating to countries with high incidence show elevation in breast cancer rates, and substantially increased rates are observed among the second-generation immigrants (Ijaduola and Smith, 1998, Kliewer and Smith, 1995, Winter, *et al.*, 1999, Ziegler, *et al.*, 1993).

Ethnic differences in breast cancer incidence and mortality have been investigated within the United States. Incidence rates were highest among non-Hispanic white women, followed by African American women, Asian and Hispanic women, and American Indian women during 1988-1992 (Parkin, *et al.*, 1997). Breast cancer mortality rates were highest for African Americans, followed by whites, Hispanics, American Indians/Alaska Natives, and Asians/Pacific Islanders. Breast cancer-related death rates during 1990-1998 decreased for white (2.5% per year) and Hispanic (1.2% per year) women, and were unchanged for African American, American Indian/Alaska Native, and Asian/Pacific Islander women (Murphy, 2000).

The fetal mammary gland and hormones in utero

Normal development and differentiation of the mammary gland are regulated by ovarian, pituitary, and placental hormones (Imagawa, *et al.*, 2002, Russo and Russo, 1996). The developing mammary gland may be susceptible to exposure of numerous endogenous factors (Bernstein and Ross, 1993), and it has

been suggested that prenatal exposures may influence breast cancer risk in the female offspring (Trichopoulos, 1990).

Estrogens

Endogenous hormone exposure, preferably by ovarian estrogens, has been linked to risk of breast cancer. In vitro, estrogens stimulate normal (McManus and Welsch, 1984, Sheffield and Welsch, 1988) as well as malignant breast cell proliferation (Jones and Russo, 1987). Additionally, estrogens increase breast cancer risk in postmenopausal women (Key, 1999, The Endogenous Hormones and Breast Cancer Collaborative Group, 2002).

Furthermore, endogenous estrogen exposure may initiate carcinogenesis in utero by increasing the number of cells and the rate of cell division, thus increasing the risk of malignant cell transformations in the yet undifferentiated and highly proliferating fetal mammary epithelium (Anbazhagan and Gusterson, 1994, Russo, *et al.*, 1982). Human pregnancy is characterised by elevated levels of circulating estrogens, which increase with advancing gestational age (Buster, *et al.*, 1976, Lindberg, *et al.*, 1974, Tulchinsky, *et al.*, 1972). Animal studies have indicated that prenatal exposure to estrogens increase the susceptibility to mammary tumorigenesis in the offspring (Hilakivi-Clarke, *et al.*, 1997, Hilakivi-Clarke, *et al.*, 1999, Hilakivi-Clarke, *et al.*, 2000, Walker, 1990).

Androgens

Animal studies indicate that androgens may act as a promotor of mammary gland carcinogenesis (Xie, *et al.*, 1998), and possibly act synergistically with estrogens in induction of mammary tumours (Liao, *et al.*, 1998). Androgens are precursors of estrogens, and have also higher binding affinity for sex-hormone-binding protein globulin than estrogens, thereby increasing the bioavailability estrogens (Davis, 1999). Additionally, elevated serum androgens (Dorgan, *et al.*, 1997, Secreto, *et al.*, 1991) and testosterone (Dorgan, *et al.*, 1996, Secreto, *et al.*, 1991, Thomas, *et al.*, 1997, Zeleniuch-Jacquotte, *et al.*, 1997), via its conversion to estradiol, have been associated with increased risk of breast cancer. During pregnancy, maternal serum androgens are elevated compared to non-pregnant women (Harrison and Mansfield, 1980).

Progesterone

Ovarian progesterone is considerably elevated during pregnancy (Johansson, 1969, Tulchinsky, *et al.*, 1972), and has mitogenic effects on human mammary epithelial cell proliferation (Pike, *et al.*, 1993). However, experimental results with progesterone and breast cancer cell lines have been conflicting in humans (Cappelletti, *et al.*, 1995, Groshong, *et al.*, 1994, Kalkhoven, *et al.*, 1994, Thuneke, *et al.*, 1995).

Progesterone interacts with prolactin, increasing the level of prolactin receptors and inducing growth in the developing mammary gland (Nagasawa, *et al.*, 1985). Furthermore, progesterone probably acts synergistically with estrone in promoting mammary tumorigenesis (Bigsby, 2002).

Prolactin

The peptide hormone prolactin is required in development and differentiation of the mammary gland, and might influence risk of breast cancer in humans. In mammary carcinogenesis, it has been suggested that prolactin may act both as a circulating hormone and through an autocrine/paracrine pathway (Clevenger and Plank, 1997, Goffin, *et al.*, 1999, Vonderhaar, 1999). The latter may explain the lack of a clear correlation between prolactin levels and the aetiology or prognosis of breast cancer (Ingram, *et al.*, 1990, Love, *et al.*, 1991, Moore, *et al.*, 1986). Circulating levels of prolactin increases 10 to 20 times during pregnancy (Öström, 1990).

Human placental lactogen, growth hormone, insulin, and insulin-like growth factors

Human placental lactogen and growth hormone are structurally related to prolactin. In vitro, human placental lactogen and growth hormone stimulate breast cancer cell lines (Vonderhaar, 1998), and act in concert to induce insulin-like growth factor (IGF) production in the mother (Handwerger and Freemark, 2000). In the fetus, human placental lactogen stimulates the production of both insulin and IGFs (Handwerger and Freemark, 2000). In vitro, insulin and IGF-I have direct effects on mammary tumour development (Dickson and Lippman, 1995, Lee, *et al.*, 1998, Sachdev and Yee, 2001, Westley and May, 1994), and IGF-I acts synergistically with estrogens in promoting breast cancer cell line proliferation (Yee and Lee, 2000). Furthermore, insulin enhances IGF-I synthesis and downregulates insulin-like growth factor binding proteins (IGFBP), thereby increasing the bioavailability of IGF-I (Kaaks, 1996). Prospective studies have shown elevated plasma levels of IGF-I in women with breast cancer (Hankinson, *et al.*, 1998, Toniolo, *et al.*, 2000).

Alpha-fetoprotein

Alpha-fetoprotein is produced by the fetus and reaches the maternal circulation via placenta. Alpha-fetoprotein antagonises estrogen-stimulated growth of human breast cancer cell lines (Vakharia and Mizejewski, 2000). Furthermore, it has been reported that the incidence of breast cancer is significantly reduced among women with high levels of alpha-fetoprotein during pregnancy (Melbye, *et al.*, 2000).

Human chorionic gonadotropin

Human chorionic gonadotropin, a glycoprotein produced by the placenta, has suggested to have a protective effect against breast cancer, e.g., promoting cell differentiation and increasing IGFBPs and

DNA repair mechanisms (Rao, 2000). One study indicates a reduced breast cancer risk of women who took human chorionic gonadotropin as a part of a weight-loss regimen (Bernstein, *et al.*, 1995a). In contrast, results from another study in women with a history of hydatidiform moles, which is linked to human chorionic gonadotropin expression, suggested if anything, a slightly increased risk of breast cancer among these women (Erlandsson, *et al.*, 2000).

Lastly, associations between fetal serum levels of these hormones and later breast cancer risk have yet to be assessed. Hitherto, studies in humans have used indirect measures of intrauterine exposures when assessing the association with breast cancer risk. Animal studies indicate that besides estrogen exposure, intrauterine exposure to progesterone, prolactin, and androgens induce mammary tumorigenesis (Mori, *et al.*, 1979, Yanai, *et al.*, 1977).

Fetal experiences and breast cancer risk

Maternal characteristics

There is limited evidence of a positive association between maternal age and breast cancer risk in the offspring. Some studies have observed an increased breast cancer risk with older maternal age (Janerich, *et al.*, 1989, Rothman, *et al.*, 1980, Thompson and Janerich, 1990, Titus-Ernstoff, *et al.*, 2002), but most studies found no association (Colditz, *et al.*, 1991, Ekbom, *et al.*, 1992, Ekbom, *et al.*, 1997, Holmberg, *et al.*, 1995, Janerich, *et al.*, 1994, Le Marchand, *et al.*, 1988, Mogren, *et al.*, 1999, Sanderson, *et al.*, 1996, Weiss, *et al.*, 1997). Maternal levels of estrogens and age has shown a non-linear relationship, being lowest in women younger than 20 years, high in women between 20-24 years, and intermediate in women 25 years or older (Panagiotopoulou, *et al.*, 1990). A recent Swedish study found no clear association between maternal age and serum levels of estriol during pregnancy among parous women (Kaijser, *et al.*, 2000).

Levels of estrogen are lower during the second pregnancy than during the first pregnancy (Bernstein, *et al.*, 1986, Panagiotopoulou, *et al.*, 1990), and cord blood levels of estrogen and progesterone are lower for later-born than first-born infants (Maccoby, *et al.*, 1979). Second-born women have reduced risk of premenopausal breast cancer, compared to first-born women (Hsieh, *et al.*, 1991). Additionally, a recent study reported a protective effect of having an older sister (Titus-Ernstoff, *et al.*, 2002). However, most studies observed no effect of birth order on breast cancer risk in the offspring (Ekbom, *et al.*, 1997, Janerich, *et al.*, 1989, Le Marchand, *et al.*, 1988, Mogren, *et al.*, 1999, Rothman, *et al.*, 1980, Sanderson, *et al.*, 1996). Notably, serum levels of estrogen are highly correlated in successive pregnancies in the same woman (Bernstein, *et al.*, 1995b), and the variability of estrogens is indicated to be greater between women than the variability for successive pregnancies in the same woman (Potischman and Troisi, 1999).

High-fat diet increases estrogen levels (Goldin, *et al.*, 1986), whereas low-fat diet has the opposite effect in non-pregnant women (Ingram, *et al.*, 1987, Rose, *et al.*, 1987). One study, investigating maternal weight gain, found increased risk of breast cancer among offsprings to mothers with pregnancy weight gain of 11 to 16 kg, but higher weight gain was not associated with additionally increased risk of breast cancer (Sanderson, *et al.*, 1998a). Alcohol consumption may lead to elevated levels of estriol, whereas coffee consumption may decrease levels of estriol during pregnancy, possibly affecting breast cancer risk in the offspring (Petridou, *et al.*, 1992, Stevens and Hilakivi-Clarke, 2001). Nevertheless, neither alcohol nor coffee consumption have been significantly related to risk of breast cancer (Sanderson, *et al.*, 1998b). Maternal smoking reduces levels of estriol (Bremme, *et al.*, 1990, Kaijser, *et al.*, 2000, Mochizuki, *et al.*, 1984, Petridou, *et al.*, 1990), prolactin (Bremme, *et al.*, 1990), and human placental lactogen (Mochizuki, *et al.*, 1984). However, no association between maternal lung cancer and reduced breast cancer risk in the offspring has been reported (Sanderson, *et al.*, 1996, Sanderson, *et al.*, 1998a, Weiss, *et al.*, 1997).

Pregnancy characteristics

There is little evidence of an association between placental weight and breast cancer risk in the offspring (Ekbom, *et al.*, 1992, Ekbom, *et al.*, 1997, Vatten, *et al.*, 2002a). However, birth weight has shown to be positively correlated with placental weight (Heinonen, *et al.*, 2001), and the effect of birth weight on breast cancer risk could be mediated through pregnancy factors produced by the placenta (Vatten, *et al.*, 2002a).

Intrauterine exposure to preeclampsia, i.e., pregnancy-induced hypertension with proteinuria, has in most studies been found to reduce the risk of breast cancer (Ekbom, *et al.*, 1992, Ekbom, *et al.*, 1997, Innes, *et al.*, 2000, Sanderson, *et al.*, 1998a). In preeclamptic women, some studies have reported decreased levels of both estrogens (Rosing and Carlström, 1984, Wald and Morris, 2001), and IGF-I in maternal serum (Diaz, *et al.*, 2002, Giudice, *et al.*, 1997, Halhali, *et al.*, 2000, Lewitt, *et al.*, 1998). In contrast, maternal serum levels of testosterone (Acromite, *et al.*, 1999), alpha-fetoprotein (Raty, *et al.*, 1999), and human chorionic gonadotropin (Hamasaki, *et al.*, 2000, Lambert-Messerlian, *et al.*, 2000, Wald and Morris, 2001) have been observed to be higher among preeclamptic women. In umbilical cord sera, significantly higher levels of alpha-fetoprotein and no differences in estradiol have been found among infants exposed to preeclampsia in utero (Vatten, *et al.*, 2002c).

Twin pregnancies are associated with generally higher levels of estrogens (Duff and Brown, 1974, TambyRaja and Ratnam, 1981, Thomas, *et al.*, 1998, Trapp, *et al.*, 1986, Wald, *et al.*, 1991), testosterone (Thomas, *et al.*, 1998), human placental lactogen (Trapp, *et al.*, 1986), alpha-fetoprotein (Wald, *et al.*,

1991), and human chorionic gonadotropin (Wald, *et al.*, 1991). Two thirds of monozygotic twin pairs are monochorionic, i.e., they share one placenta, while virtually all dizygotic twins are dichorionic, i.e., have two placentas. Data suggest that risk of breast cancer in twins might be due to placentation, and studies indicate that there is an increased risk of breast cancer among dizygotic twins (Braun, *et al.*, 1995, Cerhan, *et al.*, 2000, Ekbom, *et al.*, 1997, Swerdlow, *et al.*, 1997, Verkasalo, *et al.*, 1999). In addition, higher levels of human placental lactogen have been observed in dizygotic than in monozygotic pregnancies (Kappel, *et al.*, 1985), and maternal serum levels of estrogens are higher in dizygotic twin mothers than in monozygotic or singleton mothers (Martin, *et al.*, 1984). Women with male co-twins may be further at increased risk of breast cancer, since females are not only exposed to high levels of endogenous estrogens in utero, but also to androgens from male co-twins (Hsieh, *et al.*, 1992, Kaijser, *et al.*, 2001).

Birth characteristics

Birth weight may be an indicator of total estrogen exposure in utero. Hence, low birth weight may indicate low levels of accumulated estrogen exposure or a shorter period of exposure to estrogens, and high birth weight may indicate the reverse (Ekbom, *et al.*, 1992, Trichopoulos, 1990). Birth weight is reported to be positively correlated with maternal serum estriol levels (Chew, *et al.*, 1976, Hardy, *et al.*, 1981, Hay and Lorscheider, 1976, Kaijser, *et al.*, 2000), and umbilical cord levels of IGF-1 (Diaz, *et al.*, 2002, Fant, *et al.*, 2002, Osorio, *et al.*, 1995, Spencer, *et al.*, 1993, Vatten, *et al.*, 2002b). Several studies have investigated the association between birth weight and risk of breast cancer, but results are not entirely consistent. Eight studies have demonstrated a positive link, although weak, between higher birth weight and breast cancer risk (Ekbom, *et al.*, 1992, Innes, *et al.*, 2000, Kaijser, *et al.*, 2001, Michels, *et al.*, 1996, Sanderson, *et al.*, 1996, Stavola, *et al.*, 2000, Titus-Ernstoff, *et al.*, 2002, Vatten, *et al.*, 2002a), while five studies reported no associations (Andersson, *et al.*, 2001, Ekbom, *et al.*, 1997, Le Marchand, *et al.*, 1988, Sanderson, *et al.*, 1998a, Sanderson, *et al.*, 2002). Also, birth length might be associated with increased risk of breast cancer (Ekbom, *et al.*, 1992, Vatten, *et al.*, 2002a).

Gestational age is presumably related to total hormonal exposure in utero (Kaijser, *et al.*, 2000). Two studies have shown an increased risk of breast cancer among women with high gestational age, i.e., gestational age of 40 weeks or more (Kaijser, *et al.*, 2001, Sanderson, *et al.*, 1998a). Severe prematurity, i.e., birth before the 33rd gestational week, has been reported to increase the risk of breast cancer, possibly induced by an immature hormonal regulation, resulting in excessive estrogen production neonatally (Ekbom, *et al.*, 1997, Ekbom, *et al.*, 2000). Yet, one study reported a reverse association (Innes, *et al.*, 2000) and two studies reported no effect (Le Marchand, *et al.*, 1988, Sanderson, *et al.*, 1996) of prematurity on breast cancer risk.

Cardiovascular disease

Trends in cardiovascular disease

Cardiovascular disease is the leading cause of death in both men and women in the Western world. Before the 1960s, age-specific cardiovascular mortality rates increased in most industrialised countries, but have later declined in the United States, Western and Southern Europe (Levi, *et al.*, 2002, Thom, 1989, Uemura and Pisa, 1988). Decreased incidence and increased survival of myocardial infarction have contributed to the decline in mortality (Hammar, *et al.*, 1992, Hammar, *et al.*, 1996, McGovern, *et al.*, 1996, McGovern, *et al.*, 2001). In women, the overall decline in cardiovascular disease rates has been slower than in men (Higgins and Thom, 1989, Linnersjö, *et al.*, 2000, Rosamond, *et al.*, 1998). Despite decline in rates of cardiovascular disease, socioeconomic differences in mortality persist and might even increase (Hallqvist, *et al.*, 1998, Marmot, 1989, Marmot and McDowall, 1986). In Eastern Europe cardiovascular mortality rates are still increasing (Levi, *et al.*, 2002, Thom, 1989, Uemura and Pisa, 1988).

Growth in utero and cardiovascular disease

The hypothesis

Barker et al. (Barker and Osmond, 1986) observed that geographical variations in coronary heart disease mortality between 1968 and 1978 were positively correlated with infant mortality in the early 1920s in England and Wales. Barker suggested that this association resulted from poor maternal nutrition in fetal and early life. Studies of interregional migrants in England and Wales have shown that both place of birth and place of residence influence risk of mortality from cardiovascular disease (Strachan, *et al.*, 1995). Another British study found that place of residence was more important than place of birth for the risk of cardiovascular disease among foreign immigrants as well as for migrants within Great Britain (Elford, *et al.*, 1989).

Biological mechanism

Barker has hypothesised that coronary heart disease is associated with specific patterns of disproportionate fetal growth that results from fetal malnutrition from middle to late gestation (Barker, 1995). The fetus adapts to this malnutrition by redistributing blood flow to the most vital parts (e.g., the brain) and develops insulin resistance to reduce growth (Barker, 1995). Insufficient energy supply for organ development could then permanently alter organ development and functioning, thereby increasing disease susceptibility later in life. Malnutrition can permanently change the number of cells in the body and the distribution of cell types, hormone secretion pattern, metabolic activity, and organ structure (McCance and Widdowson, 1974, Widdowson and McCance, 1975).

Experimental studies

Animal studies have further supported the hypothesis. Maternal protein malnutrition leads to reduced fetal growth rate, lower birth weight, and raised systolic blood pressure throughout life (Kwong, *et al.*, 2000, Langley and Jackson, 1994, Langley-Evans, *et al.*, 1999). Furthermore, exposing pregnant rats to excess glucocorticoids reduces birth weight in the offspring and produces higher blood pressures and hyperglycaemia in the adult offspring (Benediktsson, *et al.*, 1993, Lindsay, *et al.*, 1996, Nyirenda, *et al.*, 2001). In addition, animal studies have shown that intrauterine malnutrition can lead to changes in cholesterol metabolism as well as other metabolic, endocrine, and immunological processes (Widdowson and McCance, 1975).

Starvation during World War II

Studies from the Netherlands and Leningrad during World War II show an effect of severe starvation on birth weight. During the Dutch famine (calorie intake below 1000 a day for 5 months), birth weight was only reduced among infants exposed to famine during the second half of gestation: compared to infants born before the famine, these infants were 327 grams lighter. The extremely severe Leningrad siege from 1941 to 1943 (calorie intake during the winter 1941-1942 was about 300 calories a day) reduced birth weight by 530 grams (Barker, 2001). In studies of subjects exposed to famine in the Netherlands, obesity in women (Ravelli, *et al.*, 1999), higher low density lipoprotein-high density lipoprotein ratios (Roseboom, *et al.*, 2000a), and contrastingly lower factor VII (Roseboom, *et al.*, 2000c) have been linked to famine in early gestation, and impaired glucose tolerance to famine in mid and late-gestation (Ravelli, *et al.*, 1998). Among subjects exposed to famine in early gestation, higher prevalence of coronary heart disease has been reported independent of birth weight (Roseboom, *et al.*, 2000b). Blood pressure did not seem to be affected by intrauterine starvation, albeit positively associated with reduced fetal growth (Roseboom, *et al.*, 1999). Diet during pregnancy, assessed through official rations, indicated an increase in adult blood pressure when maternal diet was low in protein, i.e., low protein-carbohydrate ratio in the third trimester (Roseboom, *et al.*, 2001b). Lastly, pre-and postnatal exposure to famine did not raise the mortality after the age of 18 (Roseboom, *et al.*, 2001a). In the Leningrad siege study (no data on individual exposure status were available), no associations between intrauterine malnutrition and glucose tolerance, dyslipidaemia, hypertension, or cardiovascular disease were reported (Stanner, *et al.*, 1997). Female subjects exposed to intrauterine starvation had a stronger interaction between obesity and systolic and diastolic blood pressure than females not exposed to starvation in utero, indicating that intrauterine starvation and obesity may act synergistically to increase susceptibility to hypertension (Stanner, *et al.*, 1997).

Birth anthropometrics and cardiovascular disease

Several studies from different countries have demonstrated an association between low birth weight and increased risk of cardiovascular morbidity and mortality in men and women.

Coronary heart disease

The first epidemiological study by Barker et al. (Barker, *et al.*, 1989) of the association between birth weight and adult risk of cardiovascular disease included 5654 men born in the Hertfordshire area 1911-1930. The highest death rates from ischaemic heart disease were reported among men with the lowest weight at birth and at one year. The second study, included 1586 men born at Jessop Hospital in Sheffield 1907-1924. This study showed falling cardiovascular death rates with increasing birth weight, head circumference, and ponderal index (Barker, *et al.*, 1993c). Results from the extended Hertfordshire cohort, including both men (n=10141) and women (n=5585), confirmed previous findings of lower death rates from cardiovascular disease among subjects with low birth weight (Osmond, *et al.*, 1993). In combined analyses of the two cohorts from Hertfordshire and Sheffield totalling 13 249 men, standardised mortality ratios for coronary heart disease fell by 10% from the lowest birth weight to the highest birth weight groups (Martyn, *et al.*, 1996). Prevalence of coronary heart disease in 290 males born in East Hertfordshire 1920-1930, was not related to birth weight (Fall, *et al.*, 1995b). However, lower weight at one year was linked to higher rate of coronary heart disease. In a study from South India (n=517), low birth weight, short birth length, and small head circumference at birth were associated with increased prevalence of coronary heart disease among participants aged 45 years or over (Stein, *et al.*, 1996).

Studies of the Caerphilly cohort (n=1258) reported an inverse association between birth weight and fatal and non-fatal coronary heart disease, and the association was independent of childhood and adulthood socioeconomic status, and established risk factors for coronary heart disease (Frankel, *et al.*, 1996a). Importantly, the increased risk of coronary heart disease was restricted to subjects with low birth weight who also had high body mass index in adulthood, indicating an interaction between early-life and later-life exposures (Frankel, *et al.*, 1996b). Among women born at term included in the Nurses' cohort (n=70 297), coronary heart disease (including myocardial infarction and coronary revascularisation) showed an inverse trend with birth weight independent of potential confounding factors including body mass index, smoking, hypertension, raised cholesterol concentration, diabetes, menopausal status, and use of hormone replacement therapy (Rich-Edwards, *et al.*, 1997).

Studies of Finnish men born 1924-1944 and women born 1924-1933 in Helsinki, showed that increased risk of fatal coronary heart disease was associated with lower birth weight (n=3641) (Eriksson, *et al.*,

1999) (n=4630) (Eriksson, *et al.*, 2001), ponderal index (n=3302) (Forsen, *et al.*, 1997) (Eriksson, *et al.*, 1999, Eriksson, *et al.*, 2001), and placental weight (Forsen, *et al.*, 1997) among men, and lower birth weight and short birth length among women (n=3447) (Forsen, *et al.*, 1999).

In Sweden, one study of 855 men in Gothenburg found no evidence of an inverse association between birth weight and fatal myocardial infarction (Eriksson, *et al.*, 1994). However, two other Swedish studies reported an inverse association between cardiovascular disease and birth weight. The first study included 14 611 men and women in Uppsala. The study reported a significant association between birth weight and ischaemic heart disease among men, and the association was independent of childhood and adulthood socioeconomic status. When birth weight and birth weight for gestational age among men were included in the same model, the results indicated that fetal growth rate may be more aetiologically important than size at birth (Leon, *et al.*, 1998). The second study from the Longitudinal Study of Uppsala Men cohort (n=1334), reported an inverse association between birth weight and mortality from circulatory diseases including ischaemic heart disease and cerebrovascular disease, independent of established confounding factors (Koupilova, *et al.*, 1999).

Cerebrovascular disease

Risk of fatal stroke fell with increasing birth weight among men with birth weight of 5.6 lb or more, born in Hertfordshire and Sheffield (Martyn, *et al.*, 1996). However, compared with birth weight of 6.6-7.5 lb, men with birth weight of 5.5 lb or less had a slightly decreased risk of fatal stroke. In the Nurses' cohort, risk of non-fatal ischaemic (occlusive) and non-fatal haemorrhagic stroke fell progressively with increasing birth weight (Rich-Edwards, *et al.*, 1997). Similarly, in a cohort of Swedish men and women born in Uppsala, risk of fatal cerebrovascular disease decreased significantly with 1000 grams increase in birth weight (Leon, *et al.*, 1998). Further analyses revealed that impaired fetal growth was strongly associated with haemorrhagic but not occlusive stroke (Hypponen, *et al.*, 2001). Lastly, in Finnish men (n=3639) birth weight adjusted for head circumference was inversely associated with fatal haemorrhagic and occlusive stroke, albeit the association was stronger for haemorrhagic stroke (Eriksson, *et al.*, 2000b).

Hypertension

Epidemiological studies have consistently shown an inverse association between birth weight, head circumference, and systolic blood pressure (Eriksson, *et al.*, 2000a, Gunnarsdottir, *et al.*, 2002, Huxley, *et al.*, 2000, Law and Shiell, 1996, Law, *et al.*, 2002, Leon, *et al.*, 2000). Further, highest blood pressure was found among individuals with low birth weight and high postnatal growth rate. Ponderal index, placental weight, and gestational age have not consistently been related to hypertension (Huxley, *et al.*, 2000, Law and Shiell, 1996). Additionally, heredity for myocardial infarction and stroke (Mogren, *et al.*,

2001), as well as body mass index (Leon, *et al.*, 1996) have been reported to interact with low birth weight with respect to blood pressure.

Glucose and insulin metabolism

Lower birth weight and lower weight at one year have been associated with impaired glucose tolerance and non-insulin dependent diabetes among males in Hertfordshire (n=468) (Hales, *et al.*, 1991). Also, men (n=140) and women (n=126) in Preston (Lancashire) with impaired glucose tolerance and non-insulin dependent diabetes had lower birth weight, smaller head circumference, and lower ponderal index (Phipps, *et al.*, 1993). In combined analyses of Hertfordshire (n=407) and Preston (n=266) data, simultaneous presence of non-insulin dependent diabetes, hypertension, and hyperlipidaemia were associated with low birth weight, small head circumference, and low ponderal index among men and women (Barker, *et al.*, 1993a). Furthermore, in men and women from Preston (n=103), insulin resistance measured by insulin tolerance test was associated with lower ponderal index (Phillips, *et al.*, 1994). In addition, fasting plasma concentration of glucose and insulin fell with increasing birth weight, and glucose and insulin concentration after oral glucose tolerance test showed similar trends among women in Hertfordshire (n=297) (Fall, *et al.*, 1995a).

The Barker group has investigated populations in South India, China, and Finland. In South India, non-insulin dependent diabetes was more common among men and women who had high ponderal index and among men and women who had mothers who were heavier than average. These results suggest that non-insulin dependent diabetes may be triggered by mild obesity in mothers, which could lead to glucose intolerance during pregnancy, macrosomic changes in the fetus, and insulin deficiency in adult life (n=506) (Fall, *et al.*, 1998). In China, however, elevated plasma levels of glucose and insulin were found among subjects with low birth weight (n=627) (Mi, *et al.*, 2000). In Finland, incidence of non-insulin dependent diabetes decreased with increasing birth weight, birth length, ponderal index, and placental weight among 3639 men and 3447 women (Forsen, *et al.*, 2000).

An inverse association between birth weight and risk of non-insulin dependent diabetes has been reported, from studies of different ethnic groups in the United States (Curhan, *et al.*, 1996, McCance, *et al.*, 1994, Rich-Edwards, *et al.*, 1999, Valdez, *et al.*, 1994). Studies from the Longitudinal Study of Uppsala Men cohort have reported that lower ponderal index tends to increase the risk of non-insulin dependent diabetes (Lithell, *et al.*, 1996). Moreover, insulin sensitivity, assessed by the euglycaemic clamp method, was positively associated with birth weight in men born at term, but negatively associated with birth weight in men born preterm (McKeigue, *et al.*, 1998).

Fat deposition

Two large cohort studies have found that low birth weight is not a risk factor for adult obesity (Seidman, *et al.*, 1991, Sorensen, *et al.*, 1997), but high birth weight seems to increase the risk of adult obesity (Curhan, *et al.*, 1996, Yarbrough, *et al.*, 1998). Waist to hip ratio showed no association with birth weight in two studies (Fall, *et al.*, 1995a, Law, *et al.*, 1992), while another study reported an inverse association (Byberg, *et al.*, 2000). Truncal fat obesity has been linked to low birth weight (Byberg, *et al.*, 2000, Valdez, *et al.*, 1994).

Serum lipids and blood clotting factors

The Barker group has investigated associations between birth characteristics and serum concentrations of lipids in adulthood with relatively consistent results. Men and women (n=219) who had small abdominal circumference at birth had elevated serum total cholesterol, low density lipoprotein, and apolipoprotein B (Barker, *et al.*, 1993b). High density lipoprotein rose with increasing birth weight among 297 women (Fall, *et al.*, 1995a). Also, serum total cholesterol was significantly higher among low birth weight men and women with a mean age of 69 years (Martyn, *et al.*, 1998).

Studies by others are less consistent. No effects of birth weight on plasma lipids in adults have been reported by some investigators (Byberg, *et al.*, 2000, Kolacek, *et al.*, 1993, Leger, *et al.*, 1997). Others have reported elevated serum triglycerides among women with low birth weight (Mogren, *et al.*, 2001), whereas serum cholesterol has been observed to increase with decreasing birth weight among men but not in women (Mogren, *et al.*, 2001, Ziegler, *et al.*, 2000). A large study of subjects at 20 years of age (n=4626) found an inverse association between birth weight and serum cholesterol in adult life (Miura, *et al.*, 2001).

A study of clotting factors among men and women showed that neither plasma fibrinogen nor factor VII were related to birth weight (Barker, *et al.*, 1992). Another study of men reported significantly decreased plasma fibrinogen for each pound increased in birth weight, yet no relation between factor VII and birth measurement was observed (Martyn, *et al.*, 1995). In women, neither fibrinogen nor factor VII were associated with low birth weight (Fall, *et al.*, 1995a). Leger et al. (Leger, *et al.*, 1997) found that fibrinogen concentrations were not different between subjects born small for gestational age and normal birth weight infants. Plasminogen activator inhibitor-1 has been observed to decrease with increasing birth weight among men (Byberg, *et al.*, 2000).

Atherosclerosis

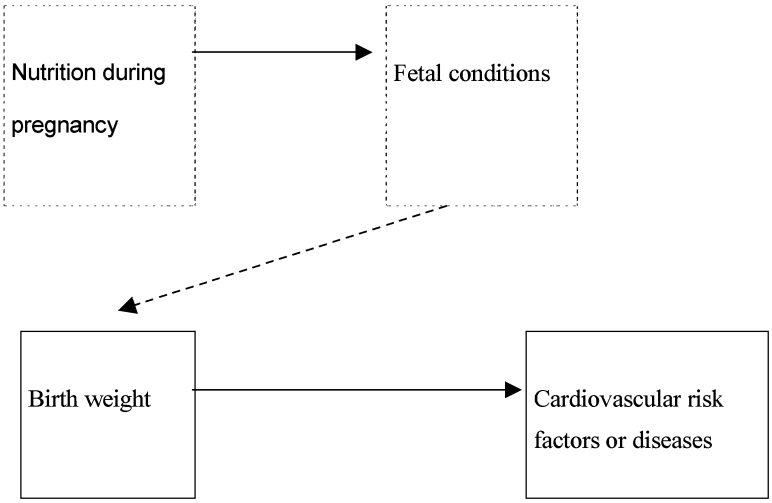
The prevalence and severity of carotid atherosclerosis in subjects of 70 years, assessed by ultrasonographic examination, was inversely associated with birth weight (Martyn, *et al.*, 1998). Also, pre-clinical atherosclerosis of the carotid artery at age 49-51, measured by intima-media thickness, was found to be non-significant negatively associated with birth weight (Lamont, *et al.*, 2000).

Criticism

Studies by the Barker group, investigating exposures in utero and adult risk of cardiovascular disease have been criticised. Results are inconsistent between studies performed by the Barker group, and there are often conflicting results compared with findings of other investigators. The control for potential confounding factors is often limited, and there is a risk of selection bias in the studied cohorts (Ben-Shlomo and Smith, 1991, Joseph and Kramer, 1996, Kramer and Joseph, 1996, Paneth and Susser, 1995, Paneth, *et al.*, 1996). In addition, laboratory studies suffer from substantial loss of follow-up. Furthermore, the Barker hypothesis is not entirely compatible with ecological trends observed in Europe since World War II of rising trends of cardiovascular disease in Finland and Norway whose birth weight distributions have been among the highest in the world for some time, and the recent increase of cardiovascular mortality in Eastern Europe (Kramer and Joseph, 1996).

The most serious criticism towards studies on the "fetal programming hypothesis" is that other factors have not been properly taken into account. Figure 1 presents the hypothesis in its simplest form. It has been shown that birth weight and other conditions in the newborn child are associated with cardiovascular risk factors or disease later in life. It has also been shown that nutrition during pregnancy influences fetal growth (Kramer, 1987).

Figure 1. The fetal programming hypotheses.



However, in empirical studies, maternal nutrition and fetal growth (change in fetal size over time) have not been assessed. Thus, malnutrition in the fetus is assumed based on the size or body proportions of the infant at birth. There are at least two alternative ways – both of which have empirical evidence that make them plausible – that can explain the association between birth weight and coronary heart disease in adult age. These are socioeconomic/life-style factors and genetic factors.

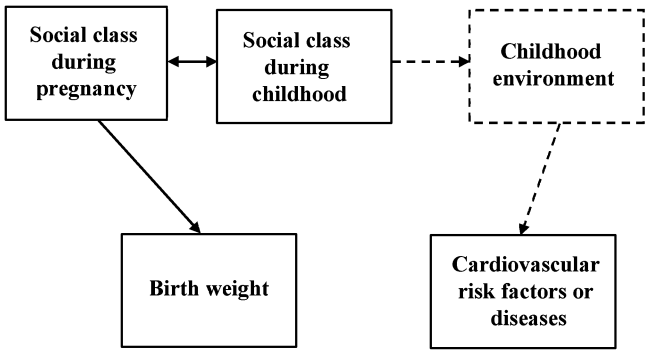
Socioeconomic factors

Confounding by socioeconomic status and other measures of environment early in life remains a concern of studies of the fetal programming hypothesis (Ben-Shlomo and Smith, 1991, Paneth and Susser, 1995). Only a few studies have controlled for socioeconomic status at the time of birth (Frankel, *et al.*, 1996a, Leon, *et al.*, 1998). Parental socioeconomic status is one of the most universally reported factors influencing birth weight and fetal growth (Kramer, 1987, Peters, *et al.*, 1983).

Social conditions during pregnancy and childhood are strongly correlated (Bartley, *et al.*, 1994, Rodriguez, *et al.*, 1995), and several studies have shown an association between social conditions during childhood (e.g., the father's social class) and coronary heart disease later in life, even after social class in adult age is accounted for (Gliksman, *et al.*, 1995, Peck, 1994, Wannamethee, *et al.*, 1996). Thus, it is

possible that the association between birth weight and coronary heart disease is explained by social conditions before birth or during childhood (Figure 2).

Figure 2. Conditions in childhood.



A double arrow indicates correlation

Socioeconomic class in early life may influence risk of subsequent coronary heart disease by affecting social class in adulthood and risk factors for coronary heart disease associated with social class, such as obesity, smoking, and alcohol use (Wannamethee, *et al.*, 1996). In studies controlling for social class during childhood, the association between birth weight and coronary heart disease has decreased, despite the crude methods used to measure social class (Fall, *et al.*, 1995b, Leon, *et al.*, 1998). Even if information about social class is available, the shortcomings of measuring social factors may still be a major obstacle. Morley et al. (Morley and Dwyer, 2001) recently proclaimed that it is difficult to encompass all relevant information using conventional socioeconomic status measures, and there is likely to be residual confounding influencing the association between birth weight and cardiovascular disease.

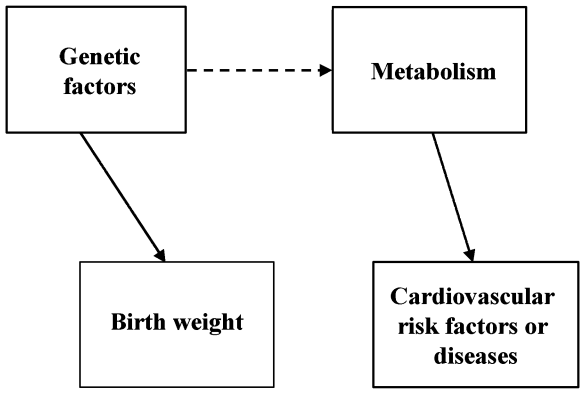
Genetic factors

There may also be genetic similarities in mechanisms of restricted growth and risk of developing cardiovascular disease. Genetic factors are of substantial importance for birth weight (Clausson, *et al.*, 2000, Magnus, 1984a, Magnus, 1984b), and cardiovascular morbidity and mortality and non-insulin dependent diabetes have a considerable genetic component (Elbein, 1997, Marenberg, *et al.*, 1994, Wienke, *et al.*, 2001), and so do most of the known hyperlipidaemias (Heller, *et al.*, 1993). Thus, the association between birth weight and risks of subsequent diseases may also be confounded by genetic factors. For example, preeclampsia (pregnancy-induced hypertension usually combined with proteinuria)

has a considerable genetic component (Salonen Ros, *et al.*, 2000), and women with preeclampsia are at higher risk for developing essential hypertension (North, *et al.*, 1996) as well as ischaemic heart disease (Smith, *et al.*, 2001). Preeclampsia is one of the most well known factors restricting fetal growth (Cnattingius, *et al.*, 1997, Kramer, 1987). Thus, offspring to women with preeclampsia should be more likely to develop subsequent hypertension, but the reason for this is a genetic susceptibility for hypertension rather than the reduced fetal growth. Factors associated with diabetes, such as IGF- I, IGFBP-1, and insulin resistance are also substantially genetically influenced (Hong, *et al.*, 1994, Hong, *et al.*, 1995, Hong, *et al.*, 1997). Fetal insulin resistance could lead to fetal growth restriction, and could, independently of fetal growth, lead to glucose intolerance and type-2 diabetes in adulthood (Hattersley and Tooke, 1999).

Figure 3 depicts how genetic factors can be responsible for the association between birth weight and cardiovascular diseases. If the same set of genes is important for birth weight and for metabolic factors later in life – as suggested by recent findings (Dunger, *et al.*, 1998), – the association between birth weight and coronary heart disease might be explained by genetic influences rather than intrauterine malnutrition.

Figure 3. The genetic hypothesis



Twin studies

Twin studies can add additional knowledge whether the association between the fetal environment and adult diseases is mediated by genetic and/or environmental factors (Leon, 1999). Within monozygotic

and dizygotic twin pairs, differences in birth anthropometrics and adult disease are controlled for maternal factors – including e.g., socio-economic circumstances, smoking, and diet during pregnancy – and infant and adolescence environmental factors linked to socioeconomic circumstances. Further, within monozygotic twins birth anthropometrics and differences in adult diseases are controlled for genetic factors.

Compared to singletons, twins tend to have lower birth weight, due to shorter gestational age as well as slower fetal growth, especially during the third trimester (Fliegner and Eggers, 1984, Naeye, *et al.*, 1966). In addition, twins experience a substantial postnatal catch-up growth. At 9 years of age twins do not significantly differ from singletons regarding height and weight (Wilson, 1979). As fetal growth restriction, especially if combined with catch-up growth during childhood, is associated with increased risk of coronary heart disease (Eriksson, *et al.*, 1999, Eriksson, *et al.*, 2001, Forsen, *et al.*, 1999) one would expect that the risk of coronary heart disease is higher among twins than among singletons. However, one Swedish study found no difference in risk of mortality from ischaemic heart disease in twins compared with the general population (Vågerö and Leon, 1994). Moreover, the overall mortality after 6 years of age were similar among Danish twins compared to the general population (Christensen, *et al.*, 2001b). Two studies have compared blood pressure in twins and singletons. The first study of systolic blood pressure at age 9 years found significantly lower blood pressure in twins compared with singletons after adjustment for potential confounders (Williams and Poulton, 1999). The second study reported no differences in mean systolic or diastolic blood pressure between twins and singletons, despite a significant difference in birth weight (de Geus, *et al.*, 2001).

AIMS OF THE THESIS

The overall aims of this thesis were to investigate the possible role of the intrauterine environment on the development of breast cancer (Paper I), acute myocardial infarction (AMI) (Paper II) and angina pectoris (III), and, to increase our understanding about the biological mechanisms preceeding preeclampsia (Paper IV). The specific aims were:

To evaluate the possible role of maternal and birth characteristics on the risk of breast cancer (Paper I), AMI (Paper II) and angina pectoris (Paper III).

To assess whether a possible association between birth characteristics and adult disease is due to genetic and/or early environmental factors (Papers I-III).

To clarify whether levels of IGF-I, IGF-II, and IGFBP-3 differ between women who subsequently develop or do not develop preeclampsia (Paper IV).

MATERIAL AND METHODS

The national registration number

From January 1st 1947 and onwards, all Swedish residents are assigned a unique 10-digit national registration number. The national registration number is composed of 6 digits based on year, month and date of birth, supplemented with registration number (3 digits) and a check-digit (Lunde, *et al.*, 1980). This personal identifier is used in public administration, including population-based registers and hospital archives. Through the national registration number, it is possible to identify individual medical records and to link information from different registers.

Registers

The Swedish Twin Register includes information about twins born in Sweden from 1886 to 1967 (Cederlöf and Lorich, 1978, Lichtenstein, *et al.*, 2002). In 1960-1961, same-sexed twin pairs born between 1886-1925 where both twins were alive and living in Sweden in 1959 were contacted by mail ("the first cohort"). It is estimated that approximately 95% of the entire same-sexed twin population was traced. Of 12 889 traced twin pairs, 10 945 twin pairs completed the questionnaire in 1961 and constituted the first birth cohort of the Swedish Twin Register. The first cohort has received questionnaires in 1963, 1967, and 1970. The second cohort of twins includes 50 000 twin pairs born between 1926-1967, and was established in 1970 by use of nationalised birth registrations. In 1973, a similar questionnaire to those given to the first cohort was sent to all same-sexed twin pairs living in Sweden born between 1926-1958. Both members of about 14 000 twin pairs completed the questionnaire. Zygosity was determined by the questionnaires sent out in 1961 to same-sexed twin pairs born between 1886 and 1925, and in 1973 to same-sexed twins born between 1926 and 1958. Zygosity was determined on the basis of self-reported childhood resemblance, which correctly classifies more than 95% of twin pairs (Cederlöf, *et al.*, 1961, Crumpacker, *et al.*, 1979, Sarna, *et al.*, 1978).

In 1998-2000, living twins included in the Swedish Twin Register born 1944 or earlier were contacted and asked to participate in a telephone interview, Screening Across the Lifespan Twin Study (SALT). Of 35 698 individuals, 25 694 participated. Non-participation was due to refusal (18.0%), the twin could not be contacted (7.8%), or was incapable to be interviewed (2.3%). Zygosity was, yet again, assessed from self-reported childhood resemblance. In a validation study of zygosity diagnoses, DNA-analyses with 13 polymorphic DNA markers were used. Out of 186 twin pairs, 184 (99 %) were correctly classified using self-reported information on zygosity (Lichtenstein, *et al.*, 2002).

The Swedish Twin Register is regularly updated by individual record linkages to the Hospital Discharge Register, the National Cancer Register, and the Cause of Death Register.

Since 1958, when the Swedish Cancer Register was established, reporting of newly detected tumours is compulsory for all physicians and pathologists, in both public and private care. The pathologists separately report the cancer diagnoses based on surgical biopsies, cytological specimens, and autopsies. The Cancer Register includes information on the national registration number, date of diagnosis, and the clinical and morphologic diagnosis. Initially, coding of sites was done according to the International Classification of Diseases, Seventh revision (ICD-7) but later revisions have been introduced since then (World Health Organization, 1955). However, all newly diagnosed cancers are also recoded according to ICD-7, thus simplifying comparisons and follow-up over time. The overall reporting rate is 95.5% (Mattsson and Wallgren, 1984), and in 1999 approximately 98% of the reported cases were morphologically verified (rate of morphologically verified breast cancer was 100% in 1999) (National Board of Health and Welfare, 2001a).

The Swedish Hospital Discharge Register handles data on individual hospital discharges. The register has a nation-wide coverage from 1987 and onwards (National Board of Health and Welfare, 2001b). The Register includes information on personal identification number, up to 6 discharge diagnoses, and from 1997 up to 8 discharge diagnoses. Diagnoses are coded according to the International Classification of Diseases, seventh through tenth revisions. Discharge diagnosis of AMI has been validated, and 86% of the reported AMI diagnoses have proved to be correct (National Board of Health and Welfare, 2000).

The Cause of Death Register provides information on all deceased Swedish residents irrespective whether the death occurs in Sweden or abroad. Register information on underlying and contributing causes of death, date and age at death are obtained from medical death certificates. Causes of death and diagnoses are coded according to the International Classification of Diseases (World Health Organization, 1955), seventh through tenth revisions. The reporting rate was 99.6% in 1999 (National Board of Health and Welfare, 2001a).

Archives

Information about each hospital birth in Sweden has been recorded on standardised delivery charts since the beginning of the 20th century. The most recent records are kept in the archives of the delivery hospitals. Older records are transferred to the county council archive (Landstingsarkivet), the city archive

(Stadsarkivet) or the regional archive (Landsarkivet). Hospital births in Sweden have increased from 4.1% in 1900 (Kungliga Medicinalstyrelsen, 1902), 12.4% in 1920 (Kungliga Medicinalstyrelsen, 1922), 69.0% in 1940 (Kungliga Medicinalstyrelsen, 1942), to 99.4% in 1960 (Kungliga Medicinalstyrelsen, 1962). The frequencies of twin births in hospitals were 12.5% in 1910 (Kungliga Medicinalstyrelsen, 1912), 21.5% in 1920 (Kungliga Medicinalstyrelsen, 1922), and 32.1% in 1930 (Kungliga Medicinalstyrelsen, 1932).

Study design

Paper I

Study population

We conducted a case-control study nested within the Swedish Twin Register, to assess the impact of birth characteristics on breast cancer risk. Potentially eligible cases were all female same-sexed twin pairs born between 1886 and 1958, diagnosed with invasive breast cancer in the Cancer Register (ICD-7 code 170) between 1958 and 1997, whose female co-twin was alive and had no history of breast cancer at the time when the case patient was diagnosed. Of 1092 potentially eligible twin pairs, we obtained birth records from 143 (13.1%) cases. Correct birth identification for each individual in the same-sexed twin pair was confirmed by restriction to twins who were either baptised (and named) at birth (n=82), or who reported birth order with mutual within-pair agreement in the SALT survey (n=14). In the remaining 47 cases, identity for each twin within the twin pair could not be assessed with certainty.

In the first part of the study, we compared twins who were diagnosed with breast cancer with matched external controls (i.e., unrelated controls). Both twins in the control twin pair had to be alive and without a history of breast cancer at the age when the case was diagnosed with breast cancer. A control pair with registered gestational age in the hospital records was matched to each case for sex and person-years at risk of developing breast cancer. One twin in the matched control twin pair was randomly selected for analyses. Of 96 breast cancer cases with correct birth identification, 9 cases without registered gestational age in the hospital records were excluded. The external case-control comparison is therefore based on 87 breast cancer cases and 87 external controls. The difference in birth year was two years or less for 94% of cases and their matched external controls. The second part of the study was a within-pair comparison including 96 twin pairs discordant for breast cancer (i.e., only one twin of the pair has the disease). Controls were co-twins who were alive and without a history of breast cancer at the time when the case (twin sister) was diagnosed with breast cancer.

Data collection

We restricted the study to hospital births, and identified the following hospitals with standardised birth records since the late 19th century: Stockholm, Göteborg, Malmö, Uppsala, Lund, Umeå, Sundsvall, Falun, Gävle, Örnsköldsvik, Örebro, Nyköping, Vänersborg, Västerås, and Linköping. Recorded information about the mothers included age at the twins' birth, age at menarche, marital status, socioeconomic status (father's or single mother's profession), area of residence, parity, health status, preeclampsia/eclampsia or other pregnancy-related diseases, and the duration of stay at the maternity ward. Available information about the infants was zygosity, gestational age, birth weight, birth length, birth order, presentation at birth, instrumental delivery, neonatal disease, and neonatal jaundice.

Paper II

Study population

We conducted a case-control study nested within the Swedish Twin Register to evaluate the effect of birth characteristics on risk AMI. Cases of AMI were identified using the following ICD-codes: ICD7, ICD8, ICD9 410-414, and ICD10 I21. Potentially eligible cases were same-sexed twins born between 1886 and 1958 diagnosed with fatal AMI between 1961 and 1997 or non-fatal AMI between 1987 and 1996, with a co-twin who was alive and without a history of AMI at the time when the case was diagnosed with AMI. Classification of fatal versus non-fatal AMI was based on the first registered AMI diagnosis. Of 2397 potentially eligible cases, we obtained birth records from 189 (7.9%) cases. Correct birth identification for each individual in the same-sexed twin pair was confirmed by restriction to twins who were either baptised (and named) at birth (n=118), or who reported birth order with mutual within-pair agreement in the SALT survey (n=14). In the remaining 57 cases, identity for each twin within the twin pair could not be assessed with certainty. Potentially eligible cases (n=2397) and obtained cases included in the analyses (n=132) were similar with respect to proportions of fatal/non-fatal AMI, zygosity, and sex. Cases included in the analyses were slightly younger, owing to the inclusion criteria (hospital delivery, filed birth records, and correct birth identification) than potentially eligible cases (median birth years were 1925 and 1918, respectively).

In the first part of the study, we compared twins who were diagnosed with AMI with matched external control twins (i.e., unrelated controls). Both twins in the control twin pair had to be alive and without a history of AMI at the age when the case was diagnosed with AMI. A control pair with registered gestational age in the hospital obstetric records was matched to each case for sex and person-years at risk of developing AMI. External control pairs were obtained by retrieving birth records of twin pairs born at the same hospital as the cases. On alternating bases, we retrieved the twin pair closest before or the twin pair closest after the case birth. In 29 cases, we were not able to retrieve controls from the same hospital.

Instead, same-sexed twin pairs who were born at hospitals of similar size as the cases were selected as controls. One twin of the control twin pair was randomly selected for analyses. Of 132 AMI cases with correct birth identification, 14 (10.6%) cases without registered gestational age in the hospital birth record were excluded. The external case-control comparison is therefore based on 118 AMI cases and 118 external controls. The difference in birth year were two years or less for 95% of all cases and their matched controls. The second part of the study, a within-pair comparison included 132 twin pairs discordant for AMI. Controls were co-twins who were alive and without a history of AMI at the time when the case (twin sister or brother) was diagnosed with AMI.

Data collection

We identified hospitals that have filed birth records since the late 19th century: Stockholm, Göteborg, Malmö, Uppsala, Lund, Linköping, Borås, Sundsvall, Örnsköldsvik, and Gävle. These maternity hospitals were located in cities in densely populated counties, and in 1930 these cities and counties covered approximately 17% and 45 % of the Swedish population, respectively (Statistiska centralbyrån, 1945). Consequently, of the 2397 potentially eligible cases, we estimated that the number of births at the included maternity hospitals would be between 130 (estimated births in the city population) to 346 (estimated births in the county population) (Kungliga Medicinalstyrelsen, 1932). We obtained hospital birth records from 189 cases. Recorded information about the mothers included age at the twins' birth, age at menarche, marital status, socioeconomic status (father's or single mother's profession), area of residence, parity, health status, preeclampsia/eclampsia or other pregnancy-related diseases, and the duration of stay at the maternity ward. Available information about the infants was gestational age, birth weight, birth length, head circumference, birth order, presentation at birth, and mode of delivery (instrumental or not). Ponderal index was defined as birth weight in grams*100/(birth length in centimetres)^3.

Paper III

Study population

To assess the association between birth weight and angina pectoris, we examined a cohort of same-sexed twins included in the Swedish Twin Register that participated in the SALT survey.

Of the 25 694 participants in the SALT survey, 4594 same-sexed twin individuals had self-reported data on zygosity, birth weight, angina pectoris (if present), and information about body mass index and smoking status from surveys in 1967/70 or 1973. Mean birth weights for dizygotic and monozygotic individuals included in the cohort analyses were 2490 g and 2360 g, respectively. Intra-pair mean birth weight differences for dizygotic and monozygotic twin pairs were 460 g and 450 g, respectively. The

within-pair analyses (case-control design) within the cohort were based on 55 dizygotic and 37 monozygotic same-sexed twin pairs discordant for angina pectoris.

Validation of self-reported birth weight data

We examined the validity of self-reported birth weight by comparing self-reported birth weight data with participants' birth certificates. We selected all twins born in Stockholm between 1920 and 1939 who participated in the interview. Correct birth identification was ensured by restriction to birth certificates of twins who were baptised (and named) at birth. We retrieved birth records from 196 individuals with self-reported birth weight. As self-reported birth weight was mainly in kilogram with one decimal and birth weight from original records was in kilogram with two decimals, we rounded off birth weight from both sources to kilogram plus one decimal. Mean self-reported birth weight was 2380 g and mean weight recorded at birth was 2440 g. Pearson correlation coefficient between birth weight in birth certificates and self-reported birth weight was r=0.74. In another subsample of 264 twins born in Stockholm between 1926 and 1958 who participated in the interview, 66% reported birth weight between minus 250 g and plus 250 g of the correct value. Furthermore, the sensitivity for low birth weight (less than 2500 g) was 87% and the specificity for low birth weight was 90%.

Data collection

The SALT telephone interview included open-ended questions on birth weight. Twins were also asked about angina pectoris: "Have you or have you ever had angina pectoris?". Furthermore, smoking status (never, past, current), weight, and height were available from questionnaires in 1967 or 1970 for twins born between 1886 and 1925, and in 1973 for twins born between 1926 and 1944. Body mass index was defined as weight in kilograms/(height in metres)^2.

Paper IV

Study population

We conducted a nested case-control study within the Scandinavian small-for-gestational-age (SGA) cohort study to evaluate serum levels of IGF-I, IGF-II, and IGFBP-3 in preeclamptic and non-preeclamptic pregnancies.

The Scandinavian SGA cohort study aimed at investigating risk factors for SGA births. The study includes parous women of three cities in Norway and Sweden (Bergen, Trondheim and Uppsala), registering for antenatal care from January 1986 through March 1988 (Bakketeig, *et al.*, 1993). Eligible for the cohort study were women with one or two previous singleton births, with singleton pregnancies, and registered for participation prior to the 20th week of gestation (n=5722). A random sample of

approximately 10% of the women from the total sample was selected (n=561). Among the remaining women a high-risk group was formed, including women with one or more risk factor for having an infant born small for gestational age (n=1384). These risk factors were: a prior low birth weight infant (<2500 g), maternal cigarette smoking at conception, low pre-pregnancy weight (<50 kg), a previous perinatal death, or the presence of chronic maternal disease (chronic renal disease, diabetes mellitus, essential hypertension, or heart disease). The randomly selected group and the high-risk group were followed closely throughout pregnancy, and the women were examined and had blood samples taken in the 17th, 25th, 33rd, and 37th week of gestation. Blood samples have been kept frozen at minus 80 Celsius degrees until assayed 1998.

Preeclampsia was defined as diastolic blood pressure of at least 90 mm Hg combined with proteinuria diagnosed by a semi-quantitative dipstick (≥1+ at least one time) without presence of urethritis (Davey and MacGillivray, 1988). Blood samples taken in the 17th and/or 33rd week of gestation for analysis of IGF-I, IGF-II, and IGFBP-3 were available from 34 women diagnosed with preeclampsia. The non-preeclamptic control women were obtained from the random sample and included the two births before and the two births after the preeclamptic pregnancy (n=136). Women with previous history of diabetes mellitus, essential hypertension, chronic renal or heart disease were excluded. In all, 30 preeclamptic and 128 non-preeclamptic women were included in the analyses. Of 30 preeclamptic women, 11 women were from the 10% random sample and 19 women were from the group of women with one or more risk criteria for having a SGA infant.

Data collection

Maternal age was defined as completed years at delivery. Prepregnancy body mass index was defined as weight in kilograms/(height in metres)^2. Information about smoking was collected at the first study visit (week 17), and women were categorised as daily smokers ("smokers") or daily non-smokers ("non-smokers") if they reported smoking around time of conception. Gestational age at delivery was generally based on the first day of the last menstrual period. At the first study visit, a sonogram of the biparietal diameter was also taken to accurately date the pregnancy. If there was a discrepancy between last menstrual period and biparietal diameter gestational age of more than ±14 days, or if the first day of the last menstrual period was uncertain, the biparietal diameter of gestational age was used. Placental weight, birth weight, and infant's gender were recorded at birth.

Biochemical assays

Serum levels of IGF-I, IGF-II, and IGFBP-3 were measured by a non-extraction two-site coated tube immunoradiometric assay (IRMA) thereby avoiding interference of IGFBPs in measurements of total

IGF-I and IGF-II (Diagnostic Systems Laboratories, Inc., Webster, Texas). The IGF-1 had a minimum detection limit of 2.06 ng/mL and the intra-assay coefficients of variation were 7.0% at 34.03 ng/mL, 3.9% at 142.45 ng/mL, and 3.9% at 373.86 ng/mL. The IGF-II had a minimum detection limit of 12 ng/mL and the intra-assay coefficients of variation were 6.5% at 245 ng/mL, 3.4% at 409 ng/mL, and 4.7% at 1432 ng/mL. The IGFBP-3 had a minimum detection limit of approximately 0.5 ng/mL and the intra-assay coefficients of variation were 3.9% at 7.35 ng/mL, 3.2% at 27.53 ng/mL, and 1.8% at 82.72 ng/mL.

Statistical methods

Paper I

Explanatory variables in continuous form (gestational age, birth weight, birth length, and ponderal index) were compared by paired t-test using SAS PROC MEANS (SAS Institute Inc, 1996). Tests of statistical significance (p-values) were two-sided and statistical significance was defined as $p<0.05$. We performed conditional logistic regression analyses including categorised explanatory variables: gestational age (<33, 33-36, 37-40, >40 weeks); birth weight (<1999, 2000-2499, 2500-2999, ≥3000 g); birth length (39-44, 45-48, 49-53 cm); and ponderal index (1.80-2.29, 2.30-2.44, 2.45-3.10), by the maximum likelihood method using the SAS PROC PHREG (SAS Institute Inc, 1996). Odds ratios and 95% confidence intervals estimated from conditional logistic regression were used as measures of relative risks. For each model, observations with missing values for explanatory variables were excluded from the analysis.

Paper II

Explanatory variables in continuous form (gestational age, birth weight, birth length, and head circumference) were compared by paired t-test using SAS PROC MEANS (SAS Institute Inc, 1996). Explanatory variables in categorised form maternal age (≤19, 20-29, ≥30 years), parity (1-para, ≥2-para), marital status (married, unmarried/separated), occupational status (blue-collar, white-collar, self-employed), and area of residence (country, village, city) were compared by chi-square tests for homogeneity using SAS PROC FREQ (SAS Institute Inc, 1989). Tests of statistical significance (p-values) were two-sided and statistical significance was defined as $p<0.05$.

We performed conditional logistic regression analyses by the maximum likelihood method using the SAS PROC PHREG (SAS Institute Inc, 1996). Odds ratios and 95% confidence intervals estimated from conditional logistic regression were used as measures of relative risks. The following categorised explanatory variables were included in the multivariate model: maternal age, parity, marital status, occupational status, and area of residence. Also, birth weight was included in the model as a continuous

variable. Odds ratios for continuous variables measure the change in risk per unit of the variable. In our analyses, however, odds ratios were calculated per 500 grams increase in birth weight.

Paper III

The cohort design was analysed by unconditional logistic regression using SAS PROC GENMOD (SAS Institute Inc, 1996), correcting for within-pair similarities. The matched twin-pair design was analysed by conditional logistic regression using SAS PROC PHREG (SAS Institute Inc, 1996). Odds ratios were used to estimate relative risks with 95% confidence intervals. Birth weight was divided into three categories, <2.0, 2.0-2.9, ≥3.0 kg. Potential confounders included in the cohort model were sex, zygosity (dizygotic, monozygotic), age (≤55, 56-65, 66-75, >75 years), body mass index (<25, ≥25), and smoking status (never smoker, past smoker, current smoker), and in the within twin-pair model, body mass index and smoking status. The Wald test was used to test the overall effect of birth weight. The test considers all strata in determining significance, not only pair-wise comparisons with the reference group.

Paper IV

Maternal and birth characteristics (continuous variables were categorised) of preeclamptic women and non-preeclamptic women were compared by Fisher's exact test for homogeneity. Under the assumption that IGF-I, IGF-II, and IGFBP-3 in maternal serum were normally distributed, the differences in mean levels of IGF-I, IGF-II, and IGFBP-3 in the 17^{th} and 33^{rd} week of gestation among preeclamptic and non-preeclamptic women were analysed using t-tests. T-tests were performed under the assumption of equal or unequal variances. The strength of association between changes in the 17^{th} and 33^{rd} week of gestation in serum IGF-I, IGF-II, and IGFBP-3 concentrations were tested using Pearson's correlation coefficient. All tests of statistical significance (p-values) were two-sided and statistical significance was defined as $p<0.05$. The statistical analyses were calculated using the SAS PROC FREQ (SAS Institute Inc, 1989) for Fishers' exact test and t-tests, and SAS PROC CORR (SAS Institute Inc, 1990) for correlation analyses.

RESULTS

Birth characteristics and breast cancer (Paper I)

External comparisons

The 87 breast cancer cases did not differ significantly from the 87 external controls with regards to maternal characteristics including age at delivery, parity, chronic diseases, preeclampsia/eclampsia, marital status, socioeconomic status, and area of residence. Mean gestational age at delivery, birth weight, and birth length tended to be higher in cases than in controls. There was an increase in odds ratio with increasing gestational age to a maximum odds ratio of 8.4 (95% confidence interval 1.3 to 54.4) among individuals with gestational age of more than 40 weeks compared to gestational age of less than 33 weeks. Risk of breast cancer generally increased with birth weight. Compared to individuals with birth weight less than 2000 g, individuals with birth weight from 2500 to 2999 g had a more than two-fold increase in risk of breast cancer (odds ratio 2.4; 95% confidence interval 0.9 to 6.2). However, individuals with a birth weight of 3000 g or more were not at further increased risk (odds ratio 1.6; 95% confidence interval 0.4 to 5.6). Breast cancer risk continuously increased with increasing birth length to a maximum of 2.0 (95% confidence interval 0.8 to 5.2) among individuals 49 to 53 cm tall compared to individuals with a birth length between 39 and 44 cm. The Wald test of the overall effect on breast cancer risk of gestational age at delivery, birth weight, and birth length were non-significant.

Within-pair comparisons

In within-pair comparisons comprising 96 breast cancer cases and 96 co-twin controls, cases tended to be heavier (mean difference 75±41 g; p 0.07) than controls. Risk of breast cancer consistently increased with increasing birth weight and birth length to a peak odds ratio of 3.5 among individuals with birth weight equal or more than 3000 g compared to less than 1999 g, and 2.1 among individuals with birth length 49 to 54 cm compared to 39 to 44 cm (Table 1).

Table 1. Crude odds ratios (OR) and 95% confidence intervals (CI) of breast cancer in relation to birth characteristics within 96 female twin pairs.

Characteristic	Cases n (%)	Co-twin controls n (%)	OR (95% CI)
Birth weight (g)			
<1999	10 (10)	16 (17)	1.0 (ref)
2000-2499	33 (34)	31 (32)	2.3 (0.7-7.6)
2500-2999	38 (40)	36 (38)	2.8 (0.7-10.6)
≥3000	15 (16)	13 (13)	3.5 (0.7-18.5)
Birth length (cm)			
39-44	15 (16)	18 (19)	1.0 (ref)
45-48	52 (56)	51 (55)	1.7 (0.5-5.9)
49-53	26 (28)	24 (26)	2.1 (0.5-8.9)
Missing	3	3	
Ponderal Index*			
1.80-2.29	32 (34)	39 (42)	1.0 (ref)
2.30-2.44	23 (25)	16 (17)	2.3 (0.8-6.3)
2.45-3.20	38 (41)	38 (41)	1.9 (0.6-5.8)
Missing	3	3	

*Ponderal index is expressed as birth weight in grams*100/(birth length in centimetres)^3.

Discordant twin pairs with known zygosity, 40 dizygotic and 36 monozygotic twin pairs, were analysed separately. There were no significant differences, but within both dizygotic and monozygotic twin pairs, mean birth weight, birth length, and ponderal index were consistently higher among cases than controls, with one exception (birth length among monozygotic twins).

Birth characteristics and myocardial infarction (Paper II)

External comparisons

Regarding maternal characteristics, a significantly higher proportion of the 118 cases with AMI had unmarried mothers and parents who were blue-collar workers compared to the 118 external controls. Gestational age at delivery, maternal age, parity or mothers' residence at delivery did not differ significantly between cases and controls.

Mean birth weight, birth length, and head circumference were significantly lower in cases than in external controls (Table 2). Adjustment for gestational age at delivery, maternal age, parity, marital and occupational status, and area of residence lowered the risk estimates. A 500-gram increase in birth weight corresponded to a 35% reduction in risk of AMI (adjusted odds ratio 0.65; 95% confidence interval 0.45 to 0.95).

Within-pair comparisons

There were no significant differences between cases and co-twin controls in mean birth weight, birth length or head circumference (Table 2). Subgroup analyses showed no significant differences in birth measurement either within the 40 monozygotic, or within the 72 dizygotic twin pairs. The continuous variables (birth weight, birth length, and head circumference) were also categorised, and risks of myocardial infarction were analysed by conditional logistic regression. Within-pair comparisons showed no associations between the categorised variables and risk of AMI in any strata.

Table 2. Differences in birth characteristics in twins with myocardial infarction versus external and co-twin controls.

Characteristic	Cases Mean (SD)	Controls Mean (SD)	p*
External comparison	(n=118)	(n=118)	
Birth weight (g)	2556 (500)	2699 (530)	0.04
Birth length (cm)	47.1 (2.8)	47.9 (2.7)	0.04
Head circumference (cm)	33.0 (1.8)	33.5 (2.0)	0.03
Within-pair comparison	(n=132)	(n=132)	
Birth weight (g)	2548 (510)	2534 (530)	0.73
Birth length (cm)	47.1 (2.8)	47.2 (2.8)	0.91
Head circumference (cm)	33.0 (1.7)	33.0 (1.8)	0.92

*Paired t-test.

Birth weight and angina pectoris (Paper III)

Cohort analyses

Among 4546 individuals in the twin cohort, 381 (8.3%) individuals reported angina pectoris. Birth weight showed a U-shaped relationship to rates of angina pectoris, with the highest rates associated with low and high birth weights. Among individuals with birth weight less than 2.0 kg, rate of angina pectoris was 9.8%, while corresponding rates among individuals with birth weight from 2.0 to 2.9 kg and above 3.0 kg were 7.0% and 9.5%, respectively. Angina pectoris was more common among men (11.3%) than women (7.0%), and the rate increased with increasing age. The rates of angina pectoris among dizygotic and monozygotic twins were 8.6% and 7.9%, respectively. Information about body mass index and smoking status was obtained approximately 30 years before information about angina pectoris was collected. Compared to individuals with body mass index below 25, the rate of angina pectoris was higher among those with body mass index equal or above 25. Individuals who reported past smoking had higher rate of angina pectoris (18.8%) than both never (7.6%) and current smokers (9.3%).

Compared to individuals with birth weight from 2.0 to 2.9 kg, individuals with birth weight less than 2.0 kg or at least 3.0 kg were at an increased risk of angina pectoris (odds ratio 1.46; 95% confidence interval 1.14 to 1.87 and odds ratio 1.40; 95% confidence interval 1.09 to 1.81, respectively) (p for trend 0.003). When data was adjusted for sex, age, zygosity, body mass index, and smoking status, these risks decreased and did not reach significance.

Within-pair comparisons

The birth weight distribution differed between dizygotic and monozygotic twin pairs discordant for angina pectoris. Within dizygotic twin pairs, birth weight below 2.0 kg was more frequent among twins with angina pectoris than among healthy co-twins, 38% versus 13%. Within monozygotic twin pairs, the corresponding difference between twins with angina pectoris and healthy co-twins was negligible (41% versus 35%).

Compared with dizygotic twins with birth weight between 2.0 and 2.9 kg, dizygotic twins with birth weight below 2.0 kg were at increased risk of angina pectoris (Table 3). Among monozygotic twin pairs, no increased risk of angina pectoris was observed for any birth weight strata.

Table 3. Odds ratios (OR) and 95% confidence intervals (CI) of angina pectoris in relation to birth weight in same-sexed twin pairs included in the Swedish Twin Register.

Birth weight (kg)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Dizygotic twin pairs	(n=55)	(n=55)
<2.0	5.35 (1.52-18.81)	5.48 (1.54-19.42)
2.0-2.9	1.00 (ref)	1.00 (ref)
≥3.0	1.02 (0.22-4.82)	0.96 (0.20-4.67)
p for trend**	0.03	0.03
Monozygotic twin pairs	(n=37)	(n=37)
<2.0	1.38 (0.50-3.81)	1.30 (0.46-3.67)
2.0-2.9	1.00 (ref)	1.00 (ref)
≥3.0	1.71 (0.27-10.79)	1.87 (0.29-12.24)
p for trend**	0.75	0.76

*Adjusted for body mass index and smoking status.

**Wald test of the overall effect of birth weight (test of general heterogeneity).

Insulin-like growth factors in preeclamptic pregnancy (Paper IV)

Maternal and birth characteristics

Pregnancy duration of the 30 preeclamptic women was shorter, and infant's birth weight lower than among the 128 non-preeclamptic women. Furthermore, preeclamptic women were significantly shorter than non-preeclamptic women. Maternal age, prepregnancy body mass index , maternal smoking, and placental weight did not differ between preeclamptic and non-preeclamptic women.

Mean serum levels of IGF-I, IGF-II, and IGFBP-3

Serum levels of IGF-I and IGFBP-3 among preeclamptic and non-preeclamptic women neither differed in the 17th nor in the 33rd week of gestation. Preeclamptic women had significantly higher serum levels of IGF-II in the 33rd week of gestation than non-preeclamptic women (p 0.001), while no difference was observed in the 17th week of gestation (Table 4).

Subgroup analyses of preeclamptic women originating from the SGA high-risk group (n=19) and from the 10% random sample (n=11) showed no evidence of discrepancies in serum levels of IGF-I, IGF-II,

and IGFBP-3. Also, results were analogous when the two subgroups of women with preeclampsia were separately compared to non-preeclamptic women. Compared to non-preeclamptic women, preeclamptic women from both groups had significantly higher serum levels of IGF-II in the 33rd week of gestation.

Table 4. Maternal serum levels (means±SEM) of IGF-I, IGF-II, and IGFBP-3 at the 17th and 33rd week of gestation in preeclamptic and control women.

	Week 17			Week 33		
	Preeclampsia (n=29)	Controls (n=127)	p*	Preeclampsia (n=23)	Controls (n=126)	p*
IGF-I (ng/mL)	101±12	86±5	0.22	229±27	211±9	0.54
IGF-II (ng/mL)	817±29	769±11	0.13	896±28	800±12	0.001
IGFBP-3 (ng/mL)	5402±138	5641±73	0.15	6290±194	6526±97	0.29

*T-test performed under the assumption of equal or unequal variances.

Correlations

Significant positive correlations of IGF-I, IGF-II, and IGFBP-3 between the 17th and 33rd week of gestation were found in both preeclamptic and healthy pregnant women. There was no evidence of any correlations between maternal IGF-I concentrations in the 17th or in the 33rd week and birth weight neither among preeclamptic nor among non-preeclamptic women.

GENERAL DISCUSSION

Methodological considerations

Study design

A case-control study is well suited for studying diseases with very long latency periods from exposure to disease development. Additionally, the design makes it possible to evaluate associations between a wide range of exposures and the disease under study. We conducted two case-control studies (Papers I-II) – each with two control groups – in same-sexed twins included in the Swedish Twin Register. Cases were ascertained using the following population-based registers: the Swedish Cancer Register, the Swedish Hospital Discharge Register, and the Cause of Death Register. In the external comparison, controls were randomly selected from the Swedish Twin Register, and individually matched to each case by delivery hospital (Paper II), year of birth, and person-years at risk of developing disease (Papers I-II). In the within-pair comparison, the healthy co-twin was selected as control and that should control for a number of general characteristics, including genetic factors, early environmental exposures, dietary habits, and socioeconomic status. Exposure information was obtained from birth records completed before occurrence of disease.

A valid and cost-effective way of using cohort data is to conduct a case-control study nested within the cohort. We have used data from a cohort study on risk factors for SGA births to carry out a nested case-control study on serum IGF and IGFBP concentrations during pregnancy among women who later developed or did not develop preeclampsia (Paper IV). Cases were ascertained using strict diagnostic criteria for disease. Controls were individually matched to each case, and included the two births before and the two births after the case pregnancy. Maternal sera for analyses were collected before occurrence of the disease.

The retrospective cohort study – i.e., exposure and disease have occurred when the study is initiated – is also efficient for investigations of diseases with long latency periods. Further, the design allows assessment of the effect of one exposure on several outcomes. Our cohort included same-sexed individuals in the Swedish Twin Register, participating in a general screening of all living individuals in the Twin Register 1998-2000. The participation rate was 72%. We conducted a study estimating the effect of birth weight on risk of angina pectoris in the cohort (Paper III). Additionally, a nested case-control study of twin-pairs discordant for disease was performed within the cohort (Paper III). Information about exposure and disease was obtained from telephone interviews 1998-2000. Information

about potential confounding factors including smoking and body mass index, were available from questionnaires collected approximately 30 years before occurrence of disease.

Precision

Precision in measurement corresponds to the degree of random error. High precision corresponds to small random errors. The study size as well as the study efficiency i.e., in which way information is obtained from a given number of study participants, are important determinants of precision. We used 95% confidence intervals as a measure of the precision of our results.

The study sizes of Papers I and II were based on a power calculation indicating that, using a significance level of 5% and a power of 80%, 65 twin-pairs discordant for disease were required to be able to detect 50% increase in risk of disease for the twin with the lowest birth weight. The findings in Paper I were consistent with the a priori hypothesis. However, the obtained differences between cases and external and co-twin controls were not statistically different, and must be interpreted with caution. In Paper II, no difference in birth weight was observed between cases with AMI and co-twin controls. The statistical power to detect differences in birth measurements of similar magnitude to those detected in the external comparisons were 95%, using a significance level of 5%. In Paper III, the sample sizes in the within-pair comparisons of dizygotic and monozygotic twin pairs were small, generating odds ratios with wide confidence intervals. The difference between dizygotic and monozygotic twin pairs with birth weight below 2.0 kg was not statistically different, and results should therefore be interpreted cautiously. In Paper IV, power calculations based on the study sample, using a significance level of 5%, and a power of 80%, indicated that we were able to detect a 30% difference of IGF-I in the 33rd gestational week between women developing and not developing preeclampsia, a 10% difference of IGF-II, and a 11% difference of IGFBP-3 between the groups. Generally, there were no significant differences between groups, but we cannot exclude that there are true differences not possible to detect in our sample.

Internal validity

Internal validity corresponds to the reduction of systematic errors, commonly classified in three categories: selection bias, information bias including misclassification, and confounding.

Selection bias

Selection bias, i.e., errors in the selection of subjects related to exposure and/or outcome, can cause problems particularly in case-control studies. However, the nested case-control design in Papers I and II (study population: the Swedish Twin Register) should minimise errors associated with selection of study subjects, and facilitates random sampling of controls. Potentially eligible cases and finally included cases

(those for whom we retrieved birth records) were similar in terms of proportions of fatal and non-fatal AMI, zygosity, and sex (Paper II).

In cohort studies, selection of study subjects does not introduce selection bias. However, bias due to non-response (i.e., loss of follow-up) may be a concern in Paper III, since the obtained participation rate was moderate (72%). Non-response may lead to bias if participants and non-participants differ systematically with respect to both exposure and risk factors for the outcome. Strength and direction of non-response bias may depend on the reason for non-participation (Boersma, *et al.*, 1997, Etter and Perneger, 1997). In Paper IV, the participation rate in the cohort study was high (97%) (Bakketeig, *et al.*, 1993) and that minimised the potential for selection bias. Moreover, by using the nested case-control design we gain the validity of the cohort.

Information bias

Information bias – errors in measurements of exposure and outcome by case-control status – is introduced by the investigators (interviewer bias) or the study subjects (recall bias).

In Papers I, II, and IV, recall bias, i.e., cases tend to remember their history of exposure differently from those not affected, is not an issue since exposure information was registered before onset of disease. In Papers I and II, exposure information was obtained from birth records completed by the midwife at the time of delivery, i.e., before occurrence of disease. Similarly, in Paper IV information about maternal characteristics and blood samples for later IGF analyses were collected during pregnancy, before occurrence of disease. It is unlikely that the accuracy or completeness of these records systematically differ between cases and controls.

Potential interviewer bias, i.e., recording or interpretation of information by the investigator, may be a concern in the retrospective cohort study (Paper III). Information about exposures and outcomes were obtained by computer assisted telephone interviews, which included questions on a wide variety of factors. The hypothesis in Paper III should neither be obvious for the participants nor for the interviewers. Moreover, it is unlikely that cases remember birth weight differently from controls, and the possible impact of recall bias should therefore be of limited magnitude.

Misclassification

Misclassification, a type of information bias, occurs when study subjects are incorrectly categorised with respect to either exposure or disease. Nondifferential misclassification of exposure and disease leads to an underestimation of the true association between exposure and outcome (Rothman and Greenland, 1998).

Differential overestimation or underestimation of exposures, i.e., differential misclassification, leads to an overestimation or underestimation of the association.

Differential misclassification of exposures in Papers I and II should be a minor concern since we only included hospital births. However, correct identification at birth of each twin within the same-sexed twin pairs is a prerequisite to avoid that exposure information of one member in a twin pair was erroneously associated with the co-twin. In Papers I and II, we only included twin-pairs who were baptised at the maternity wards or twin pairs where birth order was identified with mutual agreement through the SALT screening. Paper III included self-reports of the exposure (birth weight) from telephone interviews in the SALT screening. Self-reported exposure information from SALT participants has been validated from obstetric records and has shown to be reasonably accurate (r=0.74), and any inaccuracy should produce nondifferential misclassification. In Paper IV, ascertainment of disease (preeclampsia) status was based on prospectively collected data using stringent criteria, minimising misclassification. Including a more generous definition of preeclampsia would probably have tended to dilute the difference between the exposed and nonexposed.

Virtually complete identification of potential cases in Papers I and II via population-based registers reduces bias from differential follow-up. Underreporting cannot be excluded and may result in an underestimation of measures of association. In Paper III, the outcome – angina pectoris – was reported by the study subjects. The validity of self-reports for conditions without strict diagnostic criteria like angina pectoris shows lower levels of agreement than more strictly defined conditions (Colditz, *et al.*, 1986, Haapanen, *et al.*, 1997, Lampe, *et al.*, 1999, Mittelmark, *et al.*, 1993), and this probably weakened the findings. In Paper IV, blood serum was collected before occurrence of disease in 1986 and stored at minus 80 Celsius until assayed in 1998. Data indicates that storage at minus 80 Celsius does not substantially reduce IGF-I, IGF-II, and IGFBP-3 over time (Yu, *et al.*, 1999). Compared to other studies of IGF-I in healthy pregnant women during approximately the same week of gestation, our levels IGF-I were higher (Hills, *et al.*, 1996), lower (Grobman and Kazer, 2001, Langford, *et al.*, 1995, Reece, *et al.*, 1994), and similar (Holmes, *et al.*, 1998). Total IGF-I, total IGF-II, and IGFBP-3 were analysed by laboratory technicians blinded to exposure status, by IRMA. Any possible misclassification of IGF concentrations due to storage and IRMA procedures should be equal for cases and controls, i.e., result in nondifferential misclassification.

Confounding

A confounding factor influences the risk between exposure and disease by being associated with exposure and independently affects the risk of developing the disease. A confounder cannot be an intermediate step

in the causal pathway from exposure to disease. A confounding factor introduces an overestimation or underestimation of measured association (Rothman and Greenland, 1998).

The aims of Papers I, II, and III were to assess the associations between exposures and diseases. We controlled, as far as possible, for potential confounding in the analyses by using discordant twin pairs. The within-pair comparisons of discordant twin pairs enable us to reduce the impact of genetic and early environmental factors. Thus, using co-twin controls allowed us to control for a number of unmeasured confounding factors related to genetics and the early environment. Also, the variation of the intrauterine environment is limited to inter-twin differences. Besides co-twin controls, external (i.e., unrelated) controls were selected to estimate the effect of limited adjustment for potential confounding factors obtained from birth records and registers. In Paper IV, we know that IGF-I declines with age and preeclampsia is slightly more common among older women. However, correction of IGF-I for age did not change the result. Nonetheless, influence of not yet identified confounding factors cannot be excluded.

External validity

Internal validity is a prerequisite for external validity (generalisability), and generalisability is achieved when the findings are applicable to people outside the study population.

Generalisability of studied twins to twins in general

Given the design in Papers I and II, the results are generalisable to same-sexed twins born in hospitals between 1886-1958 in Sweden. Hospital births were more common among twin mothers than among singleton mothers. For example, in 1910 12.5% of twin mothers and 7.3% of singleton mothers gave birth in hospital (Kungliga Medicinalstyrelsen, 1912), while in 1920 corresponding rates were 21.5% versus 12.4%, respectively (Kungliga Medicinalstyrelsen, 1922), and in 1930, 32.1% versus 21.6%, respectively (Kungliga Medicinalstyrelsen, 1932). Compared with infants born at home, considerably lower mean birth weight has been reported among infants delivered in hospital (Eriksson, *et al.*, 1997). Mothers delivered in hospital tended to be younger, more often from lower social classes, unmarried and nulliparous, compared to mothers delivered at home (Eriksson, *et al.*, 1997). Thus, restriction to hospital births probably implied that, compared with the general population, our study population included a larger proportion of socioeconomically less advantageous women. In comparisons between cases and external controls (Papers I-II) we were able to adjust for differences in maternal characteristics at birth (e.g., age, parity, socioeconomic status, and area of residence), and using co-twins as controls automatically provides reasonable good control for genetic and early environmental factors.

Previous reported findings of substantially elevated risk of breast cancer with increasing birth weight among dizygotic women with a co-twin brother (Kaijser, *et al.*, 2001), were considerably higher than corresponding risk among dizygotic women with a co-twin sister (Paper II). This implies that results might be limited to female same-sexed twins. Also, there has been an increased survival of twin pairs with highly discordant birth weight and very low birth weight infants during recent decades (Sadrzadeh, *et al.*, 2001). Thus, the findings reported in Papers I-III might not be generalisable to twins born today.

In Paper III, findings are based on same-sexed twins 55 years or older reporting angina pectoris in a telephone interview. Hence, the generalisability of results might be limited to same-sexed twins 55 years or older.

Generalisability of twins to singletons

In Paper I, our findings indicated an association between larger birth size and increased risk of breast cancer in same-sexed twins pairs, regardless whether external or co-twin controls were used. These results are in accordance with results in singletons.

In Paper II, we investigated the association between birth characteristics and risk of AMI. It has been argued that low birth weight in twins is unlikely to have the same significance as in singletons (Phillips, *et al.*, 2001). Philips et al. (Phillips, *et al.*, 2001) claim that factors determining size at birth in twins differ fundamentally from those in singletons. Although the birth weight-specific infant mortality differs between twins and singletons, other differences in response to malnutrition between twins and singletons remain speculative. Twins are on average 800-900 grams lighter than singletons at birth (Wilson, 1974). The lower birth weight among twins is not only due to shorter gestational age but also to that twins are more often born small for gestational age (Cohen, *et al.*, 1997, Duncan, *et al.*, 1979). Compared to the general population, there is no evidence that twins have increased mortality from coronary heart disease (Vågerö and Leon, 1994) or increased overall mortality (Christensen, *et al.*, 2001b). Thus, despite impaired growth in utero, twins do not have increased risk of cardiovascular disease. The lower birth weight among twins with AMI compared to external controls, and the cohort finding of low birth weight and increased risk of angina pectoris in twins (Paper III) is consistent with the association between low birth weight and risk of cardiovascular disease found among singletons in Sweden, and worldwide. The proposed finding in Paper III, that genetic factors could have influenced the association between low birth weight and angina pectoris, was based on a minimal sample of discordant twin pairs. Thus, this finding needs to be confirmed by further studies with higher precision.

The generalisability has been particularly questioned in monozygotic twins. Monozygotic twins have lower birth weight than dizygotic twins (Derom, *et al.*, 1995, Glinianaia, *et al.*, 1998), and monozygotic twins are less concordant at birth than dizygotic twin pairs (Falkner and Matheny Jr, 1995). Two-thirds of the monozygotic twins are monochorionic, i.e., they share a common placenta. Thus, in addition to sharing the same genotype, monochorionic monozygotic twins also share many intrauterine environmental influences. Monochorionic monozygotic twins share one placenta and are more prone to develop twin-twin transfusion syndrome, an extreme form of inequitable blood circulation, affecting approximately 10% of monochorionic twins (Symonds, *et al.*, 2000). Monozygotic monochorionic twins have a larger intra-pair birth weight difference, compared to monozygotic dichorionic twins (Loos, *et al.*, 2001a). Theoretically the type of placentation could lead to greater phenotypic similarity of adult monozygotic twins compared with dizygotic twins (Baird, *et al.*, 2001). However, a study of 424 twin pairs, including dizygotic, monozygotic dichorionic, and monozygotic monochorionic twin pairs, failed to find evidence of any differences for most adult anthropmetry indicating that chorion type does not bias the twin design (Loos, *et al.*, 2001a). Also, blood pressure in twins during the first year of life have been shown to be independent of zygosity, the number of chorions, and placental cross circulation (Levine, *et al.*, 1994). Our within-pair analyses of monozygotic twin pairs showed no differences in birth characteristics between cases and co-twin controls, neither in the study of AMI (Paper II) nor in the study of angina pectoris (Paper III). On the other hand, such differences were observed in comparisons with external controls (Papers II-III) and within dizygotic twin pairs discordant for angina pectoris (Paper III). Therefore, it is likely that our results cannot be due to the non-generalisability from twins to singletons, but rather to genetic and/or early environmental factors.

Given the high participation rate in the cohort study in Paper IV (97%), the results derived from the nested case-control study of maternal IGF levels and preeclampsia are generalisable to all parous women giving birth in Bergen, Trondheim, and Uppsala (Paper IV). The study was restricted to parous women, and we cannot exclude differences in mean levels of IGF-I, IGF-II, and IGFBP-3 between parous women with and without preeclampsia, and nulliparous women with and without preeclampsia. However, it has been reported that parity does not influence total IGF-I in non-pregnant women (Lukanova, *et al.*, 2001).

Interpretations and implications

Breast cancer

We found that gestational age and birth anthropometrics (birth weight, birth length, and ponderal index) tended to be positively associated with risk of breast cancer in same-sexed twins. Compared to twins with gestational age less than 33 weeks, twins with gestational age of more than 40 weeks had an over eight-fold increased risk of breast cancer. Mean birth weight was generally higher among cases than both

among external and co-twin controls. No linear relationship between birth weight and breast cancer risk was observed, yet higher weight at birth seems to increase the risk.

Several studies have investigated the association between birth weight and breast cancer, but results are not entirely consistent. Eight studies have demonstrated a positive, although weak, association between higher birth weight and breast cancer risk (Ekbom, *et al.*, 1992, Innes, *et al.*, 2000, Kaijser, *et al.*, 2001, Michels, *et al.*, 1996, Sanderson, *et al.*, 1996, Stavola, *et al.*, 2000, Titus-Ernstoff, *et al.*, 2002, Vatten, *et al.*, 2002a), while five studies reported no associations (Andersson, *et al.*, 2001, Ekbom, *et al.*, 1997, Le Marchand, *et al.*, 1988, Sanderson, *et al.*, 1998a, Sanderson, *et al.*, 2002). Possible explanations of discrepancies in results might be misclassification of exposure attenuating results (Michels, *et al.*, 1996, Sanderson, *et al.*, 1996, Sanderson, *et al.*, 1998a, Sanderson, *et al.*, 2002, Titus-Ernstoff, *et al.*, 2002) and limited control of potential confounding of maternal factors related to serum levels of estrogens (e.g., maternal age, birth order, gestational age, and preeclampsia). Also, birth weight might affect the risk of premenopausal and postmenopausal breast cancer differently.

Our findings of a reduced risk of breast cancer in twins born before 33 weeks of gestation is inconsistent with two previous reports of an increased risk in very preterm born (before 33rd gestational week) women (Ekbom, *et al.*, 1997, Ekbom, *et al.*, 2000). One study, however, found a reduced risk of breast cancer in women born prematurely (before 33rd gestational week), but the finding was only based on four cases (Innes, *et al.*, 2000). Sandersson et al. (Sanderson, *et al.*, 1996) reported no effect of prematurity on breast cancer risk, yet no information on the definition of preterm was included. In addition, a recent study reported increased risk of breast cancer among women born before the 33rd week only in those with a birth weight of less than 2000 grams (Kaijser, *et al.*, 2002). The divergent findings may reflect differences in maturity between preterm born twins and singletons, also indicated by the higher survival rate among preterm twins compared to preterm singletons (Kilpatrick, *et al.*, 1996).

Few studies have investigated a possible effect of high gestational age on breast cancer risk. Our finding of a significantly increased risk of breast cancer among women with gestational age of 40 weeks or more are in agreement with two studies indicating increased risk of breast cancer in women with high gestational age (40 weeks or more) (Kaijser, *et al.*, 2001, Sanderson, *et al.*, 1998a). Accumulated hormonal exposure in utero is a function of gestational age. The association between high gestational age and risk of breast cancer suggests that differences in intrauterine estrogen exposure may be due to gestational age rather than birth weight.

Low birth weight is causally associated with risk of infant death (Buehler, *et al.*, 1987), and if high birth weight is associated with increased breast cancer risk, the exclusion of breast cancer cases with dead co-twins probably have led to an underestimation of the true association between birth weight and breast cancer risk.

Lastly, the within twin pair case-control design automatically controls for a number of general characteristics, including maternal factors related to serum levels of estrogens, genetic factors, early environmental exposures, dietary habits, and socio-economic status at birth, childhood, and adolescence. In monozygotic twins, birth weight and breast cancer risk are independent of genetic factors.

Our findings, although based on small numbers, indicate that the fetal environment might influence risk of breast cancer.

Cardiovascular disease

Our studies of twins (Papers II-III) confirmed previously reported findings in singletons of an association between low birth weight and cardiovascular disease (Barker, *et al.*, 1993c, Eriksson, *et al.*, 1999, Forsen, *et al.*, 1999, Frankel, *et al.*, 1996a, Leon, *et al.*, 1998, Osmond, *et al.*, 1993, Rich-Edwards, *et al.*, 1997). Mean birth weight, birth length, and head circumference were significantly lower among AMI cases than external (i.e., unrelated) controls (Paper II). In Paper III, low birth weight (<2.0 kg) was significantly associated with increased risk of angina pectoris in the twin cohort. After adjusting for sex, age, zygosity, body mass index, and smoking, the risk decreased and did not reach significance. Also, high birth weight (≥3.0) was significantly associated with angina pectoris before adjustment for potential risk factors. Findings from a cohort of Swedish men indicated that risks of high blood pressure (Leon, *et al.*, 1996) and low insulin sensitivity (McKeigue, *et al.*, 1998) were increased among men born with high birth weight before term. These observations may to some extent be due to that a high proportion of the pre-term infants who were heavier than expected were macrosomic infants of mothers with gestational diabetes (McKeigue, *et al.*, 1998).

In Paper II, within-pair comparisons showed no differences in birth measurements between AMI cases and co-twin controls, indicating that previously reported associations between restricted fetal growth and AMI could have been influenced by genetic and/or early environmental factors. In Paper III, we were able to further elucidate the importance of genetic and early environmental factors by separately analysing dizygotic and monozygotic twin pairs discordant for angina pectoris. Within dizygotic twin pairs, low birth weight was significantly associated with increased risk of angina pectoris. In contrast, within monozygotic twin pairs, there was no association between low birth weight and risk of angina

pectoris, indicating that genetic effects may be of importance for the association between birth weight and risk of angina pectoris. However, the findings from analyses by zygosity, should be cautiously interpreted, since small numbers of dizygotic and monozygotic twin pairs were included.

Studies in singletons have indicated that low birth weight is associated with subsequent risks of hypertension (Byberg, *et al.*, 2000, Curhan, *et al.*, 1996, Huxley, *et al.*, 2000, Law and Shiell, 1996), non-insulin dependent diabetes mellitus (Curhan, *et al.*, 1996, Lithell, *et al.*, 1996, McCance, *et al.*, 1994, Rich-Edwards, *et al.*, 1999), and impaired glucose tolerance (Hales, *et al.*, 1991, Phipps, *et al.*, 1993), whereas the association with dyslipidaemia is less clear (Barker, *et al.*, 1993b, Byberg, *et al.*, 2000, Phillips, *et al.*, 1995). Twin studies estimating differences within twin pairs – primarily investigating the association between birth weight and blood pressure – are not entirely consistent. Zhang et al. (Zhang, *et al.*, 2001) and Dwyer et al. (Dwyer, *et al.*, 1999) reported no effect of birth weight on blood pressure neither within dizygotic nor monozygotic twin pairs at 7 and 8 years of age, respectively. Christensen et al. (Christensen, *et al.*, 2001a) and Ijzerman et al. (IJzerman, *et al.*, 2000) measured blood pressure in adolescence (11 to 18 and approximately 16 to 17 years of age, respectively), and both studies reported an association between low birth weight and higher blood pressure within dizygotic but not within monozygotic twin pairs. Nowson et al. (Nowson, *et al.*, 2001) evaluated blood pressure in childhood (mean age 12 years) and adulthood (mean age 32 years). In this study, no associations between birth weight and blood pressure were found in either group of twin pairs – even after adjustment for body mass index, smoking and alcohol – or when groups were analysed by zygosity. Three studies have evaluated the association between birth weight and adult blood pressure among twins (Baird, *et al.*, 2001, Loos, *et al.*, 2001b, Poulter, *et al.*, 1999). Loos et al. (Loos, *et al.*, 2001b) found no association between birth weight and blood pressure among twins from 18 to 34 years regardless of zygosity, and similar results were obtained in the study of Baird et al. (Baird, *et al.*, 2001). However, Poulter et al. (Poulter, *et al.*, 1999) found a significant association between high birth weight and lower blood pressure within dizygotic twins but not within monozygotic twins with a mean age of 54 years (IJzerman, *et al.*, 2000).

Within-pair comparisons of low birth weight and risk of non-insulin dependent diabetes mellitus and impaired glucose tolerance are based on small numbers and the results are incompatible. Poulsen et al. (Poulsen, *et al.*, 1997) reported significant within-pair birth weight differences in both dizygotic and monozygotic twin pairs: within each pair non-insulin dependent diabetes mellitus more often occurred among twins with the lowest birth weight. Bo et al. (Bo, *et al.*, 2000) assessed within-pair birth weight differences of twin pairs discordant for abnormal oral glucose tolerance test and normoinsulinaemic normotolerant twin pairs. Monozygotic twin pairs discordant for abnormal oral glucose tolerance test showed significantly higher mean birth weight differences than monozygotic normoinsulinaemic

normotolerant twin pairs. In contrast, no significant difference in mean birth weight difference was found between the two groups of dizygotic twin pairs. Baird et al. (Baird, *et al.*, 2001) reported no correlations between within-pair differences in birth weight and glucose tolerance or body mass index, neither within dizygous nor monozygous twin pairs.

A weak positive association has been reported among monozygotic twins for the within pair difference in birth weight and body mass index in young adulthood (Johansson and Rasmussen, 2001). No significant association was found for dizygotic twins.

Lastly, the study by Ijzerman et al. (IJzerman, *et al.*, 2001) – using the same study participants as in the study of blood pressure (IJzerman, *et al.*, 2000) – found that total cholesterol, low-density lipoprotein, and apolipoprotein B were significantly associated with intra-pair differences in birth weight among dizygotic twins after adjustment for differences in current body mass index. Compared with the co-twin with the higher birth weight, the twin with the lower birth weight had higher levels of these factors, and the differences increased with increasing birth weight differences. However, in monozygotic twins the association was reversed i.e., the twins with lower birth weight had lower levels of these factors.

Possible explanations of discrepancies in the results may be that some studies of birth weight and cardiovascular risk factors within twin pairs are based on relatively small numbers of twin pairs, in particular number of monozygotic twin pairs (Baird, *et al.*, 2001, Bo, *et al.*, 2000, Dwyer, *et al.*, 1999, IJzerman, *et al.*, 2000, IJzerman, *et al.*, 2001, Poulsen, *et al.*, 1997), and the use of self-reported birth weight data (Nowson, *et al.*, 2001, Poulter, *et al.*, 1999). Moreover, in the largest study of birth weight and glucose tolerance, indirect measures of insulin secretion have been used (Baird, *et al.*, 2001). Additionally, putative effects of birth weight on blood pressure may differ in childhood, adolescence, and adulthood (Huxley, *et al.*, 2000).

In conclusion, the findings of a possible influence of early environmental factors, or in particular genetic factors, affecting the association between low birth weight and increased risk of cardiovascular disease, may be reasonable. However, inconsistent and divergent findings, and a questioned generalisability of results from twins to singletons should be further considered and thoroughly evaluated before any conclusion can be drawn.

Insulin-like growth factors in preeclamptic pregnancy

We found no significant differences in serum concentrations of IGF-I or IGFBP-3 in the 17^{th} or 33^{rd} week of gestation between women who later developed preeclampsia and healthy pregnant women. Serum

levels of IGF-II were significantly higher among preeclamptic women in the 33rd gestational week, but there was no significant difference in the 17th gestational week. Furthermore, significant positive correlations between IGF-I, IGF-II, and IGFBP-3 in the 17th and the 33rd week of gestation were found in both groups. Since levels of IGF-I, IGF-II, and IGFBP-3 change throughout pregnancy, we compared serum samples obtained in the same week of gestation (the17th and 33rd week of gestation) from women who later developed or did not develop preeclampsia. Levels of IGF-I are reported to be influenced by age (Hilding, *et al.*, 1999), but IGF-I adjusted for maternal age did not change the mean values. The preeclamptic women included in the study were from two different groups of pregnant women (the SGA high-risk group and the random group) but the results were similar for both groups.

Our findings are in contrast to previous reports from cross-sectional studies of significantly lower levels of IGF-I among preeclamptic women with clinical evidence of disease (Diaz, *et al.*, 2002, Giudice, *et al.*, 1997, Halhali, *et al.*, 2000, Lewitt, *et al.*, 1998). Notably, two of these studies included cases with severe preeclampsia (Giudice, *et al.*, 1997, Lewitt, *et al.*, 1998). Our study only included preeclamptic women with gestational age of 33 weeks or more, and 80% delivered at term (≥37 weeks). Hence, the majority of our cases probably had mild preeclampsia. Grobman et al. (Grobman and Kazer, 2001) demonstrated in a nested cross-sectional case-control study of 12 women with mild preeclamptic and 24 non-preeclamptic women, significantly higher serum levels of IGF-I during the second trimester in women who later developed preeclampsia. We used a similar approach, but found no differences in IGF-I concentration in the 17th or 33rd week of gestation, although preeclamptic women tended to have higher levels of IGF-I than non-preeclamptic women. The finding of significantly higher maternal serum levels of IGF-II in the 33rd gestational week among preeclamptic women compared to non-preeclamptic women is not in line with two earlier cross-sectional studies on maternal serum levels of IGF-II, reporting no difference between preeclamptic and non-preeclamptic women (Giudice, *et al.*, 1997, Lewitt, *et al.*, 1998). Our finding of a non-significant difference in IGFBP-3 between preeclamptic and non-preeclamptic women is in agreement with two previous cross-sectional studies (Halhali, *et al.*, 2000, Lewitt, *et al.*, 1998). To our knowledge, prospectively collected serum samples from preeclamptic and non-preeclamptic women of IGF-II and IGFBP-3 have not previously been evaluated. In agreement with previous studies, no correlation between maternal serum of IGF-I and birth weight was found (Hills, *et al.*, 1996, Holmes, *et al.*, 1998, Wang, *et al.*, 1991). Umbilical cord levels of IGF-I have been shown to be the major predictor of birth weight (Diaz, *et al.*, 2002, Fant, *et al.*, 2002, Osorio, *et al.*, 1995, Spencer, *et al.*, 1993, Vatten, *et al.*, 2002b). To sum up, possible explanations of divergent findings might be that previous studies have problems with reversed causation, i.e., preeclampsia may influence levels of IGFs and IGFBP, rather than the opposite, or there may be a decrease in levels of IGF-I and IGF-II and a corresponding increase in

level of IGFBP-3 immediately before appearance of clinical signs of disease (Giudice, *et al.*, 1997, Halhali, *et al.*, 2000, Lewitt, *et al.*, 1998).

In conclusion, there were no differences in total IGF-I and IGFBP-3 between preeclamptic and non-preeclamptic women before clinical signs of disease. Serum levels of IGF-II were significantly higher among preeclamptic women in the 33rd gestational week, yet no significant difference in the 17th gestational week was observed.

Future research

The results of the studies in this thesis give rise to additional questions that merits further attention in future research.

To increase the understanding of the association between birth characteristics and risk of breast cancer, prospective studies on maternal, or ideally, fetal levels of biological plausible hormones and breast cancer risk are needed. Additionally, studies of greater numbers of monozygotic twins discordant for breast cancer including adult life risk factors for breast cancer and maternal anthropometrics are warranted.

The finding that genetic factors may at least in part influence the association between birth weight and cardiovascular disease was based on studies of a limited number of dizygotic and monozygotic twin pairs. Studies in larger numbers of monozygotic twins with additional information about placental cross circulation and placentation i.e., whether the twins are dichorionic or monochorionic, are warranted. Exploration of the biology of impaired fetal growth in twins and singletons, and the impact on adult physiology, could be beneficial concerning the generalisability of findings in twins to singletons.

Repeated serum measurement during the last trimester may elucidate timing of the decrease in levels of IGFs among preeclamptic women. The measurement of total IGF-I and IGF-II includes both IGFs bound to binding proteins and free IGF-I or IGF-II. Since 1% or less of the IGFs are present in free form, measurement of free IGF-I and IGF-II might be more advantageous.

CONCLUSIONS

Breast cancer

Length of gestation is positively associated with risk of breast cancer among same-sexed female twins.

Birth weight, birth length, and ponderal index per se tended to be positively associated with risk of breast cancer among same-sexed female twins.

Cardiovascular disease

The association between low birth weight and cardiovascular disease in singletons – known as the fetal programming hypotheses – might have been influenced by genetic and/or early environmental factors.

Insulin-like growth factors in preeclamptic pregnancy

Preeclamptic and non-preeclamptic women do not differ in levels of total IGF-I and IGFBP-3 before clinical signs of disease. Previous findings of lower levels of IGF-I among preeclamptic women could be due to reversed causality.

Preeclamptic and non-preeclamptic women do not differ in levels of total IGF-II in the 17th gestational week, but total IGF-II is significantly higher in the 33rd gestational week among preeclamptic women.

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