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The Impact of Birth Weight on Cardiovascular Risk Factors, Coronary Heart Disease and Prostate Cancer

Population-based Studies of Men Born in 1913 and Followed up Until Old Age

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Dissertation presented at Uppsala University to be publicly examined in Rudbecksalen, Rudbecklaboratoriet, Uppsala, Thursday, November 3, 2005 at 13:15 for the degree of Doctor of Philosophy (Faculty of Medicine). The examination will be conducted in Swedish.

Abstract
Eriksson, M. 2005. The Impact of Birth Weight on Cardiovascular Risk Factors, Coronary Heart Disease and Prostate Cancer. Population-based Studies of Men Born in 1913 and Followed up Until Old Age. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 77. 74 pp. Uppsala. ISBN 91-554-6359-2.

Objectives. To study whether birth weight (BW) was correlated to cardiovascular risk factors, coronary heart disease (CHD), cardiovascular disease (CVD), and prostate cancer (PCA) at adult ages, whether a possible relationship depended on mediating factors from birth time, hereditary circumstances, and adult life variables, and what importance possible associations might have for the rate of the complaint in the general population.

Material and methods. Population-based cohorts of men born in 1913 and followed up until old age. Risk of outcome was estimated using Cox's and Poisson regressions. The results were transformed to population attributable risk percentage (PAR%) of the complaint that could be attributed to low or high BW, given causality between exposure and outcome.

Results. After adjustment for the influence of covariates, systolic blood pressure at age 50 decreased by 3.7 mmHg per 1000 g increase in BW, the prevalence of antihypertensive treatment decreased by 32%, diabetes by 53%, serum total cholesterol decreased by 0.20 mmol L-1, and being in top quintile of serum cholesterol decreased by 23%. The adjusted risks were somewhat more marked relative to the crude risks. CHD and CVD incidence and mortality were virtually unaffected by BW. In the general population, the risk percentage attributable to a BW ≤3000 g was 18% for diabetes, 2.5% for cholesterol, and ≤1% for antihypertensive treatment and CHD and CVD incidence and mortality.

PCA incidence and mortality risk increased by 62% and 82%, respectively, among those whose BW was ≥4250 g compared with those whose BW was 3001-4249 g. The risk percentages attributable to a BW ≥4250 g in the general population for PCA incidence and mortality were 7.8% and 10.8%.

Conclusions. Low BW seemed to affect cardiovascular risk factors but not incidence and mortality from CHD and CVD. A high proportion of diabetes on the community level could be attributed to low BW, while the proportional burden of other cardiovascular complaints that could be attributed to low BW was modest. PCA incidence and mortality seemed to be affected by high BW.

Keywords: birth weight, coronary heart disease, cardiovascular disease, diabetes, blood pressure, hypertension, cholesterol, prostate cancer, cohort studies, follow-up studies

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Till mamma
i tacksamhet för trygghet, omsorg, insikt och förankring

Original papers

This thesis is based upon the following publications:

STUDY I   Eriksson M, Cnattingius S, Svärdsudd K, Tibblin G. Factors associated with birth weight in Sweden: the study of men born in 1913. *J Epidemiol Community Health* 1997;51:19-23.*

STUDY II   Eriksson M, Wallander MA, Krakau I, Wedel H, Svärdsudd K. Birth weight and cardiovascular risk factors in a cohort followed until 80 years of age: the study of men born in 1913. *J Intern Med* 2004;255:236-46.**

STUDY III Eriksson M, Wallander MA, Krakau I, Wedel H, Svärdsudd K. The impact of birth weight on coronary heart disease morbidity and mortality in a birth cohort followed up for 85 years: a population-based study of men born in 1913. *J Intern Med* 2004:256:1-10.**

STUDY IV   Eriksson M, Wedel H, Wallander MA, Hugosson J, Krakau I, Carlsson S, Svärdsudd, K. The impact of birth weight on prostate cancer incidence and mortality in a population-based study of men born in 1913 and followed up from 50 to 85 years of age. Submitted.

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Contents

Introduction

Of Swedish men born in 1913 about one fifth were still alive at 85 years of age, nearly one fifth had died from coronary heart disease (CHD), an additional 11% from other cardiovascular diseases (CVD) and approximately 4% from prostate cancer (PCA). Among the middle-aged men similar prevalences of the complaints were found as for comparable age groups in the whole of Sweden [1]. CHD is the most common disease both in Sweden and in other Western societies [2], while the incidence of prostate cancer varies widely among countries. Some of the highest rates are found in Scandinavia [3], and PCA is the most common cause of death in malignant diseases for men in Sweden [4].

During most of the twentieth century, researchers have been interested in very early life influences on health and disease in adulthood. For example, in 1934 Kermack *et al.* indicated the importance of the early environment and stated, based on observations from the UK and Sweden, that death rates for a specific age group depended more on year of birth than on age at death [5]. In 1977 Forsdahl showed a significant positive correlation between current prevalence of arteriosclerotic heart disease and infant mortality rates in past years for the same birth cohort in an ecological study of specific geographic areas in Norway. He concluded that the effects, in terms of CHD, could be detrimental when people born into poverty later in life adopted more affluent Western living conditions [6].

In the mid-1980s Wadsworth *et al.* noted a negative correlation between birth weight (BW) and blood pressure among middle-aged men and women in the UK [7]. Moreover, the importance of 'critical windows' in growing animals was noted more than 100 years ago [8], and in the 1960s McCance published data on a possible influence of nutrition in such windows and the imprint of permanent changes with long-term effects on developing animals [9]. Lucas proposed the term programming for such adverse effects even in humans [10].

However, it is David Barker and his research group in the UK, later also together with epigones in other part of the world, who have emphasized the importance of early life events for later life outcome. They have done this in numerous articles since the late 1980s, indicating that inadequate foetal nutrition can give rise to an association between BWs in the lower part of the weight distribution and increased disease outcomes, primarily cardiovascular risk factors and CHD [11-14].

Some indications of an association between early life events and PCA have also been published, but then associated with BWs in the higher part of the weight distribution [15, 16].

Increasing attention has been paid to interactions between birth size and growth pattern during infancy and early childhood [17]. However, this thesis was designed to assess a possible impact of BW on later complaints and hopefully to contribute to the understanding of the natural history of these conditions.

Birth weight

Whether or not BW or measurements of foetal growth are generally useful in estimating the burden of disease in adult life is still a matter of debate [18-22]. In this study BW, as well as foetal growth, was used to characterize foetal uterine circumstances in analyses based on retrospective data from the 1910s. BW can then be treated as a proxy variable, a biological marker for the complex processes during the uterine period. Sophisticated modern measurements and well-designed clinical randomised trials can not yet be used in analyses with a latency time of a whole lifespan, when estimating proposed exposure during foetal life for detrimental outcome, foremost in old age. The need for very long follow-up times has been further emphasised, as proper testing of a potential impact of events during the foetal period on health in adulthood has to include manifested CVD incidents, and not only analyses of risk factors for the disease [23].

Both BW and birth size are determined by interaction between the foetal genome and the foetal environment, with possible influences of socio-demographic factors, maternal nutritional intake before and during pregnancy, and other factors [23, 24]. A distinction between maternal nutrition and foetal nutrition can be drawn. Foetal growth is at the end of the 'supply line' and depends on functions of all the components from maternal diet through the mother's metabolic and endocrine status, uterine blood flow, placenta transport and metabolism, umbilical cord blood flow, foetal metabolic and endocrine status to foetal tissue growth [25]. It has been suggested that if there is enough safety margin in the placenta capacity for adequate nutritional transport, major changes in maternal diet in late pregnancy have relatively little influence on foetal growth, as growth in this phase of pregnancy is regulated mainly by foetal nutrient supply [22, 25]. Maternal energy intake was suggested not to be important for BW and placental growth in industrial countries [26,27]. Others have shown that maternal nutritional balance, rather than amounts of nutrition, affects patterns of foetal growth, but does not affect BW [28, 29].

Low BW is usually defined as a weight of <2500 g at ≥37 weeks of gestation [30]. But rather than being based on fixed cut-off points, it has been

suggested that the optimal BW is the weight at which the growth potential has been achieved [18, 31-33], and disturbed BW is thus not strictly a function of being born at one of the extremes.

However, an adverse uterine environment does not necessarily affect BW, as shown in analyses from the Dutch famine period at the end of World War II. The nutritional intake for pregnant women in the first trimester was estimated to be less than 800 calories a day. Despite this mean BW for the offsprings was not lower than that for those born before the famine or conceived after the famine [34]. In contrast, living through a famine during the last trimester is thought to decrease BW by approximately 300 g [21].

Birth weight, cardiovascular risk factors and cardiovascular disease incidence

Results from many epidemiological studies in human populations have shown that men with low BW or signs of restricted foetal growth have an increased risk in adult life of cardiovascular and metabolic disorders [14, 31, 35-49] as well as increased incidence of and mortality from CHD and CVD [16, 50-58].

Various explanations have been proposed. According to the 'fetal origins hypothesis' hypertension, non-insulin dependent diabetes, dyslipidemia, and increased risk of CHD and CVD may originate from foetal adaptation to malnutrition, or to more subtle variations within the normal range of maternal diet, during critical intrauterine periods, which permanently change foetal structure, physiology and metabolism [23, 32, 59]. Once the developmental window is past, the foetus had to cope with the consequences. If the long-term environment is inappropriate (*i.e.*, excessive postnatally nutrition and possibly in combination with a sedentary lifestyle) it is proposed that the disease risk will increase, because the physiological adaptations were made in order to survive in a thrifty environment [22, 60-62].

Although size for gestational age is a marker of foetal nutrition [25], and extreme nutritional stress has detrimental consequences in animals [25], it is still uncertain whether the normal variation in maternal nutrition is the main adverse environmental influence for the corresponding programming in human offspring [18, 27, 63, 64]. Inconsistencies between study results have been shown [52, 65-68] and critical analyses have been made, where it is questioned whether the results might be biased, whether the reported negative correlations are biologically plausible and clinically important, and whether the proposed foetal origin of cardiovascular outcome really is a general phenomenon [18, 69-75] or only affects subgroups.

A second possible explanation is the 'fetal insulin hypothesis', which proposes that genetically determined insulin resistance can result in impaired

insulin-mediated BW as well as an increased risk of glucose intolerance and, later, increased incidence of CVD [76]. As insulin is one of the most important hormones for foetal growth [77], mutations in genes for normal insulin efficiency are decisive to BW. A mutation in the glucokinase gene has been recognized, but as it is rare, it could not account for the demonstrated negative association between BW and diabetes. A more common genetic factor might underpin such an inverse association, but in that case it has not yet been identified [78, 79].

Polymorphism in the gene for insulin-like growth factor-I (IGF-I) has also been shown, with effects including both reduced BW and increased risk of CHD and diabetes [80]. A 'thrifty genotype' was proposed as early as 1962, perhaps created by selection during evolution, where the foetus acquired some insulin resistance to survive in times of low nutritional levels [81]. While this genotype with reduced glucose uptake has enabled our ancestors to survive in the past, in modern society, with its abundance of food, it would have negative consequences [22, 81, 82]. However, at least partial support for genetic influence has been presented [79, 83-89].

The search for risk factors for CVD in epidemiological research has thus been broadened from traditional lifestyle variables, such as smoking habits, physical activity and socio-economic influences, to processes acting in foetal life. The proponents of the 'fetal origins hypothesis' and the 'fetal insulin hypothesis' do not, however, deny the importance of adult lifestyle factors. They only argue that these factors add to an already programmed sensitivity [48, 76, 90].

Other researchers have emphasised the impact of cumulative risks over the course of a life as being the most important [91, 92]. A possible long-term impact of infant feeding on CVD risk has been shown, where infants fed formula or fed with nutrient enriched diets as compared to infants either bottle fed on human milk or breastfed, independently of BW and gestational age, had a worse CVD profile in adolescence [8], higher blood pressure in young adult life [93] and significantly higher cholesterol levels and non-significantly raised CVD mortality in old age [50, 94]. Growth acceleration following a nutrient-enriched diet in the first weeks postnatally was suggested to be a trigger for such an association [8]. However, it has not been completely excluded that the nutritional component acts as an amplifier rather than a trigger [82], since, in a meta-analysis, the feeding pattern had no significant effects after controlling for study size and social confounding [95]. Others have shown a negative influence on CVD outcome of weight gain during childhood, but not of weight gain in infancy [56, 58]. Measures taken as early as the first weeks of life were not taken into consideration in these cases. Exceptionally detrimental effects on CHD, diabetes and blood pressure were found among those with small size at birth and during infancy followed by accelerated weight gain between ages 3 and 11 [96].

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BW and adult height have been shown to be directly correlated [31, 52, 97-99]. In many but not all studies, short individuals had higher rates of CHD than taller ones [100-102]. An inverse BW – systolic blood pressure relation in middle-aged men was found to be restricted to men of above median height [31, 103].

It has been emphasized that it is necessary to make a synthesis of genetic, foetal developmental and later postnatal environmental impacts, including lifestyle factors, in order to understand the risks across the lifespan. This implies problems in disentangling events that may be highly inter-correlated, when determining which events have the greatest influence [82]. Some evidence of interaction between the gene and environmental factors has also been indicated, as the inverse association between BW and diabetes was shown to be restricted to individuals with a polymorphism in a gene involved in insulin regulation [104].

Birth weight and prostate cancer

Age, ethnic origin and family heredity are established risk factors for PCA [3, 105]. During the past decade other factors have also been claimed to be of aetiological importance [15, 106-109]. Birth size has been shown in many studies to have a positive association with breast cancer [110-113]. Since breast cancer in women has several similarities with PCA in men, one being hormone dependence [114, 115], research has been extended to examine possible links between BW and PCA [15]. One rationale for such a link is that prenatal hormonal exposure stimulating intrauterine growth also increases the risk of PCA in adult life [106, 116]. Particular interest has been focused on the IGF-I hormone [117-121]. IGF-I measured at birth has been found to be directly associated with BW [121-124], and high IGF-I measured in adults to be associated with increased PCA risk [125-128].

However, as IGF-1 is also strongly correlated to childhood nutrition [117], and a positive association with childhood and prepubertal anthropometric data has been shown [129-131], other researchers have focused on postnatal influences in terms of modified PCA incidence [132]. Moreover, where adult height, although not without restrictions [133, 134], was used as a proxy for early childhood nutrition and growth [135], childhood energy intake and adult non-smoking related cancers were found to be positively associated [133].

Adult height and weight have shown a positive association with PCA [126, 128, 134, 136-139], although not consistently [140-142], and since BW and adult anthropometric measures have been found to be directly related [31, 38, 52, 97], these variables may act as confounders in a BW-PCA association. The results regarding this association are inconclusive to date [15, 16, 112, 115, 143-146].

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Aims of the study

The aims of the thesis were to investigate:

- whether BW and other obstetrical data from 1913 are sufficiently valid for use in research on a potential association between BW and diseases in adult life,
- whether there is an association between low BW on the one hand and cardiovascular risk factors and incidence and mortality from CHD and CVD on the other,
- whether such a possible exposure-outcome association is modified by birth time variables, familial hereditary factors and adult anthropometric, life-style and socio-economic factors,
- whether there is an association between BW and PCA incidence and mortality,
- whether such a possible exposure-outcome association is modified by birth time variables and young adult anthropometric factors,
- what importance these possible associations could have for the prevalence of cardiovascular risk factors and CHD, CVD and PCA incidence and mortality rate in the general population, provided the relationships are causal.

Study populations and methods

This thesis is based on two population based cohorts — 'The Study of Men Born in 1913' *(cohort I)* and 'The Study of Men Born in Gothenburg in 1913' *(cohort II)*. In addition, parts of these cohorts were amalgamated to a third study population *(the amalgamated cohort)*.

Cohort I

The cohort is based on a systematic sample of men born in 1913 on a day divisible by three (*i.e.* the third, sixth, ninth, *etc.* day of each month) and living in the city of Gothenburg, Sweden on their 50th birthdays. The cohort has been described in detail elsewhere [147]. Briefly, 973 men fulfilled these criteria and were invited to participate in a survey, 855 (88%) of whom were examined. Forty-four men were foreign-born and therefore excluded from this report, since it was considered impossible to find their obstetrical records. Of the remaining 811 men, 12 were excluded because of being twins, and BW was unknown for 321, figure 1. Consequently, 478 (60%) singleton born men with BW information remained for analysis. These men have been followed since, with re-examinations at ages 54, 60, 67, 75 and 80. At these re-examinations, 447, 403, 336, 233 and 140 men participated.

Cohort II

The birth cohort consists of all 1847 singleton boys born in 1913 in Gothenburg, Sweden, to mothers living in the city. BW was known for 1586 (86%), figure 1. The ambition was to follow these men until 85 years of age. However, for 33 men follow-up information was incomplete: 20 have emigrated, 11 were lost to follow-up and for two men, one of whom died after age 50, the cause of death was unknown. To facilitate comparison with other studies, only those 1319 men who were alive at age 20 with BW and complete follow-up data were used in the analyses.

Figure 1. Flow chart of the study populations
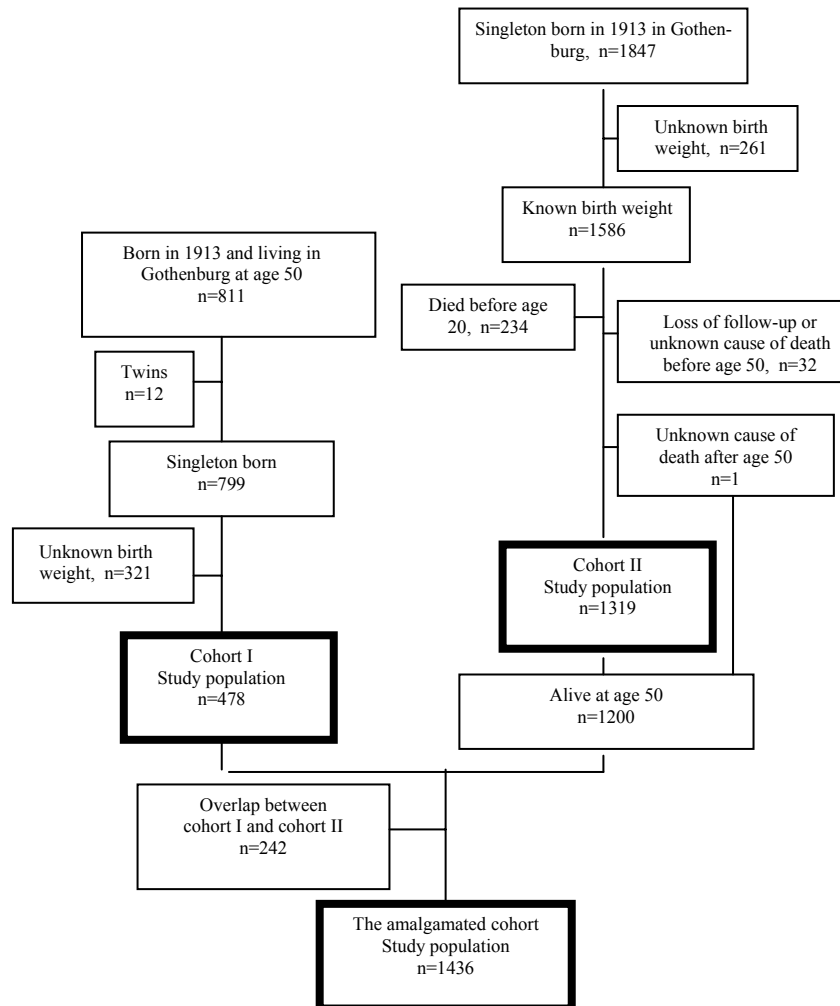
The amalgamated cohort

The amalgamated cohort was created by pooling men alive at age 50 (n=1896) in cohorts I and II. BW was known for 478 and 1200 men, respectively. After exclusion of duplicate information for 242 men who belonged to both cohorts, 1436 men constituted the study population of the amalgamated cohort, figure 1. These men were followed up until 85 years of age.

Birth weight and potential effect-modifying variables

Information from birth time

BW was mainly used as an exposure variable. In some analyses in cohort I it was also used as an outcome variable. Gestational age, place of birth, maternal parity and proteinuria, and parental social class were used as possible effect-modifying variables in the three cohorts. Maternal age and marital status and urban/rural level of the birth parish were also used in cohort I.

Information at delivery was obtained from two types of obstetrical records — case records from hospital deliveries and midwives' record books from home deliveries. The latter category also included 13 deliveries in a private maternity clinic. Information on BW, gestational age and maternal proteinuria was obtained from the obstetrical records, as were maternal parity, age, marital status, and place of birth. Supplementary information on socio-demographic variables was also derived from the midwives' original documents forwarded to the birth parish registration offices, from Nominative Extracts from Birth Registers and General Parish Registers and from Ministerial Registers and The Catechetical Examination Books of the birth parishes.

In all case records from hospital deliveries, BW was registered in grammes, while the midwives' record books from home deliveries were registered with varying levels of exactness. Hence, all BWs in this thesis were converted into grammes. The BW variable was used as a continuous variable as well as an ordinal categorical one [≤3000 g (the lowest 15%), 3001-4249 g (reference), and ≥4250 g (the highest 15%)]. As the same grouping was used in all three cohorts, the proportions given are approximate. The term 'low BW' was used to describe BW ≤3000 g and 'high BW' to describe BW ≥4250 g.

Gestational age was estimated from the date of the last menstrual period and was used as a continuous variable or as a categorical one [preterm (<37 gestational weeks or ≤258 days), term (37-41 gestational weeks or 259-293 days) and postterm (≥42 gestational weeks or ≥294 days)]. A gestational age ≥315 days was regarded as very unlikely, and such observations were excluded from the final data set. In some analyses, only term births were used; they comprised nearly three fourths of the study populations. In figure 3 gestational age is shown, divided into quartiles. Maternal proteinuria was divided into no proteinuria or proteinuria, including trace. Parity was dichotomised into mothers with no previous births and those with at least one previous birth, including stillbirths. Maternal age was defined as age at delivery. Maternal marital status was classified as married/betrothed or unmarried. The birth parishes were divided into urban or rural according to the official classification of urbanisation level in 1910 [148]. Parental occupational status, the father's or, if the mother was not married or betrothed,

mother's, was classified into high or low white collar worker, farmer and tenant farmer, and skilled or unskilled blue collar worker according to a classification used for this time period [149]. In cohort II, an urban population, only 3 parents were farmers and these were classed as low white collar workers for this study.

Information from young adulthood (Cohort II and the amalgamated cohort)

Information on adult height was obtained from military conscription records stored in the Military Archives. This variable was used in cohort II (n=1154) and in the amalgamated cohort (n=880). In the latter population, as height from military conscription was known for only 880 men, and survey data on height when the men were 50 years of age was available, information from age 50 was used for 440 men (see below). The accuracy of the height measurement at age 20 could be checked for 241 of the 1154 men in cohort II whose height was also measured at age 50. Ninety-five per cent of the height differences between ages 20 and 50 were less than 1 cm. Data on weight in young adulthood in the amalgamated cohort was obtained from military conscription records (median age 21 years, interquartile range 21-28 years) (n=826), or from recalled weight at age 20 from questionnaire information when the men were 60 years of age (n=98). For 255 men young adult weight information was available as measured weight and well as recalled weight. The interquartile range for the difference was -3 – +3 kilogrammes. However, the range must be regarded as a maximum difference and might have been narrower if the information on age had been more precise. Body mass index was computed as kg m^{-2}. These anthropometric variables were sometimes used as categorical variables divided into approximate quartiles with quartiles 2 and 3 used as reference mid-category — adult height ($\leq$170 cm, 171-179 cm, and $\geq$180 cm), young adult weight ($\leq$60 kilogrammes, 61-72, $\geq$73) and young adult body mass index ($\leq$19 kg m^{-2}, 20-23.4, $\geq$23.5).

Hereditary information (Cohort I)

Information on maternal and paternal CVD (morbidity or mortality from hypertension, myocardial infarction or stroke) and diabetes mellitus was obtained by questionnaire at ages 60 and 50, respectively.

Information from survey at age 50 or 60 (Cohort I)

Weight at age 50 was measured on a lever balance to the nearest 0.1 kilogramme with the participant in light indoor dress with no shoes, and height was measured without shoes to the nearest centimetre. Body mass index was

based on age 50 data. Information on educational level was obtained by questionnaire at age 60 and dichotomised for this report into mandatory education only or more education. Information on smoking habits was obtained by questionnaire. Data from the 1963 survey were classified for this report as currently smoking or not smoking. Information on physical activity during leisure time was obtained by questionnaire at age 50 and classified as sedentary, moderately active, active or vigorously active. Annual income was obtained from the local tax authorities when the men were 50 years of age. In the age 60 survey a quality of life instrument was used, comprising an activity score subinstrument based on 32 listed activities [150]. The men were asked to indicate, for each activity, whether they performed it often or regularly (=2), sometimes or irregularly (=1), or never (=0). A total score was given as the sum of all the activities listed.

Information from adulthood (Cohort II)

For definition of diabetes incident see below.

Outcome variables

Cardiovascular risk factors (Cohort I)

Data from the six surveys done during the follow-up period were used to define five cardiovascular risk factors. At all surveys, blood pressure was measured in the right arm in the seated position after five minutes' rest, at the first survey to the nearest 5 mmHg and at the following examinations to the nearest 2 mmHg. All measurements were performed in the morning. The measurements from age 50 were used for this report. At all surveys, men who had blood pressure ≥160/≥90 and no antihypertensive treatment were subjected to a clinical work-up and offered antihypertensive treatment if they were found to be hypertensive. A hypertension variable was created, dichotomised into those who received antihypertensive treatment at any time during follow-up and those who did not.

Information on whether or not the participant had a diagnosis of diabetes was based on questionnaire data and checked against medical record information throughout the follow up. The diabetes cases were predominantly non-insulin dependent. Serum total cholesterol and serum triglycerides were determined from blood samples drawn after an overnight fast using the same analysis method throughout the follow up. Waist circumference was measured in all the surveys with a tape measure at the level of the umbilicus. The measurements at age 50 or 54 were used. In addition, measurements that at any time during follow-up were in the top quintile for serum cholesterol,

triglycerides or waist circumference distribution were regarded in this report as being an outcome event.

Incidence and mortality from coronary heart disease, cardiovascular disease and diabetes (Cohort II)

Information on vital status and cause of death was obtained from death certificates and manually operated population registers prior to 1960, and later from the National Cause of Death Register. CHD was defined using the International Classification of Diseases (ICD) 9th revision (Swedish version) codes 410-414, CVD using codes 390-459, and diabetes using code 250. Corresponding codes were used in earlier or later ICD versions.

Information on hospital admissions was obtained from the Swedish National Register of Hospital Care, an official nationwide registry of all admissions to hospital from 1969 and onwards. For this report, date of admission, main discharge diagnosis and additional diagnoses were used. Morbidity incident cases were defined as patients discharged from hospital with a CHD or CVD diagnosis, or deceased with CHD or CVD as the underlying cause of death. In addition, a second, broader definition was used to include those who died of other causes but who had CHD or CVD as contributing diagnoses.

A diabetes diagnosis was based on the main hospital discharge diagnosis or additional diagnoses or underlying or contributing causes of death. The diabetes cases were predominantly non-insulin dependent.

Those who survived until age 20 were followed up from then on. Mortality follow-up time was calculated as number of days from the 20th birthday until first CHD or CVD event, or for those free from CVD, until the 85th birthday. Incidence follow up was measured accordingly.

Incidence and mortality from prostate cancer (The amalgamated cohort)

PCA incidents and fatalities were ascertained from information from the National Swedish Cancer Registry and the National Cause of Death Register, and defined using the International Classification of Diseases (ICD) 7th revision (Swedish version) code 177 and corresponding codes in later ICD versions. Underlying and contributing causes of death were used. Information on vital status was obtained from the National Cause of Death Register.

The study population was followed up from age 50 and on. PCA incidence follow-up time was calculated as number of days from 50th birthday until the first PCA event, or for those free from PCA, until the 85th birthday. Mortality follow up was measured accordingly. Among those who had no

incident or fatal PCA event, one person was censored for reasons other than complete follow-up time.

The study was approved by the Research Ethics Committees of Göteborg and Uppsala Universities.

Effects of non-participation

Among the 799 men in the total cohort population for cohort I obstetrical records were less often traceable in rural birth parishes than in urban ones, figure 1 and table 1. Moreover, among social class groups, farmers (social class III) had the highest rates of untraced BW. If farmers were excluded, there were no differences in the parents' social status in 1913 between those with known BW (n=478) and others (n=321). There were no significant differences between the groups regarding the traditional risk factors for CVD, including blood pressure, cholesterol, triglycerides, weight, height, body mass index and smoking habits at age 50. However, men for whom BW was known had somewhat higher systolic blood pressure (p=0.09). Among the other possible covariates from adult life the discrepancies in maternal CVD morbidity and physical activity between men with known BW and men whose BW was unknown were significant. As the study policy was to include as many as possible of the original 478 men in all re-examinations during follow up, those who missed one examination could be reincluded in a later one. This design minimised the study population attrition. Seventy-six per cent of those not participating in the examination at 80 years had died.

There were no substantial differences in the distribution of birth time variables in the total birth cohort population (n=1847), among those for whom BW data could be retrieved (n=1586), and among those who were alive at age 20 and for whom follow-up data were available in cohort II (n=1319), figure 1 and table 6. There were no significant differences in CHD incidence and mortality data or in diabetes incidence between men for whom BW and follow-up data were known (n=1576) and others (n=271). The same was true if those who died before age 20 were excluded. Men with no adult height information (n=165) were significantly younger at death than other men (n=1154), but there were no significant differences in BW, CHD mortality rate or age at CHD mortality.

In the amalgamated cohort, the cumulative rates for PCA incidence and mortality were the same in the study population (n=1436) and in the total cohort population (n=1896), and there was no significant age difference at the time of the PCA incident or mortality between those for whom BW was known and others. The same was true for differences in adult height, young adult weight and body mass index. There were thus no obvious selection effects regarding these variables.

Table 1. *Characteristics of men with known and men with unknown birth weights (Cohort I)*

	N	Known birth weight				Unknown birth weight				p-value
		N	%	Mean	SD	N	%	Mean	SD	
Variables from birth time:										
Urbanisation level of the birth parishes, 1910	799									<0.001
Urban	378	295	78.0			83	22.0			
Rural	421	183	43.5			238	56.5			
Social class	776									0.080
I: high white collar	24	14	58.3			10	41.7			
II: low white collar	124	82	66.1			42	33.9			
III: farmer	69	32	46.4			37	53.6			
IV: skilled worker	210	134	63.8			76	36.2			
V: unskilled worker	349	209	59.9			140	40.1			
Variables from adulthood (mainly age 50):										
Weight	796	476		75.9	11.5	320		75.8	10.0	0.880
Height	796	476		175.3	6.0	320		174.9	5.9	0.461
Body mass index	796	476		24.7	3.4	320		24.7	2.9	0.820
Blood pressure										
Systolic	799	478		139.2	21.1	321		136.7	20.0	0.088
Diastolic	799	478		91.8	13.6	321		90.6	12.2	0.195
Cholesterol	799	478		6.34	1.08	321		6.34	1.08	0.938
Triglycerides	799	478		1.26	0.71	321		1.23	0.71	0.591
Waist circumference (age 54)	735	444		86.8	9.7	291		86.8	8.9	0.915
Quality of life	615	373		19.0	7.0	242		19.8	7.5	0.185
Annual income	771	467		17 004	10 570	304		16 979	9 846	0.974
Smoking habits	799									0.838
Current smoker	452	269	59.0			183	40.5			
Non-smoker	347	209	60.2			138	39.8			

Education	651						0.582
Mandatory	357	211	59.1		146	40.9	
More than mandatory	294	180	61.2		114	38.8	
Physical activity	781						0.005
1	282	189	67.0		93	33.0	
2	250	138	55.2		112	44.8	
3	249	137	55.0		112	45.0	
Hereditary variables:							
Paternal diabetes	799						0.210
Yes	38	19	50.0		19	50.0	
No	761	459	60.3		302	39.7	
Maternal diabetes	799						0.545
Yes	64	36	56.3		28	43.8	
No	735	442	60.1		293	39.9	
Paternal CVD	634						0.393
Yes	147	93	63.3		54	36.7	
No	487	289	59.3		198	40.7	
Maternal CVD	644						0.008
Yes	146	101	69.2		45	30.8	
No	498	284	57.0		214	43.0	
Total	799	478	59.8		321	40.2	

Figure 2. Distribution of birth weight (grammes) for hospital and home deliveries
(Hospital deliveries are the darkest shadows)
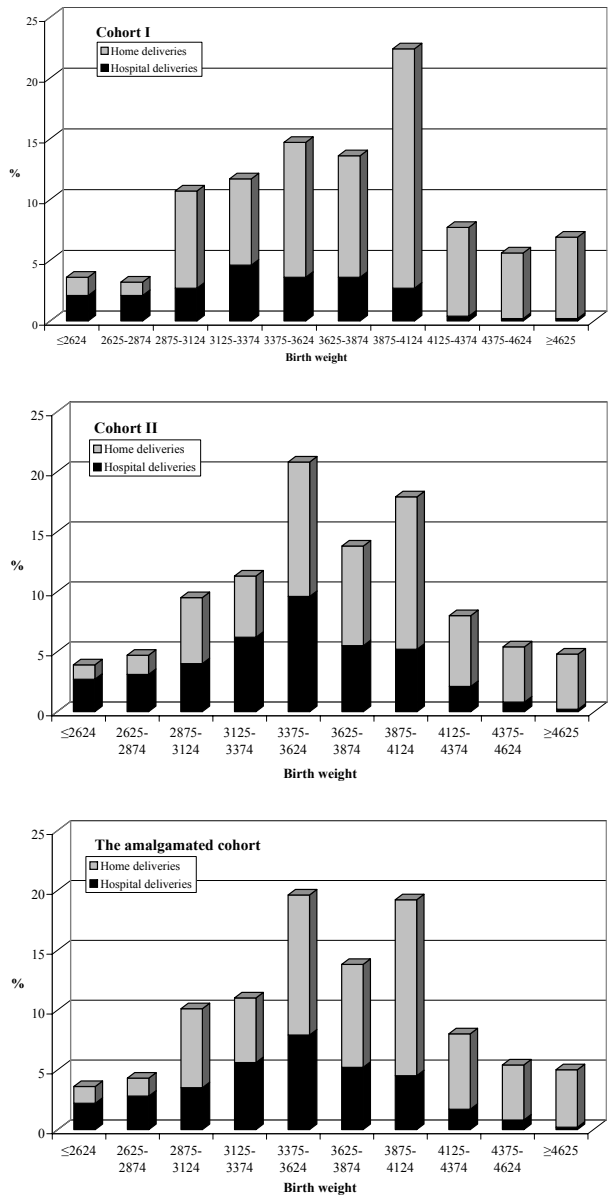
Accuracy of birth weight notations

Compared with hospital deliveries, the BW distribution of home deliveries was shifted to the right, figure 2. The mean BW of infants delivered at home exceeded mean BW of infants delivered in hospital by 465 g in cohort I, 338 g in cohort II and 329 g in the amalgamated cohort. BW notation precision differed between home and hospital deliveries, table 2. In all hospital deliveries, BWs were noted in grammes or in kilogrammes with one decimal, while in home deliveries several different notation levels were used. When home delivery BWs noted in grammes were used, the difference in BW between infants born at home and in hospital remained. In addition, home delivery BWs with less precise notation were consistently higher than BWs in hospital deliveries. In cohort I, 19% were recorded as kilogrammes, 14% to the nearest quarter of a kilogramme, and 63% with greater precision. The corresponding proportions in cohort II were 11%, 14%, and 73%.

Statistical considerations

The analyses were conducted using the SAS [151] and JMP [152] statistical programme packages. Considering the old data and the long-term follow up, the partial non-response rate (missing data in the final data set) was generally low for all potential effect-modifying variables except for weight in young adulthood (35%) and height (≤12%). It was 7-10% for gestational age and for quality of life score, 2-6% for maternal proteinuria, parity, marital status and age, parental social class and CVD risk factors, and own education, yearly income and physical activity, and <1% for the other variables.

Summary statistics, such as means, proportions and measures of dispersion were computed using standard methods. Group comparisons were performed with Student's t-test, analysis of variance or the chi-square test. For correlation analyses, Pearson's parametric and Spearman's non-parametric correlation coefficients were used.

In two regression analyses, BW was treated as a dependent variable. A stepwise regression was used to give the variables independently related to BW, and the regression surface in figure 3 was constructed by using an isotonic regression technique. Otherwise, BW was handled as an exposure variable.

Univariate and multivariate analyses of outcome in relation to BW and potentially modifying variables were performed with standard least squares linear regression analysis when outcomes were continuous and with Cox's proportional hazards regression analysis when outcomes were dichotomised. For continuous outcomes the effect estimates were presented as a difference with its 95% CI, while the effect estimates for dichotomised outcomes were presented as hazards ratios with their 95% CI.

Table 2. *Birth weights (BWs) in hospital and home deliveries by precision of notation in grammes (g)*

	Cohort I n=478				Cohort II n=1319				The amalgamated cohort n=1436			
	Hospital delivered		Home delivered		Hospital delivered		Home delivered		Hospital delivered		Home delivered	
	g	%	g	%	g	%	g	%	g	%	g	%
BW in grammes or in kilo-grammes with one decimal	3352	22.2	3770	40.8	3451	39.3	3780	33.7	3453	34.3	3760	35.8
BW in quarter kilogrammes			3866	14.4			3781	13.8			3773	13.7
BW in kilogrammes			3870	19.2			3859	10.8			3856	13.5
Other BW notations			3888	3.3			3642	2.4			3737	2.7

The analyses were performed with BW as a continuous variable or divided into three categories, in the former case to obtain the effect across the whole BW range, expressed as an incidence change associated with 1000 grammes increase in BW, in the latter case to obtain the effects in various parts of the range relative to the reference mid-category. The two sets of CHD and CVD incidence and mortality outcome data were tested separately. Since the results were similar only those based on the narrower definition are presented.

Generally all years included in the follow-up times for the individual cohorts were analysed simultaneously in the regression analyses. However, in the amalgamated cohort, analyses were also done on two follow-up groups (50-69 and 70-85 years of age).

In addition, analyses of PCA incident events in relation to BW groups were checked with Poisson regression analysis. The effect estimates of BW were then presented as hazards (exponential β–estimates) and as hazards ratios for the exposed high BW group relative to the reference BW mid-category (figure 6). A log-linear Poisson model with a hazard function, piecewise linear around 70 years of age, was used to estimate the hazards.

In the analyses of influences of BW and possible modifying variables on cardiovascular risk factors three models were used in the regression analyses, tables 11 and 12. In model 1, BW was used as the only independent variable and in model 2 BW and weight at age 50 were used. In model 3 all independently related birth time variables to BW, parental social class, and possible heredity and adult life modifying variables which were correlated to BW or an outcome variable with a p-value ≤0.01 were included. Backward elimination was done until the remaining variables except for BW, which was always kept, were significant. The third model was then repeated with restriction to term births and to those with BWs registered with the greatest exactness. In corresponding regressions on CHD and CVD incidence and mortality, table 14, only one model including BW and gestational age was used, but repeated with restrictions as above, together with home or hospital deliveries. For analyses of non-linear associations a new variable, continuous BW squared, was added in the regression re-analyses.

The non-parametric Kaplan-Meier method was used to illustrate the univariately cumulative CHD mortality course of events in relation to BW, figure 5. Parameter estimates from linear regression were used to compute the data for figure 4.

To check the magnitude of selection effects owing to missing data on young adult weight, height, and body mass index data, Cox's multivariate regression analyses were redone, with the missing data replaced by the total mean value or subgroup mean values.

Population attributable risk percentage (PAR%), a measure of the proportion of an outcome in the population that could be eliminated if the exposure were eliminated, given the assumption of causality, was calculated as: $[(I_P-I_0)/I_P] \times 100$, where I_P is the outcome incidence rate in the population and I_0 is

the outcome incidence rate in the non-exposed group. The exposed group for antihypertensive treatment, diabetes, highest quintile total cholesterol, CHD and CVD was defined as those with a BW ≤3000 g. For PCA the exposed group was those with a BW ≥4250 g.

All tests were two-tailed. Generally, p-values <0.05 were regarded as statistically significant. However, when selecting covariates for the regression analyses these variables had to be correlated to either exposure or outcome with a p-value ≤0.01, in order to avoid problems with mass-significance. Very low p-values were denoted <0.001. The confidence intervals (CI) presented for mean values, proportions, and hazards ratios were 95%.

Results

Characteristics of the study populations

Cohort I

BW was known for 60% of the study population. Mean (±SD) BW and gestational age for the 478 men who participated in the initial examination at age 50 were 3714 ±609 g and 280 ±15 days, respectively, table 3. Mean maternal age was 29.5 (±6.3) years. Eighty-four per cent of the mothers were married or betrothed, 26% gave birth for the first time and 13% had proteinuria or traces of proteinuria. Seventy-eight per cent of the men were delivered at home and 22% in a hospital. Nearly 75% of the parents were skilled or unskilled workers and more than 60% came from urban parts of Sweden.

There was no obvious selection effect in terms of mean BW for the men who participated in the examinations during follow up and those who did not, table 4. The tendency for a significant difference in BW at age 54 was of minor importance since nearly half of those who missed the examination that year were reincluded later during follow up; the BWs for permanent drop-outs and others were 3659 g and 3716 g, respectively (p=0.707). However, the proportion of men with BWs of 3000 g or less tended to decrease from age 75, table 5.

The proportion of men on antihypertensive treatment was 2.1% at age 50 and 27% at age 80, table 5. The cumulative incidence rate was 23%. The cumulative rates for diabetes mellitus and the proportion of men who at any time during follow up were in the top quintiles of total serum cholesterol, serum triglycerides and waist circumference were 11%, 40%, 39%, and 32%, respectively.

Cohort II

Mean (±SD) BW and mean gestational age were 3616 ± 621 g and 278 ± 16 days, respectively, among those 1586 (86%) for whom BW data could be retrieved, table 6. Approximately one third were their mother's first child, one tenth of the mothers had proteinuria or traces of proteinuria, and six out of ten were born at home. About 75% of the parents were skilled or unskilled workers. There were no substantial differences in the distribution of these

Table 3. *Birth weight mean and standard deviation (SD) in groups according to gestational age, maternal socio-demographic characteristics and maternal protein-uria, and place of birth (Cohort I)*

			Birth weight	
	Number	%	Mean	SD
Birth weight, grams	478	100	3714	609
Gestational age, weeks				
Preterm (<37)	28	6	3161	638
Term (38-41)	343	72	3732	573
Postterm (≥42)	53	11	3877	529
Unknown 45 + 9 excluded	54	11	3731	738
Maternal age				
15-19	21	4	3540	803
20-24	104	22	3582	652
25-29	127	27	3699	534
30-34	106	22	3851	598
35-39	83	17	3693	613
40-49	32	7	3913	501
Unknown	5	1	3742	799
Maternal marital status				
Married / betrothed	401	84	3760	606
Unmarried	68	14	3473	601
Unknown	9	2	3512	263
Maternal parity				
First child	123	26	3405	574
≥2 children	336	70	3820	590
Unknown	19	4	3848	485
Maternal proteinuria				
No	387	81	3732	617
Yes	61	13	3542	569
Unknown	30	6	3841	534
Place of birth				
Home deliveries	372	78	3817	592
Hospital deliveries	106	22	3352	528
Parental social class 1913				
I: high white collar	14	3	3631	778
II: low white collar	82	17	3683	570
III: farmer	32	7	3809	579
IV: skilled worker	134	28	3712	635
V: unskilled worker	209	44	3708	595
Unknown	7	2	4026	816
Urbanisation level of the birth parishes, 1910				
Urban	295	62	3710	616
Rural	183	38	3720	599

Table 4. *Number and mean birth weight (BW) (grammes) for participants and non-participants in the various surveys from 50 to 80 years of age (Cohort I)*

	Participants		Non-participants		
	n	mean BW	n	mean BW	p-value
Age at examination					
50	478	3714	-	-	
54	447	3701	31	3907	0.068
60	403	3715	75	3707	0.911
67	336	3711	142	3721	0.878
75	233	3703	245	3725	0.691
80	140	3755	338	3697	0.340

variables in the total birth cohort population (n=1847), among those for whom BW data could be retrieved (n=1586), and among those who were alive at age 20 and for whom follow-up data were available (n=1319). Mean (±SD) height at young adult age was 175 ±6 cm. Twelve per cent had a diabetes diagnosis during the follow-up period.

At the end of follow up, 18% of the original cohort were still alive, 80% were known to be deceased, and 2% were lost to follow up, table 7. The proportions were similar among those with known BW and those surviving until age 20 with known outcome, as was the distribution of underlying causes of death. Sixty-two per cent of the CVD cases were due to CHD. Among those who survived until age 20 and for whom BW was retrieved, 65% had had one or more CVD incidents.

The amalgamated cohort

In the study population with known BW (n=1436, 76%) mean (±SD) BW and mean gestational age were 3669 ± 583 g and 279 ± 14 days, table 8. Approximately one third were their mother's first child, 12% of the mothers had proteinuria and 66% were delivered at home. Nearly 75% of the parents were skilled or unskilled workers. Mean (±SD) height, weight and body mass index were 175.2 ± 6.3 cm, 67.2 ±8.0 kg and 21.9 ± 2.2 kg m^{-2}, respectively.

The cumulative rates for PCA incidence and mortality until age 85 were 8.4% and 4.7%. These rates were the same in both the study population and the total cohort population (data not shown).

Table 5. *Numbers and percentages of men in groups according to exposure and outcome variables (Cohort I)*

| | Survey at age | | | | | | | | | | | | 50-80 years | |
| | 50 | | 54 | | 60 | | 67 | | 75 | | 80 | | | |
	n	%	n	%	n	%	n	%	n	%	n	%	n	%
n	478		447		403		336		233		140		478	
Birth weight, grammes														
≤3000	76	15.9	72	16.1	62	15.4	54	16.1	30	12.9	15	10.7		
3001-4249	311	65.0	292	65.3	263	65.3	216	64.3	162	69.5	97	69.3		
≥4250	91	19.0	83	18.6	78	19.4	66	19.6	41	17.6	28	20.0		
Outcome,														
Antihypertensive treatment	10	2.1	31	6.9	38	9.4	55	16.4	44	18.9	38	27.3	112	23.4
Diabetes	10	2.1	12	2.7	22	5.5	29	8.6	18	7.7	11	7.8	54	11.3
Total cholesterol top quintile	99	20.7	-	-	90	22.3	67	19.9	51	21.9	29	20.7	191	40.0
Triglycerides top quintile	96	20.1	-	-	82	20.4	70	21.4	47	20.2	31	22.1	188	39.3
Waist circumference top quintile	-	-	88	19.8	80	19.9	70	20.8	45	19.3	28	20.1	147	32.0

Table 6. *Characteristics of the study population at birth (Cohort II)*

	Total population		All				Alive at 20 and complete follow up			
			Population with known birth weight							
	N	%	N	%	mean birth weight	P	N	%	mean birth weight	p
n	1847		1586				1319			
Birth weight, grams					3616				3656	
≤2750	124	6.7	124	7.8			83	6.3		
2751-3000	142	7.7	142	9.0			117	8.9		
3001-3249	115	6.2	115	7.2			90	6.8		
3250-3999	713	38.8	713	45.0			603	45.7		
4000-4249	255	13.8	255	16.1			221	16.8		
4250-4500	156	8.4	156	9.8			133	10.1		
>4500	81	4.4	81	5.1			72	5.4		
Unknown	261	14.1	0	-			0	-		
Gestational age, weeks						<0.001				<0.001
Preterm (<37)	134	7.3	126	7.9	3049		85	6.4	3331	
Term (37-41)	1215	65.8	1159	73.1	3649		982	74.5	3658	
Postterm (≥42)	174	9.4	165	10.4	3787		142	10.8	3823	
Unknown	324	17.5	136	8.6	3648		110	8.3	3677	
Maternal parity						<0.001				<0.001
First child	544	29.4	522	32.9	3440		419	31.8	3476	
≥ 2 children	1104	59.8	1033	65.1	3707		873	66.2	3742	
Unknown	199	10.8	31	2.0	3558		26	2.0	3650	

Continuation of table 6	Total population		All				Alive at 20 and complete follow up			
	N	%	N	%	mean birth weight	P	N	%	mean birth weight	p
Maternal proteinuria						>0.2				0.092
No	1414	76.6	1350	85.1	3613		1128	85.5	3658	
Yes	191	10.3	178	11.2	3596		144	10.9	3593	
Unknown	142	13.1	58	3.7	3753		47	3.6	3805	
Place of birth						<0.001				<0.001
Home	1056	57.2	942	59.4	3758		800	60.7	3789	
Hospital	646	35.0	644	40.6	3408		519	39.3	3451	
Unknown	145	7.8	0	-	-		0	-	-	
Parental social class, 1913						>0.5				>0.3
I: high white collar	67	3.6	61	3.8	3653		53	4.0	3647	
II: low white collar	309	16.7	276	17.4	3639		235	17.8	3705	
III: farmer	3	0.2	1	0.1	2700		1	0.1	2700	
IV: skilled worker	580	31.4	512	32.3	3600		432	32.8	3646	
V: unskilled worker	782	42.4	666	42.0	3617		544	41.2	3649	
Unknown	106	5.7	70	4.4	3611		54	4.1	3618	
Height at age 20, cm										<0.001
≤170							278	21.1	3528	
171-179							601	45.6	3659	
≥180							275	20.8	3810	
Unknown							165	12.5	3604	
Diabetes during follow-up period										<0.001
Yes							156	11.8	3542	
No							1163	88.2	3671	

Table 7. *Characteristics of the study population (Cohort II) during follow up. Underlying cause of death for those who died during follow up until 85 years of age and main or additional diagnosis for those who were admitted to hospital in 1969-1998*

	Total population		Population with known birth weight			
			All		Alive at age 20 and complete follow-up	
	N	%	N	%	N	%
Population at risk	1847		1586		1319	
Loss to follow up	39	2.1	31	1.9	0	-
Alive at end of follow up	332	18.0	288	18.2	288	21.8
Known fatalities	1476	79.9	1267	79.9	1031	78.2
Deaths from known fatalities	1471	81.4	1265	81.4	1031	78.2
Cardiovascular disease	563	31.1	490	31.5	487	36.9
Coronary heart disease	352	19.5	304	19.5	304	23.0
Other causes	913	50.5	777	50.0	544	41.2
Deaths from unknown cause	5	0.3	2	0.1	0	-
Morbidity						
Cardiovascular disease	991	53.7	862	54.4	859	65.1
Coronary heart disease	584	31.6	502	31.7	502	38.1

Associations between birth time variables and independent effect-modifying variables from birth time (Cohort I)

Mean BW increased with gestational age and maternal age up to the age group 30 to 34 years, was higher among infants of married mothers as compared with infants of unmarried mothers, higher among offspring of parous as compared with offspring of nulliparous women, higher among men delivered at home as compared with men delivered in hospital, and decreased with the presence of proteinuria, table 3. All these associations and differences were significant, table 9. No correlation between BW and parental social class and urbanisation level was found. Maternal socio-demographic characteristics were all significantly correlated to place of birth. Compared with mothers delivering at home, mothers delivering in hospital tended to be younger and were more often from lower social classes, unmarried and nulliparous. The same pattern was found in cohort II and in the amalgamated cohort.

Table 8. *Characteristics and follow-up data of study population (The amalgamated cohort)*

	N	%	Mean	95% CI
Birth weight (grammes)	1436		3669	3639-3699
≤3000	219	15		
3001-4249	987	69		
≥4250	230	16		
Gestational age (weeks)	1301		279	278-280
preterm (<37)	93	7		
term (37-41)	1050	81		
postterm (≥42)	158	12		
Maternal parity (percentage 1st child)		32		
Maternal proteinuria (percentage with)		12		
Place of birth (percentage home deliveries)		66		
Parental social class (percentage workers)		74		
Adult height (cm)	1320		175.2	174.8-175.5
≤170	303	23		
171-179	692	52		
≥180	325	25		
Young adult weight (kg)	924		67.2	66.6-67.7
≤60	185	20		
61-72	540	58		
≥73	199	22		
Young adult body mass index (kg m^{-2})	921		21.9	21.7-22.0
≤19	172	19		
20-23.4	571	62		
≥23.5	178	19		
Age at prostate cancer incidence			74.2	72.8-75.5
Population at risk at 50 years of age	1436	100		
Prostate cancer - incidents	120	8		
Prostate cancer – mortality	68	5		
Deaths without prostate cancer diagnose	1000	70		
unknown diagnose	1	<1		
Censored at 85 years of age	315	22		

Variables correlated to BW were included in a stepwise multiple linear regression analysis. Place of birth, gestational age, parity and proteinuria remained significantly and independently associated with BW (the first three with p-values <0.001), whereas maternal age and marital status were not. These significant variables were thenceforth used when searching for possible effect-modifying birth time variables in analyses of relations between BW and outcomes. Parental social class were added despite not being significantly related to BW.

Table 9. *Correlation matrix of variables possibly correlated to birth weight. r=correlation coefficient and p=the corresponding p-value (Cohort I)*

		Birth weight	Gestational age	Maternal age	Maternal marital status	Maternal parity	Maternal proteinuria	Parental social class	Urbanisation level
Gestational age	r	0.258							
	p	<0.001							
Maternal age	r	0.137	0.053						
	P	0.003	0.280						
Maternal marital status	r	- 0.160	- 0.137	- 0.389					
(Married=1; Unmarried=2)	P	<0.001	0.005	<0.001					
Maternal parity	r	0.301	0.084	0.456	- 0.271				
(No children=0; ≥1 child=1)	P	<0.001	0.093	<0.001	<0.001				
Maternal proteinuria	r	- 0.111	- 0.007	- 0.003	0.005	0.001			
(No=0; Yes=1)	P	0.018	0.884	0.950	0.917	0.987			
Parental social class	r	0.009	- 0.065	- 0.114	0.166	0.020	0.103		
(I-V)	P	0.852	0.189	0.014	<0.001	0.676	0.031		
Urbanisation level	r	0.040	- 0.044	0.015	- 0.126	- 0.004	0.037	0.005	
(Urban=1; Rural=2)	P	0.382	0.362	0.752	0.006	0.936	0.438	0.922	
Place of birth	r	- 0.324	- 0.111	- 0.256	0.411	- 0.260	0.087	0.130	- 0.234
(Home=1; Hospital=2)	P	<0.001	0.023	<0.001	<0.001	<0.001	0.067	0.005	<0.001

Figure 3. Birth weight by place of birth, parity and gestational age (Cohort I)
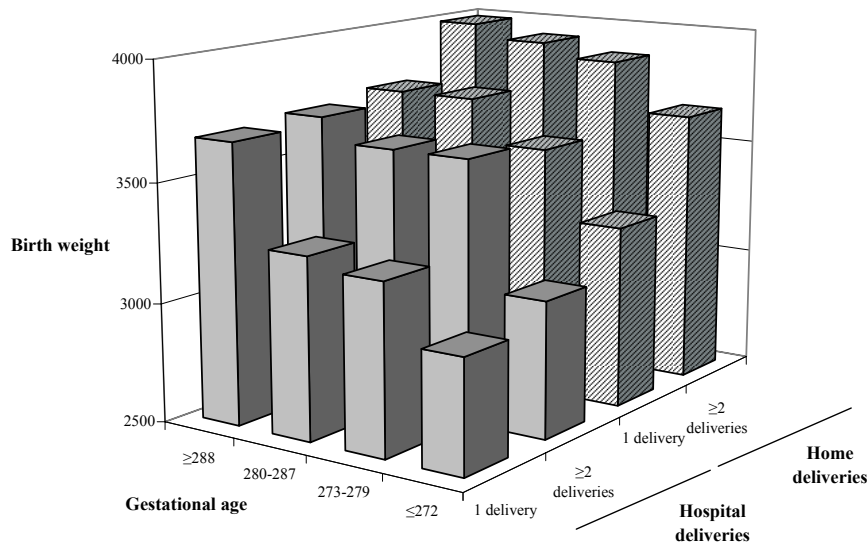
The combined impact of the variables place of birth, parity and gestational age on BW is shown in figure 3. The smallest babies were those who were born in hospital, who were their mothers's first child and where the gestational period was estimated to be 272 days or less (2975 g). At the opposite extreme were babies born at home whose mothers had given birth before and where the gestational age was estimated to be more than 288 days (3986 g).

Birth weight and cardiovascular risk factors (Cohort I)

BW and systolic blood pressure at 50 years of age were not significantly related (p=0.09), table 10. However, men who had antihypertensive treatment at any time during follow up had significantly lower BWs than other men. The same applied to men who developed diabetes during follow up. Serum total cholesterol at the age of 50 was significantly inversed associated with BW. The difference between men who had a serum total cholesterol in the top quintile at anytime during follow up and other men was of borderline significance. The association between BW and waist circumference at 54 years of age was not significant, while men in the top quintile of waist circumference anytime during follow up had higher BWs. There were no significant correlations between BW and serum triglycerides.

Table 10. *Birth weight according to outcome variables during the follow-up period 50-80 years of age (Cohort I)*

	N	Variable		Birth weight		
		Mean	SD	Mean grammes	95% CI	p
Systolic blood pressure, 50 yrs, mm Hg	478	139.2	21.1	3714		0.093
Antihypertensive treatment, 50-80 yrs	112			3605	3510-3700	0.030
No antihypertensive treatment, 50-80 yrs	366			3747	3682-3813	
Diabetes, 50-80 yrs	54			3516	3320-3712	0.011
No diabetes, 50-80 yrs	424			3739	3683-3796	
Total cholesterol, 50 yrs, mmol/l	478	6.34	1.08	3714		0.015
Total cholesterol top quintile, 50-80 yrs	191			3647	3556-3739	0.051
Not total cholesterol top quintile, 50-80 yrs	287			3759	3691-3826	
Triglycerides, 50 yrs, mmol/l	478	1.25	0.71	3714		0.537
Triglycerides top quintile, 50-80 yrs	188			3717	3633-3800	0.939
Not triglycerides top quintile, 50-80 yrs	290			3712	3640-3785	
Waist circumference, 54 yrs, cm	444	86.8	9.7	3701		0.158
Waist circumference top quintile, 54-80 yrs	147			3800	3700-3900	0.041
Not waist circumference top quintile, 54-80 yrs	312			3675	3608-3742	

However, the association found between BW and outcome may have been affected by a number of other factors. For this reason, covariates correlated with a p-value ≤0.01 to BW or to the significant or almost significant outcome variables in table 10 were chosen for further analysis. Weight at 50 years of age was correlated to BW and all outcome variables, whereas the others were either correlated to BW (gestational age, place of birth and parity) or to outcome (maternal diabetes morbidity and smoking habits). Body mass index was not used as a covariate, to prevent collinearity problems with weight.

The results of a series of standard least squares regression analyses and Cox's regression analyses are shown in table 11 and table 12. The decrease in systolic blood pressure at 50 years of age was 2.7 mmHg per 1000 g increase in BW (model 1) and was somewhat more marked (-3.7 mmHg) by adjusting for weight at 50 years (model 2) or the significant covariates (model 3). The rate ratio of receiving antihypertensive treatment decreased significantly, by 27% per 1000 g increase in BW (model 1). After adjustment for weight at age 50 (model 2) or the significant covariates (model 3), the rate ratios were largely unaffected. The effects of BW on antihypertensive treatment appeared to be linked to a low incidence rate among men with a BW ≥4250 g rather than being an effect among those with a BW ≤3000 g.

The rate ratio of getting a diabetes diagnosis decreased by 43% per 1000 g increase in BW and remained significant after the potential influence of other factors was taken into account. *Post hoc* analyses showed tendencies towards non-linear associations across the BW categories (p-values 0.07-0.10).

Serum total cholesterol at 50 years decreased by 0.20 mmol/L per 1000 g increase in BW. The rate ratio of having a total cholesterol value in the top quintile of the distribution decreased significantly by 22% per 1000 g increase in BW. These levels were largely unaffected by adjustment for other factors. The effects appeared to be linear across BW categories.

The effects of 1000 g increase in BW on waist circumference at 54 years was 1.1 cm, not significant. The rate ratio of being in the top quintile of waist circumference tended to increase with higher BW [28% per 1000 g increase in BW (CI: 0.98-1.67)]. Adjusted differences or ratios were far from significant.

When only BWs from term births or only BWs registered with the highest precision were used, the magnitude of the effects of BW on systolic blood pressure, antihypertensive treatment, diabetes, total cholesterol, and being in the total cholesterol top quintile remained fairly constant.

The influence of BW on the three outcomes antihypertensive treatment, diabetes, and top quintile total cholesterol, and their combinations, are shown in figure 4. The highest BWs were found among men with no outcome and the lowest among men with all three outcomes. The whole model was strongly significant (p<0.002).

Table 11. *Effects of birth weight (BW) on outcome variables as crude effect and after adjustment for possible effect-modifying variables in standard least square regression with parameter estimate (difference) (Diff) for systolic blood pressure (SBP) and serum total cholesterol (Cohort I)*

| | | Model 1[a] | | Model 2[b] | | Model 3[c] | | Model 3[c] | | | Model 3[c] | | |
| | | All | | All | | All | | Restricted to only term births | | | Restricted to only weights recorded in grammes or kilogrammes with one decimal | | |
	N	Diff	95% CI	Diff	95% CI	Diff	95% CI	N	Diff	95% CI	N	Diff	95% CI
SBP, 50 yrs													
BW continuous [1]	478	-2.7	-5.8;0.4	-3.7	-6.7;-0.8	-3.7	-6.7;-0.8	341	-4.4	-8.0;-0.8	300	-3.9	-7.6;-0.3
BW≤3000	76	2.0	-3.3;7.3	4.4	-0.6;9.4	4.4	-0.6;9.4	47	4.1	-2.0;10.2	48	2.4	-3.4;8.1
BW 3001-4249	311	0		0		0		228	0		203	0	
BW≥4250	91	-4.9	-9.8;0.1	-5.4	-10.0;-0.8	-5.4	-10.0;-0.8	66	-6.6	-11.9;-1.3	49	-4.6	-10.2;1.1
Total cholesterol, 50 yrs													
BW continuous [1]	478	-0.20	-0.36;-0.04	-0.21	-0.37;-0.05	-0.20	-0.36;-0.04	343	-0.17	-0.38;0.03	301	-0.14	-0.34;0.06
BW≤3000	76	0.34	0.07;0.61	0.36	0.09;0.64	0.34	0.07;0.61	47	0.25	-0.10;0.59	48	0.12	-0.21;0.44
BW 3001-4249	311	0		0		0		230	0		204	0	
BW≥4250	91	-0.04	-0.29;0.22	-0.04	-0.29;0.21	-0.04	-0.29;0.22	66	-0.06	-0.36;0.24	49	-0.14	-0.46;0.18

[a] Univariate analysis with birth weight.
[b] Apart from birth weight, the model includes weight at 50 yrs.
[c] Apart from birth weight, the model initially includes weight at 50 yrs, gestational age, place of birth, parity, maternal diabetes and smoking before successive elimination of the least significant covariate until all are significant.
[1] The difference for an increase of 1000 grammes in birth weight.

Table 12. *Effects of birth weight (BW) on outcome variables as crude effect and after adjustment for possible effect-modifying variables in a Cox's regression with hazards ratio (HR) for antihypertensive treatment, diabetes and serum total cholesterol top quintile (Cohort I)*

| | | Model 1[a] | | Model 2[b] | | Model 3[c] | | Model 3[c] | | | Model 3[c] | | |
| | | All | | All | | All | | Restricted to only term births | | | Restricted to only weights recorded in grammes or kilogrammes with one decimal | | |
	N	HR	95% CI	HR	95% CI	HR	95% CI	N	HR	95% CI	N	HR	95% CI
Antihypertensive treatment													
BW continuous [1]	478	0.73	0.54-0.98	0.68	0.50-0.93	0.68	0.50-0.93	341	0.48	0.32-0.73	300	0.68	0.44-1.03
BW≤3000	76	0.99	0.60-1.65	1.10	0.66-1.84	1.10	0.66-1.84	47	1.46	0.81-2.62	48	0.90	0.44-1.83
BW 3001-4249	311	1.00		1.00		1.00		228	1.00		203	1.00	
BW≥4250	91	0.39	0.20-0.75	0.37	0.19-0.71	0.37	0.19-0.71	66	0.25	0.10-0.63	49	0.40	0.17-0.92
Diabetes morbidity													
BW continuous [1]	478	0.57	0.37-0.89	0.48	0.30-0.75	0.47	0.30-0.74	341	0.41	0.23-0.74	300	0.44	0.24-0.80
BW≤3000	76	2.45	1.33-4.53	3.11	1.66-5.82	3.11	1.66-5.82	47	4.19	2.02-8.70	48	4.38	2.02-9.52
BW 3001-4249	311	1.00		1.00		1.00		228	1.00		203	1.00	
BW≥4250	91	1.24	0.60-2.55	1.13	0.55-2.33	1.09	0.53-2.25	66	1.32	0.57-3.03	49	1.15	0.46-2.91
Total cholesterol top quintile													
BW continuous [1]	478	0.78	0.62-0.99	0.80	0.63-1.01	0.77	0.61-0.98	343	0.82	0.62-1.10	301	0.70	0.51-0.97
BW≤3000	76	1.36	0.94-1.97	1.30	0.90-1.90	1.37	0.95-1.99	47	1.11	0.69-1.78	48	1.21	0.75-1.95
BW 3001-4249	311	1.00		1.00		1.00		230	1.00		204	1.00	
BW≥4250	91	0.87	0.59-1.28	0.88	0.59-1.29	0.88	0.59-1.29	66	0.81	0.52-1.27	49	0.60	0.34-1.08

Explanations of the models see table 11. [1] The difference for an increase of 1000 grammes in birth weight.

Figure 4. Mean birth weight and its 95% confidence interval for men with diabetes (a) and without diabetes (b), in combinations with and without antihypertensive treatment and being or not being in the top quintile of serum total cholesterol at any time during follow up from 50 to 80 years of age in a population-based cohort followed until 80 years of age. P-value for the whole model = 0.002. (Cohort I)
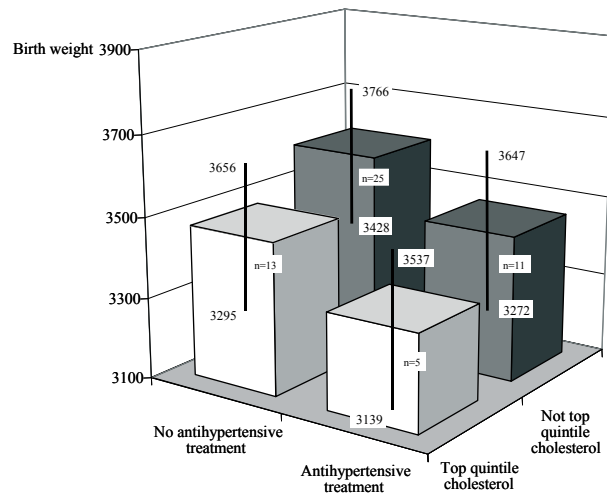
With diabetes any time between 50 and 80 years of age
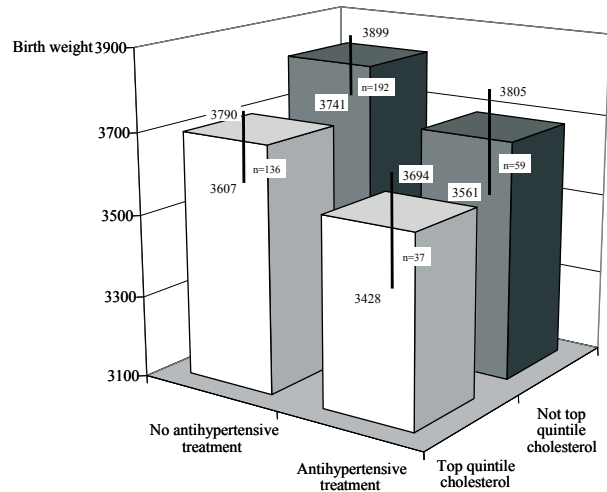
Without diabetes any time between 50 and 80 years of age

Table 13. *Birth weight in groups according to the outcome variables during the follow-up period 20-85 years of age (Cohort II)*

	N	Birth weight		
		Mean grammes	95% CI	p
CHD incidence	502	3665	3615-3716	0.640
No CHD incidence	817	3650	3610-3690	
CHD incidence	304	3625	3561-3689	0.285
No CHD incidence	1015	3665	3629-3701	
CHD incidence	859	3656	3617-3695	0.980
No CHD incidence	460	3656	3603-3710	
CHD incidence	487	3653	3601-3704	0.873
No CHD incidence	832	3658	3618-3698	

Birth weight and coronary heart disease and cardiovascular disease incidence and mortality (Cohort II)

Mean BW did not significantly differ between men with a CHD incident during follow up and those without (3665 g versus 3650 g, p-value=0.64), table 13. Corresponding BWs for CHD mortality were 3625 g and 3665 g.

When BW was divided into categories, incidence and mortality rates for CHD and CVD were fairly equally distributed across the weight classes, table 14. The hazards ratios for CHD and CVD incidence and mortality in relation to BW adjusted for gestational age (model 1[a]) were all non-significantly different from unity. The most deviating rate was CHD mortality [hazards ratio=0.91 (CI: 0.74-1.12) per 1000 g BW increase]. The results were similar whether or not gestational age was taken into account. Restricting the analysis to term births (model 1[b]) or to BWs registered with the highest precision only (model 1[c]) had only a minor influence on the hazards ratios. A Kaplan-Meier analysis indicated that there were no significant differences between the BW groups at any time during follow up (p=0.45), figure 5, and a Cox's survival analysis gave a nearly identical course of CHD mortality events for the gestational age adjusted BW categories during the 65 years of follow up (p=0.64).

The birth time variables that were univariately correlated to BW or to outcome (place of birth, gestational age and parity) had little if any influence on the CHD and CVD hazards ratios. One example of the effect of stratifying for one of them, place of birth, showed a non-significant hazards ratio difference between the groups, table 14 (model 1[d]).

The influence of BW on CHD mortality was not significantly different for those who developed diabetes [hazards ratio=1.10 (CI: 0.67-1.82)] and those

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Figure 5. Proportion free from CHD mortality in three birth weight categories using Kaplan-Meier survival estimates. Men born in 1913 and followed up from 50 to 85 years of age (Cohort II)
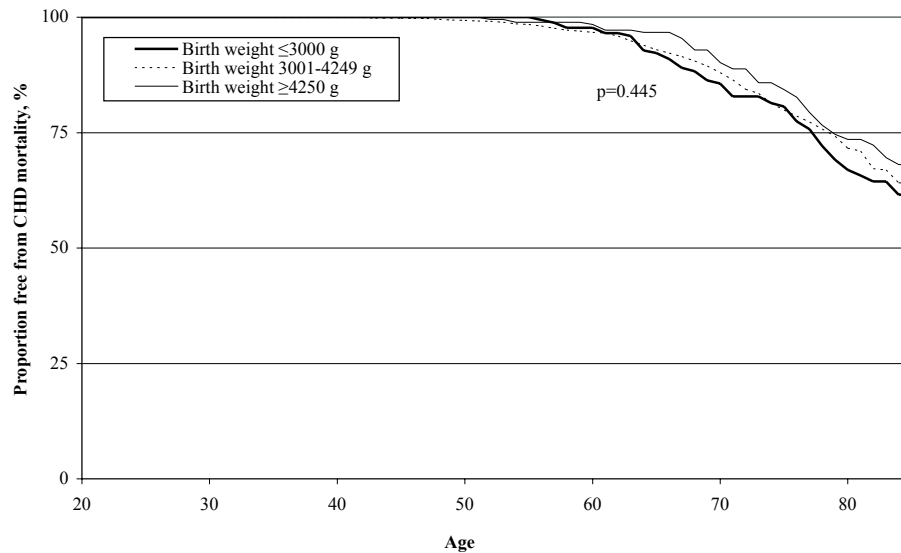
who did not [hazards ratio=0.90 (CI: 0.73-1.11)]. Taking diabetes into account did not alter the BW-CHD relation [hazards ratio=0.92 (CI: 0.76-1.12)] shown in model 1[a].

Adult height was inversely related to CHD, but controlling for height had no influence on the BW-CHD relation [hazards ratio=0.93 (CI: 0.77-1.13)]. The highest CHD death rates were found among men with the shortest adult height, irrespective of BW. In a multivariate analysis with BW, diabetes and adult height as independent variables the decrease in CHD mortality was less than 5% per 1000 g increase in BW (p=0.64). Corresponding analyses with CHD incidence, CVD incidence or CVD mortality as dependent variables gave similar results.

Birth weight and prostate cancer incidence and mortality (The amalgamated cohort)

Men with a PCA incident during follow up before age 70 (n=30) had a non-significantly higher mean BW [3830 g (CI: 3540-4119)] than those with no incident [3665 g (CI: 3635-3696)]. The corresponding mean BWs for men who had or did not have an event by end of follow up at age 85 (n=120) were 3736 g (CI: 3618-3854) and 3663 g (CI: 3632-3694).

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Table 14. *Effect of gestational age adjusted birth weight (BW) on outcome variables using Cox's regression analyses with hazards ratios (HR) for CHD and CVD incidence and mortality (Cohort II)*

	Alive at 20 years of age		Model 1[a]			Model 1[b]		
						Restricted to only term births		
	N=1319		N=1209			N=982		
	n[1]	rate	n[1]	HR	95% CI	n[1]	HR	95% CI
CHD incidence								
BW continuous[2]	502		459	1.02	0.87-1.20	370	1.07	0.89-1.28
BW ≤3000	76	38.0	69	1.08	0.83-1.41	49	0.99	0.73-1.34
BW 3001-4249	350	38.3	318	1.00		264	1.00	
BW ≥4250	76	37.1	72	1.01	0.78-1.31	57	1.02	0.76-1.35
CHD mortality								
BW continuous[2]	304		276	0.91	0.74-1.12	222	0.95	0.74-1.20
BW ≤3000	49	24.5	43	1.08	0.77-1.51	30	0.96	0.65-1.42
BW 3001-4249	215	23.5	196	1.00		164	1.00	
BW ≥4250	40	19.5	37	0.85	0.60-1.21	28	0.81	0.55-1.22
CVD incidence								
BW continuous[2]	859		788	1.00	0.89-1.14	635	1.02	0.89-1.18
BW ≤3000	129	64.5	115	1.04	0.85-1.28	88	1.05	0.83-1.32
BW 3001-4249	596	65.2	549	1.00		448	1.00	
BW ≥4250	134	65.4	124	1.00	0.82-1.22	99	1.06	0.85-1.32
CVD mortality								
BW continuous[2]	487		444	0.98	0.83-1.16	354	1.01	0.84-1.22
BW ≤3000	74	37.0	66	1.02	0.78-1.34	48	0.97	0.71-1.32
BW 3001-4249	344	37.6	316	1.00		259	1.00	
BW ≥4250	69	33.7	62	0.89	0.68-1.17	47	0.87	0.67-1.19

[1] Number of events. [2] HR for an increase of 1000 g in birth weight.

In the three BW categories ≤3000 g, the reference group, and ≥4250 g the crude incidence rates for a PCA event per 1000 person years were 3.36, 3.00 and 4.68, table 15. The univariate Cox's hazards ratio for a PCA incident before 70 years of age in the highest BW group, as compared with the reference mid-category was 2.39 (CI: 1.06-5.40), for 70-85 years of age 1.39 (CI: 0.82-2.36), and for 50-85 years of age 1.62 (CI: 1.04-2.51). When the analysis was restricted to BW registered with the highest precision, the hazards ratio was 2.51 (CI: 1.52-4.12) for the whole follow-up period (data not shown).

In the Poisson regression analysis, the hazard functions for PCA incidence in the lowest BW category and in the reference group were fairly simi-

Continuation of table 14

	Model 1[c]			Model 1[d]					
	Restricted to only weights recorded in grams or kilograms			Restricted to home births			Restricted to hospital births		
	N=895			N=719			N=490		
	n[1]	HR	95% CI	n[1]	HR	95% CI	n[1]	HR	95% CI
CHD incidence									
BW continuous[2]	349	1.14	0.94-1.39	272	0.93	0.75-1.14	187	1.38	1.02-1.87
BW ≤3000	52	1.12	0.83-1.52	37	1.28	0.89-1.84	32	0.89	0.60-1.32
BW 3001-4249	247	1.00		178	1.00		140	1.00	
BW ≥4250	50	1.13	0.84-1.54	57	0.97	0.72-1.31	15	1.44	0.84-2.45
CHD mortality									
BW continuous[2]	209	1.02	0.79-1.31	161	0.79	0.60-1.03	115	1.30	0.88-1.91
BW ≤3000	33	1.15	0.78-1.69	24	1.33	0.84-2.08	19	0.86	0.52-1.43
BW 3001-4249	151	1.00		106	1.00		90	1.00	
BW ≥4250	25	0.92	0.60-1.40	31	0.91	0.61-1.35	6	0.84	0.37-1.92
CVD incidence									
BW continuous[2]	581	1.05	0.90-1.22	481	0.98	0.84-1.14	307	1.08	0.85-1.38
BW ≤3000	81	1.00	0.79-1.27	60	1.19	0.90-1.58	55	0.92	0.67-1.24
BW 3001-4249	424	1.00		315	1.00		234	1.00	
BW ≥4250	76	0.96	0.75-1.23	106	1.02	0.82-1.27	18	1.04	0.64-1.68
CVD mortality									
BW continuous[2]	325	1.07	0.88-1.31	263	0.91	0.73-1.12	181	1.21	0.89-1.65
BW ≤3000	47	1.01	0.74-1.40	36	1.23	0.85-1.77	30	0.84	0.56-1.25
BW 3001-4249	239	1.00		175	1.00		141	1.00	
BW ≥4250	39	0.91	0.65-1.27	52	0.93	0.68-1.27	10	0.91	0.48-1.73

lar throughout the follow-up period, figure 6. In the BW category ≥4250 g, the risk increased proportionately to that of the reference group until the years around mean age for PCA morbidity (74.2 ±7.3 SD). During these years the risk was approximately twice that of the reference group, after which it increased at a slower pace. The hazards ratios decreased throughout the follow up period.

To study whether the association between BW and outcome was affected by other factors, covariates correlated to BW or to outcome with a p-value ≤0.01 were chosen for further analysis. Gestational age, place of birth, maternal parity, adult height, young adult weight, and young adult body mass index were associated with BW, but not with PCA, and none influenced the BW-PCA association (data not shown).

Table 15. *Crude effect of birth weight (BW) on outcome variables using Cox's regression with hazards ratios (HR) for prostate cancer (PCA) incidence and mortality (The amalgamated cohort)*

	50-69 years of age [a]				70-85 years of age [a]				50-85 years of age [a]			
	n[1]	Crude rate [2]	HR	95% CI	n[1]	Crude rate [2]	HR	95% CI	n[1]	Crude rate [2]	HR	95% CI
PCA incidence												
BW continuous [3]	30		1.59	0.87-2.90	90		1.12	0.79-1.62	120		1.24	0.91-1.68
BW ≤3000	5	1.29	1.46	0.54-3.99	13	8.74	1.09	0.60-1.99	18	3.36	1.17	0.70-1.96
BW 3001-4249	16	0.90	1.00		59	8.17	1.00		75	3.00	1.00	
BW ≥4250	9	2.16	2.39	1.06-5.40	18	11.33	1.39	0.82-2.36	27	4.68	1.62	1.04-2.51
PCA mortality												
BW continuous [3]	11		1.61	0.60-4.33	57		1.37	0.87-2.15	68		1.41	0.93-2.12
BW ≤3000	1	0.26	0.66	0.08-5.38	9	5.83	1.36	0.65-2.83	10	1.84	1.23	0.62-2.45
BW 3001-4249	7	0.39	1.00		34	4.52	1.00		41	1.62	1.00	
BW ≥4250	3	0.71	1.81	0.47-6.98	14	8.18	1.82	0.98-3.40	17	2.87	1.82	1.03-3.21

[a]Univariate analysis with birth weight
[1] Number of events [2] Unit: per 1000 person-years [3] HR for an increase of 1000 g in birth weight

Figure 6. Hazards (exponential β–estimates) for prostate cancer incidence in three birth weight (BW) categories and hazards ratio (HR) for BW ≥4250, as compared with the reference group (BW 3001-<4250 g). Men born in 1913 and followed up from 50 to 85 years of age (the amalgamated cohort)
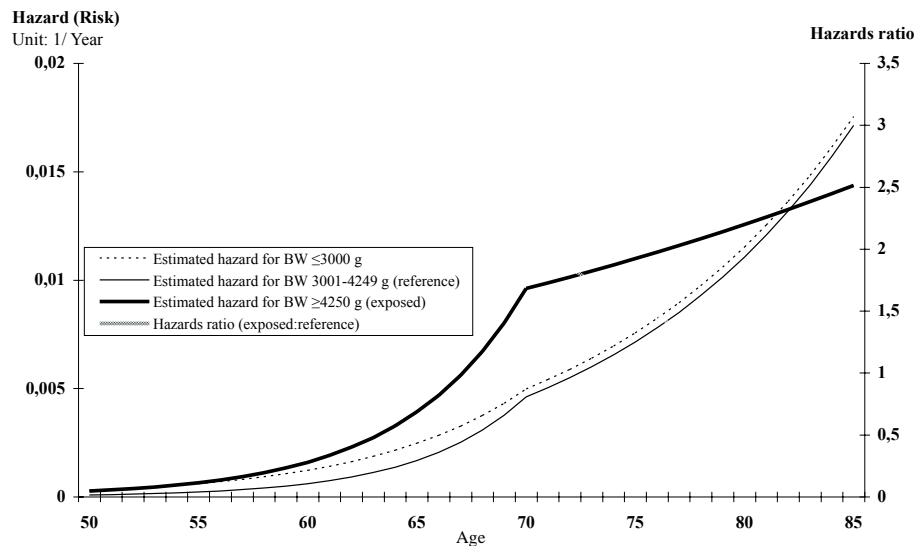
BW was significantly higher among those with information on young adult weight and body mass index than others (3695 g versus 3621 g and 3697 g versus 3619 g, respectively), and tended to be so among men with known adult height but not for men whom there was no such information (3677 g versus 3578 g). However, sensitivity analyses of the BW-PCA association gave similar BW parameter estimates in analyses where missing values of height, weight and body mass index were replaced with mean values as in the crude BW-PCA analysis (data not shown). The proportion of men with a PCA incident or fatality was approximately the same, irrespective of whether or not adult anthropometric data were known.

Population attributable risk per cent

The importance of BW for the effects on incident and fatality events in the general population was estimated, provided the associations between exposure and outcome are causal. The measure gives a maximum proportion of outcome that could be eliminated if the exposure were eliminated. Low BW (≤3000 g) was used as exposure variable for cardiovascular outcomes and high BW (≥4250 g) for PCA outcomes.

Figure 7. Population attributable risk percentage for incidence and mortality in some cardiovascular risk factors (incidence only), coronary heart disease, cardiovascular disease and prostate cancer using different exposure variables. Men born in 1913 and followed up until old age
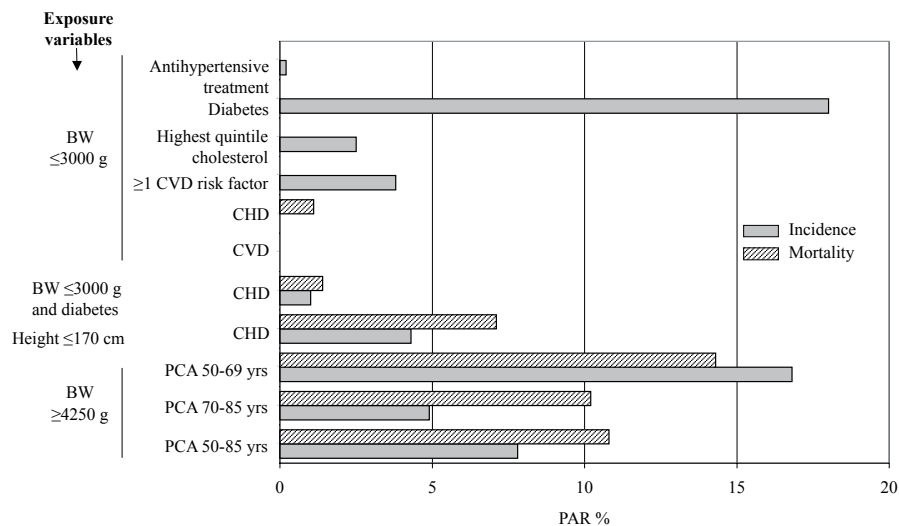
Eighteen per cent of the diabetes incidence could be attributed to low BW, figure 7. For other cardiovascular risk factors and CHD and CVD incidence and mortality, low BW contributed little to the burden of these events on a community level — the PAR% for receiving antihypertensive treatment, top quintile total cholesterol, at least one cardiovascular outcome, and CHD mortality was 0.2%, 2.5%, 3.8%, and 1.1%, respectively, while it was 0% for CHD and CVD incidence and CVD mortality. Only a few per cent of CHD incidence and mortality could be attributed 'low BW and diabetes' (1.0% and 1.4%, respectively). As short stature is a known risk factor for CHD outcome, ≤170 cm in adult height was used as an exposure variable. The PAR% for CHD incidence and mortality were 4.3% and 7.1%, indicating that height ≤170 cm could be at least as important as low BW for CHD outcomes.

The PAR% of a high BW for PCA incidence during the follow-up periods 50-69 years of age, 70-85, and 50-85 were 16.7%, 4.9%, and 7.8%. Corresponding PAR% for fatal events were 14.3%, 10.2%, and 10.8%.

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Discussion

Methodological considerations

Selection

The study populations did not differ significantly from those for whom BW could not be retrieved in terms of obstetrical variables and in outcomes. The distributions of possible effect-modifying variables in the groups in cohort I were not different in any way that gave us reason to believe that the results would be affected, since urbanisation level, maternal cardiovascular morbidity and physical activity were neither significantly correlated to BW nor to outcome. Selection due to loss of follow-up was small in all three cohorts and in cohort I the attrition was, in fact, minimized since men missing one examination were reincluded if possible in later ones.

The only obvious selection bias was linked to anthropometric data from young adulthood among those in the study populations. Among men in cohort II those without adult height data died at younger ages. In the amalgamated cohort those without young adult weight and body mass index data had lower mean BW than those with known anthropometric data. However, sensitivity analyses, when missing data were replaced with total or group mean values in the two cohorts, gave similar parameter estimates for BW as the crude analyses.

Validity of BW and birth time variables

The obstetrical records proved to have reasonably good validity. Factors well known to influence BW in contemporary studies also influenced BW in 1913. For example, the increase in BW with gestational age was very similar to that reported in more recent studies [153, 154]. The mother's proteinuria-related BW decrease has also been confirmed in other studies [155, 156]. The mean BW difference between first-born infants and others was of greater magnitude than obtained in investigations using data from more recent deliveries [157, 158]. However, compared with the present situation, mean parity number was generally higher in Sweden 80 years ago, which may be one explanation for the relatively high BW difference obtained for first-born infants as compared with others in cohort I. In cohort II, based on an urban population, this difference was only of minor importance and may

have been caused by a smaller number of children per 100 adults in towns than in rural areas [148]. The BW difference between home and hospital deliveries was surprisingly large, although it was somewhat reduced when the influences of other factors were taken into account.

Many circumstances have most certainly increased the validity of the obstetrical data. For example, all midwives were required to have formal education and one of the two schools in Sweden for training midwives was located in Gothenburg. All hospital births in this area took place in the hospital affiliated with the school. In 1913 Swedish law stipulated that there was to be at least one midwife in each parish, the smallest administrative unit. The improved quality of midwifery education also influenced the quality of home deliveries. The midwife's record books, used in home deliveries, were streamlined from 1912 to be uniform all over Sweden. The introduction to the book stated that the midwife must note all the requested information from all deliveries immediately. The new record books were therefore easy to use, and they were also conveniently sized to fit into the pocket of the midwife's apron. The midwife received the book from the local general practitioner and when it was full, or the midwife moved, it was returned to the general practitioner. The local general practitioner also generally supervised the midwives. This supervision was, in Gothenburg in 1913, documented in specially kept conduct books, which are still available for study. From the notes in these books, it is possible to evaluate the skill and performance of individual midwives at the time. The general practitioners seemed to be quite satisfied with conduct of the midwives.

However, recall bias or other notational errors cannot be excluded as a possible source of the difference in BW between hospital and home deliveries. In spite of the fact that BW measurements were less precise at home deliveries, the data indicate that the BW difference is unlikely to be due to measurement diversities. Using only the most exactly recorded BWs did not substantially change the hazards ratios, irrespective of whether cardiovascular risk factors, CHD incidence or mortality, or PCA incidence were used as outcome variable.

The hospital-home BW difference has been found in other studies as well. For example, in a study of men born in Sweden 1920-24 and who were residents of Uppsala in 1970, the men born at the Academic Hospital had significantly lower mean BW than those born elsewhere (3501 g *vs.* 3680 g) [31]. The corresponding mean BWs in cohort I for hospital and home deliveries were 3352 g and 3770 g, respectively. In Hertfordshire, England, the mean BW was around 3600 g among predominantly home deliveries from 1911 to 1930 [11, 50, 66], but it was 3311 g for hospital deliveries from 1907 to 1924 in Sheffield, England [51]. In the cohorts from Helsinki, Finland 1924-33 and 1934-44 the mean BWs for the hospital-born men were 3443 g and 3456 g, respectively [55, 56]. Consequently, the hospital-home BW difference seems to be real and may reflect differences in other socio-

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economic or demographic factors than those which could be controlled for in the present study.

As compared with reported BWs in the literature, the mean BWs in our study were high (3714 g in cohort I and 3616 g in cohort II). The men in cohort I were born everywhere in Sweden, while those in cohort II were born in Gothenburg. However, men delivered in the Greater Reykjavik area, Iceland in 1914-35 were either hospital or home deliveries, and their mean BWs were similar to ours (3820 g) [57]. In the study by Leon *et al.* the mean BW was 3597 g, with 46% born at the Academic Hospital and the others a mixture of home deliveries and being born at other hospitals. The importance of access to delivery records reflecting the birthing practice of the time period as a way of avoiding selection bias has been emphasized [159].

In cohort I we used BW instead of estimates of foetal growth (BW adjusted for gestational age) or ponderal index (kg/m^3), as the hazard ratios of the last two were not substantially different from the ratios for BW (data not shown). Furthermore, BW has been shown to be valid as a crude measure [46, 160] and ponderal index has been shown to be closely associated with the degree of growth reflected by BW for gestational age [21]. The parental social classification used in this study has been validated and a strong direct correlation to income has been shown [161].

Consequently, there is reason to believe that the BW and other birth time variables are reasonably valid and that BW is good enough to use as the exposure variable in this type of study.

Validity of covariates from adult life

We used education and annual income as social stratification variables in cohort I, since these have been shown to have a stronger correlation to CVD incidence than the official social class classification in this data set [162]. Using body mass index instead of weight at 50 years of age as the covariate in the regression analyses did not change the hazards ratios (data not shown).

Diabetes treated only in primary health care was not included as a potential covariate in cohort II. However, the register data used showed a cumulative diabetes incidence rate similar to that in cohort I, which was a similar population but with more complete diagnostic information from questionnaire data checked against medical records.

It was possible to check the anthropometric data used in cohort II and in the amalgamated cohort against similar information in the study populations. Both height and weight were found to be reasonably valid.

Validity of outcome variables

We used data from the first obtained measurements (continuous variables) as well as information based on data from repeated measurements from 50 to

80 years of age (dichotomised variables) as outcome variables in analyses of cohort I. Outcome variables based on more than one examination probably contributed to more valid data. However, for blood pressure it was necessary to use only the first survey data since later measurements were biased by antihypertensive treatment.

As in a number of other studies [52, 56, 96], we used both incidence and mortality data to increase the study power in cohort II, since the proposed 'fetal origins hypothesis' is assumed to be valid for both incidence and mortality [90]. Restricting analyses to CHD and CVD main diagnoses or including both main or contributing diagnoses made no difference. The morbidity and mortality follow up was practically complete. To test the overall influence of data loss on outcome, a sensitivity re-analysis was done after assigning a BW ≤3000 g to men with unknown BW and a CHD mortality incident at age 50 to men with unknown follow up. The hazards ratio for the low BW group changed from 1.08 to 1.07.

We used cancer register data covering the whole country for analyses in the amalgamated cohort. Internal checks and corrections of the register were performed, resulting in very high validity of data [163]. However, other biases could have been introduced. In elderly men with an increased chance of co-morbidity, a detection bias cannot be excluded, *i.e.*, seeking medical attention for other diseases might increase the chance of a PCA diagnosis. If BW *per se* is associated with the risk of co-morbidity, such an explanation may contribute to the findings in terms of PCA incidence but it cannot explain the difference found in PCA mortality. Another possible bias is related to the positive association between body size and benign prostatic hypertrophy which may, in turn, indicate an increased rate of prostate surgery in large men and thus an increased probability of having a PCA detected. The fact that adult body size is correlated to BW [31, 38, 52, 97] might also give rise to detection bias, but cannot explain the observed differences in PCA mortality. All causes of death for men in cohort I were scrutinized retrospectively [164], and PCA mortality rates were found to show the same pattern as for PCA morbidity. Törnblom *et al.* also estimated that PSA testing in Sweden during this period and in this relatively elderly population was only done on a small scale during the follow-up time [164]. We therefore have no reason to expect that diagnostic or detection bias or PSA screening had any major impact on the results in the amalgamated cohort.

Thus, outcome variables seemed not to be biased to such an extent that the conclusions would be affected.

Discussion by findings

Cardiovascular risk factors and cardiovascular disease incidence

The decrease in crude systolic blood pressure (-2.7 mmHg) per 1000 g increase in BW in cohort I was similar to results in similar studies of middle-aged men [31, 45], however, in the Swedish study confined to the subgroup of men with above median adult height [31]. An inverse association between BW and hypertension based on blood pressure and antihypertensive treatment after adjustment for body mass index has been found [47]. In a group of US male health professionals, the effects of BW on treated hypertensive men remained after adjustment for body mass index and parental history of hypertension [37]. In the Swedish study, there was a tendency towards protection from antihypertensive treatment or having systolic blood pressure >160 mmHg at age 60 and at age 70 among those with high BWs, rather than an increased risk associated with lower BWs [39]. A similar pattern, but weaker, has been shown in a Finnish study [42]. Our hypertension treatment variable in cohort I tended to confirm these findings. However, others have found an inverse progressive slope across all BWs [48]. No significant associations between BW and blood pressure were found amongst Swedish men at young middle-age [103] and at late middle-age [99] or amongst middle-aged men in the UK [52, 75].

A number of studies have shown an inverse correlation between BW and glucose intolerance or diabetes [14, 40, 43, 165], especially after taking the influence of body mass index into account [37, 38, 166, 167]. The increased diabetes risk associated with BW ≤3000 g in the present study remained significant after adjusting for covariates, confirming the results reported by others [37], but the tendencies towards non-linear relationships in our study were different from the results of many other studies [14, 37, 38, 43, 165]. The highest diabetes rates in relation to BW have been found among those who had heredity for diabetes but the same tendency, although not significant, was also found for those with no heredity [41].

Study results on the possible association between low BW and dyslipidemia are inconsistent. No correlation between BW and serum triglycerides or HDL-cholesterol was found in some studies [38, 75, 99, 168], while others have found a non-significant negative correlation between BW and serum cholesterol (total and low density lipoprotein) [36]. In our cohort I data, we found an inverse correlation between BW and serum total cholesterol but not between BW and triglycerides. However, contrary findings have also been reported [52, 169]. In a meta-analysis (n≈23000) a weak but significantly inverse association of BW on total cholesterol was found [74]. Waist circumference has previously been reported to be positively related to BW in univariate analysis, but not after adjustment for body mass index [168]. In

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our study population, the variables were not found to be related after adjustments.

An inverse association between BW on the one hand and CHD and CVD incidence and mortality on the other was found in a number of studies [16, 50-52, 54-56, 58]. The decreased risk has been referred to as continuous across the BW range [46, 50, 90] or confined to subgroups, such as those with severe foetal growth restriction or those who showed exaggerated postnatal growth [68], those in the highest body mass index tertile as adults [170], or those with low socio-economic status in adulthood [171, 172]. CHD, as well as cardiovascular risk factors, have been claimed to originate from small size at birth followed by compensatory growth [96]. Interaction between birth size and anthropometric influences on outcome has been shown primarily for body mass index and weight gain [43, 56, 170], as well as for adult height [57]. We found no interaction between BW and adult height in cohort II, and there was no indication that boys with low BWs who became tall adults had any increased risk. On the contrary, those who became tall tended to have lower risk than others, irrespective of BW.

However, in some studies, no inverse BW-outcome relationship was found. There was no relationship between prevalence of CHD and BW (p=0.9) in a study of men still alive in Hertfordshire [66]. In young adults the overall BW was not related to common carotid intima-media thickness, a strong predictor for CVD [68]. A positive trend (p=0.05) between BW and myocardial infarction has previously been shown in a sub-group analysis from cohort I [65].

The sensitivity of BW as a biological marker for and a summary measure of optimal foetal growth has been questioned [82, 173]. The relationship between BW and outcome has been suggested to be only an epi-phenomenon, as the reduced BW is said only to be part of a wider panorama of changes with possible impact on outcome [174, 175]. As a proxy variable, BW may not be graded in relation to actual adverse intrauterine influence [23]. Arguments for BW for gestational age as a measure good enough to cover the effects of maternal nutrition have been given [21]. Ponderal index, a frequently used measure of restricted foetal growth, has shown an inverse relation to CHD in some studies [51, 54, 55] but not in others [57]. In cohort II we applied these measures only to the hospital born, since birth length was not required to be given in home delivery records (data not shown). However, BW and ponderal index in this subgroup gave the same results. Ponderal index has been described as not measuring foetal growth restriction any better than BW [21].

The possibility of confounding for shown negative associations has been mentioned [71, 73], but it has also been argued that it is unlikely that the association has arisen simply because of unmeasured adult lifestyle variables, as the associations were demonstrated in children as well [33], and, as well as in the present study, taking some possible adult confounding vari-

ables into consideration in unselected study populations, did not modify the results substantially [54]. The hazards ratios for the exposure-outcome associations in cohort II were unaffected by adjustment for the influence of covariate birth time variables or by restricting the analyses to term births, whereas such modelling strengthened the associations in other studies [55]. In early twentieth century Sweden, place of birth could be an indicator of social context, since children born in hospital tended to be first-borns (and thus have below average BWs) to young unmarried mothers of low social class to a larger extent than children delivered at home. The same has been found by others [176]. But although boys born in hospital had significantly lower BW than those born at home, place of birth still did not significantly affect the BW-outcome results, and parental social class was neither correlated to BW nor to outcome.

As in other studies, we found a positive correlation between BW and adult height [31, 52, 98, 99] and a negative correlation between height and outcome [100, 101]. Whether adult height might be a proxy for birth size adjusted for the influence of modifying factors during childhood and adolescence remains to be shown.

No evidence for an association between maternal nutrition and cardiovascular risk factor outcome was shown in a study of adults in the UK [75]. However, little information is available on the specific role of maternal and foetal nutritional status during pregnancy and its impact on adult cardiovascular outcome [18, 19, 22, 25, 45, 75]. Moreover, the optimal nutritional recommendations for women at different stages in the reproductive cycle is still not known [82]. Maternal high circulating nutrients during pregnancy was shown to have any impact on BW in a study from the UK and it was suggested that maternal energy intake has no importance for populations in industrial countries [26, 27]. In some 'natural experiments' with famine in humans, the offsprings' health has not been different among the exposed and unexposed [67, 177]. Prenatal exposure to the Dutch famine was correlated to impaired glucose tolerance [40], but not to significantly higher systolic blood pressure [178]. Quite small differences in maternal balance of nutrients in late pregnancy have shown a complex relationship to increased blood pressure in offsprings, independent of BW or starvation [28, 44]. However, although there was no effect on BW, individuals exposed to famine in early pregnancy, but not mid or late, had both a higher prevalence of CHD and poorer perceived health. The perceived health could only partly be explained by increased prevalence of CHD and CVD risk factors and cancer [34, 179].

The BW difference in our study between men who died from CHD and those who did not was only 41 g, or 1% of the mean BW, the same magnitude as the measurement errors. This was estimated to be approximately the same as that found in a previous study [31, 54, 180]. In this situation the statistical power was, of course, low. This is in contrast to the traditional CHD risk factors, where population sizes as in our study usually provide

statistical power of over 80%. The question is whether the small difference is of clinical significance. A reasonable difference in clinical importance would be approximately 100-200 g, or 2.5-5% of the mean BW. In that situation the statistical power in this study would have been satisfactory. BW was not shown to significantly affect CHD. All things considered, a population size of approximately one tenth of all men born in Sweden in 1913 would have been required to reduce the variance in outcome sufficiently to obtain significant results.

The difference in BW between men who had a cardiovascular risk factor (antihypertensive, diabetes or in the highest top quintile of total cholesterol) during follow up and other men was more than 100 g, and this difference can be suggested to be clinically important. For these cardiovascular risk factors a significantly negative association between BW and outcome was shown, in spite of the much lower population size and not so many cases in cohort I than in cohort II.

It has been pointed out that there is an inverse correlation to risk factors for CVD across the whole BW panorama, which means that the inverse associations between BW and outcome should not only be confined to men with the most severely retarded foetal growth [23, 46], but low BW is continuously emphasised as a risk factor [58, 160, 181]. We have chosen a BW ≤3000 g as the potential marker for increased cardiovascular risk.

Bradford-Hill's cause-and-effect criterion [182], a strong and graded association, from various countries by various researchers, in various age groups and supported by experiments, has been shown for BW-CVD outcomes. However, whether the relationship can be interpreted as causal on the basis of available evidence has been questioned [8, 18, 63, 71, 73, 82, 174].

As in a number of other studies [39, 58, 63, 71, 73, 96], we have assumed causality in order to estimate the effects of the study results for public health. On a population level, the effect of a BW ≤3000 g for prevalence of hypertension treatment, diabetes and high cholesterol was estimated to be 3.8% in cohort I. However, the corresponding level specifically for hypertension was only 0.2%. In the male health professionals study in the US, it was concluded that low BW was not likely to be a major cause of hypertension because less than 10% of the general population had low BW [37]. In two Finnish studies of men born 1924-33 and 1934-44 and followed up until 1997, where BW ≤3000 was a marker for exposure, the PAR% of antihypertensive medication was 1.3 and 3.9 [42, 48]. In a Swedish study with follow up from 50 to 70 years and exposure equal to BW <3250 g, the estimated PAR% of antihypertensive treatment or systolic blood pressure over 160 mmHg successively decreased from 7.1% at 50 years of age, to 2.8% at age 60, and to 0.5% at age 70 [39]. In this study the PAR% for diabetes and diabetes or impaired glucose tolerance at age 70 was 6.5% and 5.7% [166] substantially lower than in the present study (17.6%), but fairly similar to the Finnish estimates for diabetes (PAR% = 7.4) [43]. The effects of BW on serum total

cholesterol have been shown to be too little to have any importance in public health [74]. This is in line with our estimation of PAR% of 2.5%.

In cohort II 1.1% of the CHD mortality on a population level could be attributable to BW ≤3000 g. Corresponding estimates among men born in the early decades of the 20th century were 2.7% in Hertfordshire, England [50], -0.4% in Helsinki, Finland [55], and 5.5% for BW <3250 g in Uppsala, Sweden [183] corresponding to 2.2% for that BW level in this study. In the Finnish cohort of men born 1924-44 the PAR% for CVD was 3.6%. In spite of the fact that 29.5% of all the deaths in our study were due to CHD mortality, only a modest proportion could be attributed to low BW.

Consequently, we found that low BW seemed to affected cardiovascular risk factors but not CHD and CVD incidence and mortality. In the general population the risk percentage attributable to low BW was only important for diabetes, while low BW contributes little to the burden of other cardiovascular risk factors and to CHD and CVD outcome at a community level.

The associations between BW and cardiovascular risk factors may be consistent with both the foetal origins hypothesis and the foetal insulin hypothesis. However, low BW *per se* did not seem not to be one of the principal causes of CHD or CVD outcome.

Prostate cancer

The association found between BW and PCA in the amalgamated cohort confirms previous findings from a sub sample of cohort I [15]. Given the increased number of events in the present analysis, the precision of risk estimates should be better than those previously reported. Effects of about the same order of magnitude as in the present study was found in a Finnish cohort [16]. The gestational age adjusted hazards ratio for PCA mortality in that study was 0.42 (CI: 0.17-1.01) per 1000 g decrease in BW (n=22). In some studies a non-significant positive association between BW and PCA morbidity [115] and mortality [143] were found, in others a modest positive association was observed among men with severe PCA [144] and in metastatic PCA [115]. In one study a non-significant inverse relation was found [146]. In any case, the assumption of importance of high BW to an overall increased PCA risk was not generally supported [112, 115, 143-145].

We used only BW to assess prenatal growth in the amalgamated cohort. However, adjusting for gestational age in the regression analysis did not modify the impact of BW on PCA. Significantly reduced PCA incidence with higher gestational age has been found [145], but so have decreased incidence rates for individuals born at both shorter and longer gestational ages as compared with term births (week 40) [112]. In the amalgamated cohort it was not possible to test whether length at birth, a marker of linear growth *in utero* [184], also related to PCA, but in other studies this has not been found [112, 115, 145]. Birth length information was only known for

men born in hospital, which, as mentioned above for cohorts I and cohort II, is a selected part of the data set. Other correlates of BW, such as maternal parity, seemed not to influence the BW-PCA relationship [115]. However, increased PCA mortality among men who were not the first-born child of their mothers has been observed [145]. Place of birth (home or hospital), with a higher proportion of first-borns of unmarried younger mothers from lower social class among the hospital born than among the home delivered was tested as a more potent indicator of social circumstances than parental occupational status, but none of the variables substantially altered the univariate BW-PCA relation. The choice of variables with possible impact on the exposure-outcome association was narrow because of the high age of the study population, and may have left residual confounding effects.

In the study by Kajantie *et al.* with a positive exposure-outcome relation, the men were born between 1924 and 1944 and the potential conclusion of follow up was between ages 54 and 74. The mean age for a PCA fatal event was found to be 65 [16]. However, in a somewhat older cohort, where the men were born from 1915 to 1929 and the potential conclusion of follow up was between ages 72 and 86, the BW-PCA association approached unity irrespective of whether crude or adjusted hazards ratios were used [112]. The amalgamated cohort study population was followed up until age 85, *i. e.* including those ages with highest PCA incident rates. Mean age at diagnosis was 74 years, identical to that reported in the pre-PSA era in Sweden. If the BW-PCA risk varies in different age groups then studies incorporating different age groups may, of course, come to entirely different conclusions. However, this cannot explain the dissimilar results reported for the amalgamated cohort and the study by McCormack *et al.* [112]. The hazards ratio based on follow up until age 70 in the amalgamated cohort indicated that the association between high BW ($\geq$4250 g) and PCA incident may have been stronger among the younger men than the older ones. As PCA incidence increases exponentially with age, it may be difficult to discern a risk primarily restricted to high BW younger men, with a peak around 70, in an analysis covering all ages. Since the Cox's regression model may be sufficient but not optimal for the statistical analysis, we also used the Poisson regression, which has fewer presumptions regarding the risk ratio between exposed and unexposed men. The hazards ratio indicates that the younger men may have an increased risk of developing clinical PCA symptoms. At population level, the higher risk percentage attributable to a BW $\geq$4250 g also implies that a high BW might be of relatively great importance regarding PCA incidence among middle-aged men if the influence of BW on the PCA morbidity is a causal one. The hazards ratios for PCA mortality appear to be independent of age. However, since the number of events was small in the amalgamated cohort, chance findings cannot be excluded.

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Concluding remarks

In this thesis, based on population cohorts of men born in 1913, it was shown that

- BW and other obstetrical data from 1913 seemed to be reasonably valid as exposure variable and potential effect-modifying variables, when estimating effects of birth size on diseases in adult life,
- men with low BW have a significantly increased risk in adult life of developing cardiovascular risk factors. This was largely unaffected by adjustment for the influence of covariates,
- CHD and CVD incidence and mortality were not influenced by BW, irrespective of whether crude or adjusted data were used. Low BW *per se* did not seem to be one of the principal causes of CHD or CVD outcome,
- men with high BW have a significantly increased risk in adult life for PCA incidence and mortality as compared with men whose BW was in an intermediate reference group. This finding was not modified by any covariates,
- provided that the associations are causal, the population attributable risk percentage due to low BW was substantial for diabetes, while it contributed little to the proportion of other cardiovascular risk factors and to CHD and CVD outcome at a community level. The population attributable risk percentage due to high BW for PCA incidence and mortality was marked.

Acknowledgements

I would like to express my sincere thanks to

- Linda Schenck and John Gulliver, for their valuable viewpoints during linguistic revision of the manuscripts.
- all those working in the archives of Sweden who helped me search for data from 1913 — special thanks to the personnel at The Gothenburg City Archives, the parish archives of Gothenburg, The Regional Archives in Gothenburg and The Swedish Military Archives in Stockholm.
- all the members of the 'Epidemiology group' in Gothenburg who examined the men and collected data during more than 40 years of follow up.
- and last but not least to the late Professor Gösta Tibblin, the creator of 'The Study of Men Born in 1913', my friend and mentor for many years and my first main supervisor, whose encyclopaedic vision and contagious enthusiasm opened up to me the opportunity to do this work. How I wish I could have shared the pleasure of the working progress with him!

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