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Body size at birth and coronary heart disease-related hospital care in adult men –
Findings from the Helsinki Birth Cohort Study

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Running title: Body size at birth and coronary heart disease

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ABSTRACT

Aim. We investigated, among those who had been hospitalized at least once due to coronary heart disease (CHD), the relationship between ponderal index at birth (PI, birthweight/length^3), a measure of thinness, and the age at first hospitalization due to CHD, the number of CHD-related hospital care episodes, and cost of CHD-related hospital care from young adulthood to old age.

Methods and results. Data from the Helsinki Birth Cohort Study included 964 men born in Helsinki, Finland during 1934-44, who had been hospitalized due to CHD and had birth anthropometrics data. PI (kg/m^3), was categorized into low (<25.0), medium (25.0-27.5) and high (>27.5). CHD-related hospital care data were available from 1971-2013. We observed an earlier onset of (*P*=0.014 for linearity) and a higher rate of CHD-related hospital care episodes among those in the lowest PI group (Incidence Rate Ratio 1.35 [95% confidence interval 1.16-1.59, *p*<0.001]), compared to the highest PI group. CHD-related hospital care costs in the lowest PI group were 25% (*p*=0.001, 4% to 46%) higher compared to those in the highest PI group.

Discussion. Thinness at birth is associated with earlier onset, higher prevalence, and higher accumulated costs of CHD-related hospital in-patient care among men who developed CHD.

Key message:

- Findings from this large birth cohort indicate that the onset of CHD-related hospital in-patient care occurred at younger age during the 42-year time period among men who were born thin.
- Lower ponderal index (PI) was associated with a higher rate of CHD-related hospital in-patient care during the time period. We observed a linear increase in CHD-related hospital in-patient care costs across PI groups.

INTRODUCTION

Several measures of non-optimal in-utero growth, such as low birthweight, and thinness at birth are associated with an increased risk of cardiovascular disease, such as coronary heart disease (CHD), in adulthood. (1, 2, 3) This association, which is likely to result from suboptimal prenatal conditions, such as lack of nutrients at particular stages of gestation, also known as sensitive periods (4) or variation in the normal placental development. (5) These conditions may cause long-lasting changes in the developing organ structures and functioning of biological systems placing an individual at risk for negative health outcomes in adulthood. (6) Yet, little is known about whether the increased risk of cardiovascular disease, associated with thinness at birth, is reflected on the prevalence and onset of CHD-related hospital inpatient care across adulthood and old age.

Coronary heart disease is one of the most common chronic diseases among aging individuals, which generates health care costs and is strongly associated with later health and physical functioning and subsequently increases the risk of disability, dependence in older age and premature mortality. (7, 8) In the European Union, economic costs of CHD have been estimated to be over 60 billion Euros per year, which represents over 30% of the overall estimated costs of cardiovascular disease. (9) According to a recent American Heart Association (AHA) report, heart condition (including CHD) was the leading cause for direct health expenditures in the US in 2011, with a total cost of 116 billion US dollars. (8) Of these costs, more than 60 percent were attributable to hospital in-patient care. Establishing early life risk factors for the onset and health care expenditures due to CHD, such as body size at birth, may help us in tackling one of the leading causes of hospital care and premature mortality.

Findings from younger cohorts indicate that compared to normal sized children at birth, those with small body size at birth, e.g. low birthweight or children born preterm, are likely to use more health care services, such as in-patient, out-patient, and physician services (10-13) not only during the first year after birth, (14) but also in adolescence. (10) While there is evidence on the costs arising from preterm birth and low birthweight incurred during the neonatal stage, (15, 16) the long-term economic consequences of non-optimal development in utero on health in adulthood and old age have not been studied to our knowledge. The Helsinki Birth Cohort Study (HBCS) enabled us to monitor whether these higher economic costs, in the form of CHD-related hospital in-patient care, prevailed from early adulthood to old age.

We have previously established in this birth cohort the relationship between low birthweight and thinness at birth and the higher prevalence of CHD in adulthood and older age. (1, 5, 17, 18) In the present study we investigated in more detail the onset of CHD-related hospital care, according to thinness at birth, and the magnitude of the relationship between thinness at birth and the proportion of CHD-related hospital in-patient care among men. Further, we estimated the economic consequences of thinness at birth using costs of CHD-related hospital in-patient care episodes spanning a 42-year time period. We used current rates of care from published sources to adjust the estimate of CHD-related hospital care.

METHODS

Study population

The Helsinki Birth Cohort Study (HBCS) includes 6975 men who were born in Helsinki, Finland at Helsinki University Central Hospital or Helsinki City Maternity Hospital between 1934 and 1944 and who had data available on birth anthropometrics extracted from birth records. (17, 19) These data were linked using a unique identification number allocated in 1971 to each member of the Finnish population. The cohort was followed up for hospital in-patient care from the National Hospital Discharge Register for a 42-year time period, from 1971 to 2013. The analytical sample in this study consisted of 964 men who had been hospitalized at least once care due to CHD-related reasons during the 42-year time period. Of the analytical sample, 370 (38.4 %) had died during the 42-year time period. Of those men excluded from this study, 4947 had been hospitalized at least once due to some other condition besides CHD. Some 248 had died without receiving hospital care and 812 were alive and had not received hospital care. Four (4) participants, who had received CHD-related hospital care, had missing register information on PI. Compared to the analytical sample in the current study, those excluded from this study did not statistically differ according to the three ponderal index groups, i.e. low, medium, and high, described below (x^2=7.766, df=6, p=.256). The study was approved by the Ethics Committee of Epidemiology and Public Health of the Hospital District of Helsinki and Uusimaa and that of the National Public Health Institute, Helsinki.

Infant and childhood measures

Birth date, weight (kg), length (m) and birth order of the newborn boys were extracted from the hospital birth records described in detail previously. (17, 19, 20) Ponderal index (PI), a measure of thinness at birth, was calculated as weight (kg) divided by height (m) raised to the power of 3. PI was divided into three groups; 1) low, <25.0 kg/m^3, 2) medium, 25.0-27.5 kg/m^3 and 3) high, >27.5 kg/m^3. (17)

Date of the mothers' last menstrual period prior to pregnancy was also extracted from the hospital birth records and was used to calculate gestational age. Birth order, ranging from firstborn to fifteenth born, was coded as firstborn versus second or higher. Childhood socioeconomic status was ascertained based on father's highest occupation status extracted from birth, child welfare and school healthcare records and coded as upper middle class, lower middle class and manual workers based on the original social classification system issued by Statistics of Finland. (21)

Hospital in-patient care

Data on cause-specific hospital in-patient care, which took place between January 1, 1971 and December 31, 2013, were extracted from the national hospital discharge register using the unique personal identification number of each cohort member. A hospital care episode was defined as one or more days of hospital in-patient care. Causes of hospital admissions were recorded according to ICD-8 (international classification of diseases, eighth revision) until 1986; thereafter ICD-9 was used until 1995 and ICD-10 until 1997. The first three digits from the cause of admission were used to identify CHD-related hospital care (ICD-8 and ICD-9 codes 410-414, ICD-10 code I21-I25). Mortality dates and causes of death from January 1, 1971 to December 31, 2013 were obtained from the national mortality register.

Statistical health economic analyses

Time to event in the regression analyses was the first hospitalization due to CHD. The number of CHD-related hospital care episodes indicated the cumulative number of care episodes during the 42-year time period. Mixed-effect Poisson regression analyses were used to model the association between PI groups and CHD-related hospital care episodes expressed as incidence rate ratios (IRR) and 95% confidence intervals (CI) using the lowest PI group as the reference. An un-structured covariance structure was assumed in the mixed effects model. Analyses were adjusted for gestational age, chronological age measured at baseline in 1970, parity, and childhood socioeconomic status. Statistical significance for hypotheses of linearity according PI groups was evaluated by using bootstrap type analysis of variance (ANOVA) or regression analyses. Linearity was tested using orthogonal polynomial interlevel of PI groups 1) low, <25.0 kg/m^3, 2) medium, 25.0-27.5 kg/m^3 and 3) high, >27.5 kg/m^3. The bootstrap method is significantly helpful when the theoretical distribution of the test statistic is unknown or in the case of violation of the assumptions. The test was performed in order to explore how increasing of the PI was associated with CHD-related care. Time-to-event analysis was based on the product limit estimate (Kaplan-Meier) of the cumulative survival function. Cox proportional-hazard models were used to estimate the adjusted difference between groups. All analyses were performed using STATA 14.1 (StataCorp LP, College Station, TX).

To demonstrate the consequences of thinness at birth in monetary terms, the number of hospitalizations due to CHD was valued by the costs of CHD-related hospital episodes. Due to the over 40 year time period and significant treatment advances during that time, the recent national average cost unit of internal medicine-related hospital care episode was used to value the number of hospitalizations due to CHD. (22) The applied unit cost estimate was adjusted to the 2013 price level (i.e. 2878 € per episode) using the official health care price index determined by Statistics Finland and then the number of hospitalizations in each patients was multiplied by this average unit cost estimate of care episode. This applied approach provides a raw life-course cost estimate about the additional costs of small body size at birth in terms of CHD-related hospital care. To demonstrate the relative cost differences between the PI groups, cost difference ratios between the PI groups were estimated using the lowest group as a reference. These ratios were adjusted for gestational age, age measured at baseline in 1970, parity, and childhood socioeconomic status. The use of these ratio estimates enables the estimation of additional costs of thinness at birth using virtually any unit cost estimate for a CHD-related hospitalization episode.

RESULTS

Characteristics of the 964 men are presented in Table 1. Mean age measured in 1971 was 29.9 (2.8, range 26-37 years). They typically came from a manual worker background (fathers' highest occupational status manual worker for 62.8%). Mean ponderal index was 26.7 (SD 2.3) kg/m^3 and 24.8 percent belonged to the lowest PI group (PI<25 kg/m^3). During the 42-year time period, 3299 (24.7%) men died, 563 (17.1%) due to CHD causes. The adjusted mortality rates, expressed in 1000 person years for the low, medium, and high PI groups were 33.1 (95 % confidence interval 27.5-39.4), 32.1 (27.9-36.8), and 28.2 (23.5-33.5), respectively, (P for linearity 0.57). The distribution of CHD-related hospital care according to PI during the 42-year time period is presented in Figure 1. During this time period, the number of CHD-related hospital care episodes ranged between 1 and 20 episodes during which cohort members had spent 1 to 546 days in hospital care due to CHD causes. We performed sensitivity analysis where we explored the distribution of "1 hospital care episode" in the high, medium, and low PI groups. We found no statistically significant differences between the three groups (x^2=0.813, df=2, p=.666).

The onset age of CHD (i.e. the age of first hospitalization due to CHD) according to PI are presented in Figure 2. The lowest age of onset was observed in the lowest PI group (57.2, SD 9.6 years) and the highest age in the highest age group (58.9, SD 8.9 years, adjusted P for linearity 0.014). The age-specific rates of CHD-related hospital care per 1000 person-years are presented in Figure 3. The adjusted IRR for the lowest group was 1.35 (1.16-1.59, p=0.001) compared to the highest group. The rate of CHD-related

hospital care increased with older age. In the age groups ranging from age 25-34, 35-44, 45-54 and 55 and older, men in the lowest PI group had a higher rate of CHD-related hospital care compared to those in the medium and high PI groups (IRRs 4.49, 5.68, 18.08, 1.58, and 4.08, and p=0.034, 0.017, <0.001, 0.21, and 0.043, respectively). Similar findings were found when using PI as a continuous measure (Figure 3).

Hospital in-patient costs due to CHD-related reasons per person and person-year are presented in Table 2. During the 42-year time period, the costs of CHD-related hospital care episodes were lower in the higher PI group, compared to the lower PI group (adjusted P for linearity 0.012). The CHD-related hospital care costs were highest for the lowest PI group compared to the highest PI group (cost difference ratio 1.25, 1.04 to 1.46). Parallel differences were observed when costs were estimated per person-years. For men in the lowest PI group, these average CHD-hospital care costs were relatively 13% (-4% to 31%) and 25% (4% to 46%) higher than for the medium or high PI groups, respectively. The cost difference was statistically significant for the comparison between the highest and the lowest PI groups.

DISCUSSION

We present findings on the relationship between non-optimal in-utero growth and CHD among men, who belong to a large birth cohort, the Helsinki Birth Cohort Study. The current results indicate that the onset of CHD-related hospital care occurred at younger age during the 42-year time period among men who were born thin. Lower PI was associated with a higher rate of CHD-related hospital in-patient care during the time period. To the best of our knowledge, this is the first study to show that compared to those in the higher PI group, the rate of CHD-related hospital in-patient care costs were higher in the groups with children who were born thin. Taken together, thinness at birth may be a risk factor for an earlier onset of CHD and higher hospital care rates and costs across the life span among men.

The accumulation of hospital care is a central element of health care expenditures associated with CHD. (8) We followed up the HBCS cohort for hospital care related to CHD from early adulthood to old age. During that time period we witnessed an earlier occurrence of CHD-related care for the men who had lower PI at birth. Furthermore, they had more CHD-related hospital care than those who had higher PI at birth. Thinness at birth as a risk factor for early onset of CHD is of global public health importance. First, in many industrialized countries, large age-cohorts, i.e. baby boomers born after the Second World War, are aging. As the current findings illustrate, among these ageing individuals, small body size at birth continues to be a potential risk factor for negative health outcomes in old age. Second, in many developing countries, the prevalence of low birthweight, a measure of early growth, continues to be high.

According to recent meta-analysis 10.6 million infants worldwide were born at term and low birthweight (under 2500g) (23), which is of importance when considering the large portion of direct health care expenditures attributable to cardiovascular disease. (8)

Evidence suggests that there is a pathway from non-optimal in-utero growth to CHD. (1-3) The key mechanisms underlying this negative association have been identified. (4, 5, 6) Low birthweight, typically brought on by non-optimal in-utero growth, is associated with structural abnormalities in the myocardium. (24) Inadequate fetal nutrition may suppress fetal myocyte proliferation and depress the rate of cardiomyocyte maturation. (25, 26) At birth, the heart contains an inadequate endowment of cardiomyocytes. As the number of coronary micro vessels is linked to the myocyte number, the heart also has an inadequate coronary tree. The mediated effects of small body size at on the risk of CHD in adulthood include hypertension, type 2 diabetes, and the metabolic syndrome. (4) These factors are likely to both increase the rate of CHD-related hospital care, as well as advance the onset of CHD, especially among those men who are born thin.

Strengths and limitations

The strengths of our study include a well-characterized sample and a long follow-up with information on birth anthropometrics collected from birth records, spanning from adulthood to old age. However, our study was restricted to men who were born in Helsinki University Hospital or Helsinki City Maternity Hospital, where the majority of all births in the city occurred. Further, there is a 10-year difference in the HBCS caused by the differences in the age at entry to the baseline study. Due to this lag and given that the prevalence of CHD increases with age, the younger members could have been in a lower risk of sustaining CHD during the follow-up. However, adjusting for age at baseline measured in 1971 did not attenuate the main results. The validity of national hospital discharge and mortality registers has been established. (27, 28) Register data on hospital admission and discharge data were available for practically all original cohort members, who had not migrated or died without any hospital in-patient care, thus minimizing loss to follow-up. We were also able to use register data on childhood socioeconomic status.

Some limitations of the study should be recognized. Birth size is a crude measure of the intrauterine environment, however, it has been extensively used in the literature as a marker of prenatal development. The relationship between birth size and CHD was independent of length of gestation, suggesting that it can be attributed to slow fetal growth rather than preterm birth among men. The men in this study were born in one of the two public hospitals of the city of Helsinki, thus the participants may not represent all Finnish men. In this historical cohort, most participants were born or grew up during the Second World

War, a time during which families might have suffered from food shortages in Finland. This needs to be considered when generalizing these results into contemporary cohorts. Finally, we cannot determine the extent to which the associations between thinness at birth and CHD are mediated through standard coronary risk factors, as we do not have these data available.

In the present study, due to significant treatment advances over more than 40 years, we used a constant valuation approach (i.e. a recent national average cost of internal medicine-related hospital care episode was used to value all hospitalizations) to value the economic consequences of thinness at birth. However, this approach may underestimate the real economic consequences related to inpatient hospital care among the study cohort. Nevertheless, we also reported adjusted cost difference ratios that could be used to estimate the additional costs of thinness at birth using virtually any unit cost for CHD-related hospitalization episode. In the future, the results of the present study could be used in detailed health economic modelling studies aiming to estimate the health and economic consequences of thinness at birth. Additional avenues for further studies include e.g. replicating these study results according to hospital care related to another major chronic illness, such as mental health disease or metabolic disease.

CONCLUSION

Thinness at birth is associated with an slightly earlier onset, a higher rate, and higher cumulated costs of CHD-related hospital in-patient care among men who had been hospitalized due to CHD during the 42-year time period. These findings indicate that prevention of non-optimal in-utero growth may be one of the contributing factors in the efforts to prevent coronary heart disease. Furthermore, the higher rate of CHD-related hospital care translated into higher costs among those men who were thin at birth. These higher costs can be attributed to a higher frequency of hospital care episodes.

Conflict of interest

JM is a partner of ESiOR Oy, which carries out health economic and outcome research studies for pharmaceutical and food companies.

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Figure legends

Figure 1 Distribution of hospital in-patient care episodes during the 42-year time period according to PI groups.

Figure 2 The onset of CHD-related hospital care (i.e. age at first hospitalization due to CHD) per 1000 person years and 95% confidence intervals (CIs) according to PI groups and as continuous among men. Adjusted (for gestational age, chronological age, parity, and childhood socioeconomic status), whiskers and grey area indicate 95% CIs.

Figure 3 Rates of CHD-related hospital care (i.e. first hospitalization due to CHD) per 1000 person-years and 95% confidence intervals (CIs) according to PI groups and as continuous among men. Adjusted (for gestational age, chronological age, parity, and childhood socioeconomic status), whiskers and grey area indicate 95% CIs.

Table 1 Characteristics of men in the Helsinki Birth Cohort Study. Respondents with register data on CHD-hospital care and ponderal index, (n=964)

	Mean/Percentage	Range
Birth anthropometrics, mean (SD)		
Weight, kg	3.4 (0.5)	1.6-5.1
Length, cm	50.2 (1.9)	41.0-58.0
Low birthweight,<2500g, %	3.4	
Birthweight z-score	0.04 (1.0)	-3.8-3.4
Ponderal index, kg/m^3, mean (SD)	26.7 (2.3)	15.1-56.7
Ponderal index, kg/m^3, %		
< 25	24.8	
25-27.5	43.6	
>27.5	31.6	
Birth order, %		
Firstborn	48.2	
Second or higher	51.8	
Father's occupational status, %		
Upper middle	14.1	
Lower middle	23.1	
Manual worker	62.8	
Gestation age (days), mean (SD)	278.3 (13.3)	211-308
Age measured in 1971, mean (SD)	30.4 (2.9)	26-37
Died between 1971-2013, %	38.4	

Table 2 Estimated costs (€) of hospitalizations due to CHD-related hospital care according to PI groups during the 42-year time period. The estimated costs are reported as mean costs per person and averaged over person-years. Cost difference ratios shows the relative differences between the PI groups (<25 PI group as reference).

	<25 Mean (95% CI)	25–27.5 Mean (95% CI)	>27.5 Mean (95% CI)	P for linearity*	Cost difference ratio* (<25 vs. 25-27.5) (95% CI)	Cost difference ratio* (<25 vs. 27.5) (95% CI)
Mean cost of hospitalization per person	8672 (7714 to 9790)	7800 (7200 to 8488)	7324 (6633 to 8147)	0.012	1.13 (0.96 to 1.31)	1.25 (1.04 to 1.46)
Costs averaged over1000 person years	87 (77 to 97)	80 (76 to 84)	84 (72 to 95)	0.90	1.09 (0.78 to 1.19)	0.99 (0.78 to 1.19)

* Adjusted for gestational age, chronological age, parity, and childhood socioeconomic status, CI= confidence interval
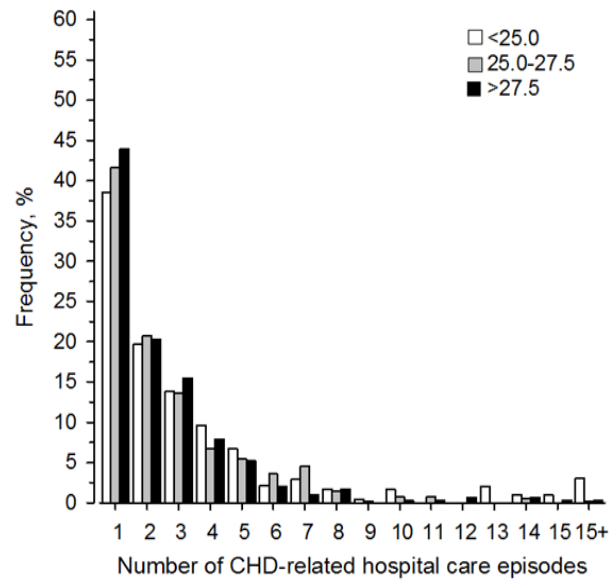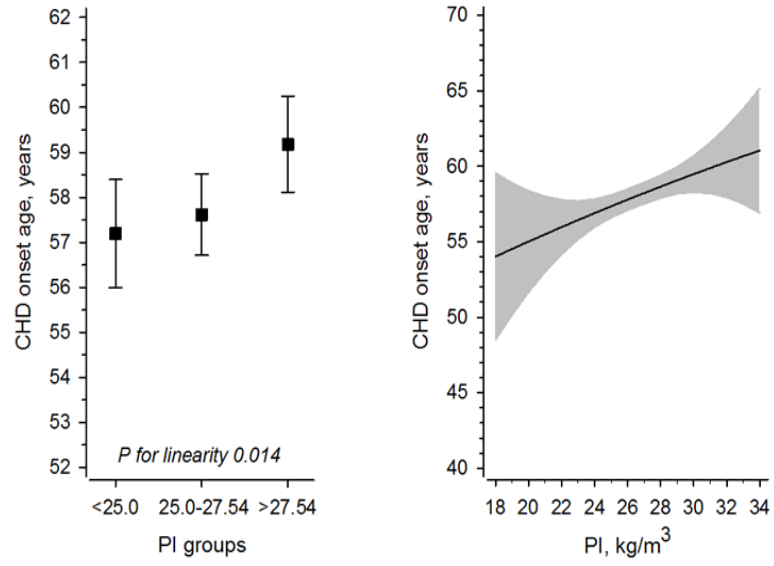
Figure 1.

Figure 2.

Figure 3.