Head size at birth and long-term mortality from coronary heart disease

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Background Many studies have shown that low birthweight is associated with increased risk of heart disease in adulthood. It is controversial whether this association is caused by genetic or non-genetic factors, and whether life course exposures, such as adult overweight, could modify the association. We have studied the association of head circumference at birth with later deaths from coronary heart disease (CHD), and assessed whether maternal height and adult body mass could modify the association.


Results During follow-up, 630 people died from CHD and there was an inverse association of head circumference with deaths from CHD ($P_{\text{trend}} = 0.010$). The association was modified by maternal height ($P_{\text{interaction}} = 0.01$) and by adult body mass ($P_{\text{interaction}} = 0.05$). People in the lowest third of head circumference, who had a tall mother or a high body mass index in adulthood, were at the highest risk of death from CHD.

Conclusions Head circumference at birth was inversely associated with deaths from CHD, and the combination of small head and tall mother, or small head and high adult body mass, was associated with the highest risk. These findings suggest that combined effects of genetic factors (growth potential and intrauterine growth) and non-genetic factors acting throughout the life course (intrauterine growth restriction and later weight gain) could mediate the effects of birth size on adult heart disease.

Keywords Birth size, head circumference, coronary heart disease, mortality

Introduction Many studies have shown an inverse association of birthweight with adult risk and mortality from heart disease.1 A dominant hypothesis to explain these findings has been that intrauterine under-nutrition causes fetal adaptations that are related to higher risk of heart disease later in life.2 Alternatively, common genetic factors could be associated with both small birth size and later risk of heart disease.3,4
Current evidence, however, suggests that genetic and non-genetic factors that operate throughout the life course interact to predict cardiovascular disease (CVD). A small child delivered by a tall mother, indicating lack of coherence between mother and offspring, may suggest that the child was truly growth restricted in utero, and therefore, at increased risk of heart disease in adulthood. Also, small birth size followed by high weight gain has been associated with increased risk.

Genetic and non-genetic factors appear to influence measures of birth size differently. Whereas weight and adiposity at birth is strongly influenced by non-genetic factors, such as variation in intrauterine nutrition, fetal longitudinal growth and head size at birth appear to be less susceptible to nutritional factors, but more closely associated with genetic factors. However, most studies have used information on birthweight to assess long-term effects, whereas the effect of head size at birth has only been studied in one small cohort of men, where the investigators reported an inverse association with deaths from heart disease.

In this large population-based cohort study of people with perinatal information from hospital birth charts, we have assessed the association of head circumference at birth with deaths from coronary heart disease (CHD) in adulthood, and paid particular attention to whether the association of head size could be modified by maternal height (indicating growth potential), or by adult body mass (indicating adult obesity).

Methods
Study cohort
We abstracted information from archived birth charts of all 46 311 births that took place at St. Olav’s University Hospital in Trondheim, Norway, from 1920 to 1959. In the charts, each child is registered by the mother’s name, the child’s birth date and the child’s given name.

For identification, we depended on the 11-digit identification number assigned to all Norwegian citizens in 1960. Vital status and residential history of all residents in the country is continuously updated through the National Population Register, and we used this information to identify men and women who were born at St. Olav’s Hospital between 1920 and 1959 and were alive and resided in Norway in 1960. Linkage between mother and child could not always be reliably verified, especially for women whose last name had changed through marriage. Also, if the mother had died before 1960, we could not always ascertain linkage with the child. Among a total of 22 522 female offspring, we reliably identified 17 339 (77%), and among 23 789 males, we reliably identified 21 145 (89%). In this study, we excluded 916 twins, 712 pre-term births and 1010 with missing data on gestational age, birth size or other factors. This left a total of 19 691 men, and 16 155 women for mortality follow-up.

Follow-up
Using the unique identification number of each person, we linked birth record data to information from the Cause of Death Register at Statistics Norway to ascertain cause specific deaths that occurred in the cohort during follow-up. Each person contributed person-years of follow-up from 1 January 1961 until death from any cause, emigration or until the end of follow-up, 31 December 2005.

To ensure completeness, the Cause of Death Register is cross-linked to updated vital status recorded by the National Register of Norway. Causes of death were recorded according to the International Classification of Disease (ICD), seventh–tenth revision (CVD; ICD-7: 330–334 and 420–468, ICD-8: 390–458; ICD-9: 390–459, and ICD-10: 100–199, and CHD; ICD-7: 420, 422, ICD-8 and ICD-9: 410–414, and ICD-10: 120–125).

Study variables
We abstracted information on head circumference (in centimetres), birthweight (in grams) and birth length (in centimetres) as well as information on length of gestation (in weeks or months), birth order and multiple births from the birth charts. Gestational age was indicated in the charts, either in completed weeks or in completed months. Information on first day of the last menstrual period was available for 40% of the participants, and information on week of the last menstrual period was available in 60%. On the basis of this information, term delivery was defined as pregnancies of at least 37 weeks, or alternatively, as at least 8 months of completed gestation for those where information in weeks was not available. We also abstracted information on maternal factors from the birth charts, including age, height, marital status and occupation at childbearing (manual or non-manual).

We calculated SD scores (standard deviation scores) for each birth-size variable (weight, length and head circumference) by subtracting the mean value within each sex and birth cohort stratum from the observed value, and divided the result by the stratum-specific standard deviation. Positive SD scores indicate birth size above the mean and a negative score indicates birth size below the mean. Each birth-size measure was divided into categories of thirds, according to birth cohort and sex. For maternal height, we calculated thirds according to birth cohort.

For a subgroup of the study population, we also had information on adult height and weight. This information was obtained by a linkage to previous surveys conducted by the National Health Screening Service of Norway in the 1960 and 1970s. To these studies,

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people >15 years of age were invited, and the collected data included standardized measurements of height and weight. Among the 35 846 participants of this study, data on adult height and weight were available for a total of 22 998 people (12 052 men and 10 936 women). Using this information, we calculated body mass index (BMI) in adulthood as weight (in kilograms) divided by the squared value of height (in metres). In the analyses where adult BMI was included, follow-up started from the date this information was collected.

### Statistical analysis

We used the Cox proportional hazards model to calculate hazard ratios (HR) of death from CVD, and specifically from CHD, associated with each measure of birth size. All birth size measures were analysed both as a continuous variable (SD score) and in categories (thirds). Precision of the estimates was assessed by 95% confidence intervals (CI), and two-sided P-values from trend tests were calculated by treating the birth-size categories as ordinal variables in the regression model. Our basic models were age adjusted using attained age as the time variable. We tested for effect modification by sex by including a product term between sex and each birth-size measure in the regression model. Since there was no indication of effect modification by sex (all P > 0.28), men and women were combined in the analyses and sex was included as a co-variable in the regression analyses. In the analyses of continuous variables, we also tested for non-linear associations, using a likelihood ratio test, by adding a quadratic term in the regression model. To adjust for cohort effects we included birth year in 10-year intervals from 1920 to 1959. In the multivariable analyses, we also adjusted for maternal age at childbearing (<25, 25–29, 30–34 and ≥35 years), birth order (first, second and ≥third), parental occupational status (manual labour vs other occupations) and maternal marital status (married vs unmarried).

In subsequent analyses, we studied the combined effects of head circumference and maternal height in relation to deaths from CHD, and similarly, the combined effects of categories of thirds of head circumference and BMI in adulthood in sub-samples of the populations where this information was available. We tested for interaction effects, using a likelihood ratio test, by including a product term between head circumference (thirds) and maternal height (thirds) in the analysis; and respectively, between head circumference and adult BMI. All statistical analyses were conducted using Stata for Windows (Version 9 StataCorp LP, 1985–2007).

### Ethical approval

The study was approved by the Norwegian Data Inspectorate, the Norwegian Board of Health and by the Regional Committee for Ethics in Medical Research.

### Results

In this long-term mortality follow-up of 35 846 men and women with birth-size information collected from hospital charts, a total of 3461 people died; 994 deaths were due to CVDs, including 630 deaths from CHD. Basic characteristics of the study population are shown in Table 1. Mean birthweight was 50 g higher among people born between 1950 and 1959 compared with people born between 1920 and 1929, mean head circumference remained constant across this period.

Both head circumference and birthweight were inversely associated with the risk of total cardiovascular deaths, and specifically, with deaths from CHD (Table 2). One standard deviation wider head circumference (1.5 cm) was associated with a 10% lower risk (HR 0.90, CI: 0.83–0.97) of death from CHD, and 1 SD higher birthweight (460 g) was associated with an 8% lower risk (HR 0.92, CI: 0.85–0.99). There was no evidence for any non-linear association (all P > 0.12). The main analyses were adjusted for sex and birth cohort, and further adjustments included maternal age, birth order, maternal marital status and paternal occupation, but including these variables did not substantially influence the estimated HR.

A similar analysis, using categories (thirds) of head circumference and birthweight, is shown in Table 3. The adjusted HR for the highest compared with the lowest third of head circumference was 0.69 (CI: 0.56–0.85), and the corresponding association for birthweight was 0.83 (CI: 0.68–1.00). In a supplementary analysis where we mutually adjusted for head circumference and birthweight (data not shown), the inverse association of head circumference remained nearly unchanged after adjustment for birthweight (adjusted HR 0.70, CI: 0.55–0.89), whereas the inverse association of birthweight was strongly attenuated after adjustment for head circumference (adjusted HR 0.96, CI: 0.76–1.20).

In sub-samples with available information on maternal height (n = 32 731) or adult BMI (n = 22 998), we studied the combined associations of head circumference and maternal height with deaths from CHD (Table 4), and similarly, the combined associations of head circumference and adult BMI (Table 5) with deaths from CHD.

The results showed strong evidence for an interaction effect between head circumference and maternal height (Pinteraction = 0.01). There was no evidence for a similar effect between birthweight and maternal height (Pinteraction = 0.72, data not shown). Using people in the lowest thirds of head circumference and maternal height as the reference, the adjusted HR for people in the highest third of both head
circumference and maternal height was 0.62 (CI: 0.39–0.98). On the other hand, the adjusted HR for people in the lowest third of head circumference but the highest third of maternal height was 1.43 (CI: 1.08–1.93).

For head circumference and adult BMI, there was moderate evidence for an interaction effect ($P_{\text{interaction}} = 0.05$), but there was no evidence for interaction between birthweight and adult BMI ($P_{\text{interaction}} = 0.66$, data not shown). For people in the lowest third of head circumference and the highest third of adult BMI, the adjusted HR of deaths from CHD was 2.11 (CI: 1.49–2.98), compared with the reference group (lowest third of both head circumference and BMI).

**Discussion**

We found a strong inverse association of head circumference at birth with risk of deaths from CHD in adulthood that was, however, modified by maternal height and adult BMI. In particular, this study showed higher risk of coronary death in people who...
probably had suffered from growth restriction in utero (small head at birth but tall mother), and in people with small head size at birth who were overweight or obese later in life.

**Strengths and limitations**

This population study of nearly 36000 men and women covers 44 years of mortality follow-up, and both the strength of the associations, and the

### Table 3

<table>
<thead>
<tr>
<th>Head circumference&lt;sup&gt;c&lt;/sup&gt;</th>
<th>Deaths</th>
<th>Person-years</th>
<th>HR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>343</td>
<td>681496</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>172</td>
<td>424365</td>
<td>0.86 (0.72–1.94)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>115</td>
<td>426957</td>
<td>0.69 (0.56–0.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Birthweight&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Deaths</th>
<th>Person-years</th>
<th>HR&lt;sup&gt;b&lt;/sup&gt; (95% CI)</th>
<th>(P_{\text{trend}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>240</td>
<td>514939</td>
<td>1.00 (Reference)</td>
<td></td>
</tr>
<tr>
<td>Middle</td>
<td>195</td>
<td>513428</td>
<td>0.80 (0.67–0.97)</td>
<td></td>
</tr>
<tr>
<td>Highest</td>
<td>195</td>
<td>509491</td>
<td>0.83 (0.68–1.00)</td>
<td>0.042</td>
</tr>
</tbody>
</table>

<sup>a</sup>Thirds according to sex and birth cohort (before 1930, 1930–39, 1940–49, 1950 onwards).


<sup>c</sup>Range (in centimetres) of head circumference within categories for men: lowest (28–35), middle (36–36), highest (37–41) and for women: lowest (29–34), middle (35–35), highest (36–41).

<sup>d</sup>Range (in grams) of birthweight within categories of thirds for men: lowest (1620–3410), middle (3370–3820), highest (3800–5500) and for women: lowest (1580–3280), middle (3250–3670) and highest (3640–5500).

### Table 4

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Maternal height&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest (189 deaths)</td>
</tr>
<tr>
<td>Head circumference at birth</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Lowest (249 deaths)</td>
<td>1.04 (0.74–1.45)</td>
</tr>
<tr>
<td>Middle (124 deaths)</td>
<td>1.00 (0.68–1.46)</td>
</tr>
<tr>
<td>Highest (91 deaths)</td>
<td>0.94 (0.55–1.62)</td>
</tr>
</tbody>
</table>

\(P_{\text{trend}}<sup>c</sup> 0.90 0.09 0.001 0.01

<sup>a</sup>HR adjusted for sex and birth cohort (before 1930, 1930–39, 1940–49, 1950 onwards).

<sup>b</sup>Maternal height in thirds (mean values: lowest 156.6, middle 162.7, highest 168.6 cm), by birth cohort.

<sup>c</sup>\(P_{\text{trend}}\) over categories (thirds) of head circumference at birth within strata (thirds) of maternal height.

### Table 5

<table>
<thead>
<tr>
<th>HR (95% CI)</th>
<th>Adult BMI&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lowest (99 deaths)</td>
</tr>
<tr>
<td>Head circumference at birth</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Lowest (209 deaths)</td>
<td>1.39 (0.89–2.17)</td>
</tr>
<tr>
<td>Middle (104 deaths)</td>
<td>0.94 (0.55–1.62)</td>
</tr>
<tr>
<td>Highest (63 deaths)</td>
<td>0.90 (0.55–1.62)</td>
</tr>
</tbody>
</table>

\(P_{\text{trend}}<sup>c</sup> 0.90 0.09 0.001 0.05

<sup>a</sup>HR adjusted for sex, birth cohort (before 1930, 1930–39, 1940–49, 1950 onwards) and age at measurement of adult BMI.

<sup>b</sup>Adult BMI, in thirds (mean values: lowest 19.5, middle 22.8 and highest 27.2 kg/m<sup>2</sup>.

<sup>c</sup>\(P_{\text{trend}}\) over categories (thirds) of head circumference at birth within strata (thirds) of adult BMI.
The number of coronary deaths make chance an unlikely explanation for the main findings. The participants were born between 1920 and 1959 at the only birth institution that covered a defined geographical region in Norway. Although home births were common in the 1920s, the proportion of births that took place in this institution increased from ~50% in 1920 to >90% by 1944. Therefore, the cohort members are unlikely to be selected by characteristics related to subsequent CVD.

Information on birth size was collected from standardised birth charts that were systematically recorded by midwives shortly after birth. The information was impressively detailed and complete, and we could restrict the study to singletons and to babies born at term, and adjust for factors that are known to influence birth size, such as maternal height, birth order and indicators of socio-economic position at birth. Only 0.4% had missing data on one of the birth size measures, and only 6% of those who were eligible for follow-up were excluded due to other missing data.

Measurements of head circumference may be subject to misclassification, mainly caused by factors related to obstructed labour that could either lead to overestimates (e.g., scalp oedemas, cephalhematomas) or to underestimates of head size (over-riding of sutures). The results of one study suggested that the head circumference related to vaginal deliveries was slightly less (0.3 cm) the first day after birth compared with measurements made after 1 week. It is also conceivable that the baby’s head could be compressed relatively more during labour in short mothers. However, small mothers are more likely to have small babies, and maternal height may not be associated with the cephalopelvic disproportions that often lead to obstructed labour and delivery by caesarian section. The misclassification of head circumference in our study is likely to be modest and non-differentially related to exposure and outcome, and this will usually lead to underestimates of effects.

Measurement precision is likely to differ between birth-size measures. Whereas head circumference tends to be measured more accurately than birth length, birthweight measurements are clearly more precise (in grams) than measurements of head circumference (in centimetres). Compared with the inverse association of birthweight with later risk of CHD, the association of head circumference may therefore be conservatively estimated. Also, after mutual adjustment, the inverse association of head circumference remained nearly unchanged, whereas the association of birthweight with coronary death was attenuated after adjustment for head circumference, suggesting that head size may be a stronger independent long-term predictor than birthweight.

Information on the cause of specific mortality was collected by linkage to the Cause of Death Registry at Statistics Norway. Although there are discrepancies between reported causes of death based on clinical judgment and autopsy findings, perinatal and outcome information was independently collected, and given the prospective design of the study, misclassification of birth size and causes of death would most likely be non-differential and lead to conservative results.

It is a limitation that we did not have more detailed information on potentially confounding factors, such as pregnancy complications, childhood socio-economic position and prevalence of maternal smoking and family history of CVD. It is, however, reassuring that other studies with more comprehensive co-variable information have suggested that confounding by other known cardiovascular risk factors do not explain the observed inverse association of birth size with risk of heart disease. With respect to maternal smoking, this was rare in Norway before 1955, and may not be an important confounding factor in these data.

Head circumference at birth

Previously, one small cohort study has assessed the association of head circumference at birth with risk of CHD. That study showed an inverse association of head circumference with total cardiovascular deaths, and in a subsequent analysis, an inverse association with deaths from CHD. The same investigators have also reported an inverse association of head circumference with the prevalence of CHD among 517 men and women in India. A recent meta-analysis of nearly 150,000 individuals could not include data on head size or birth length, but our results for birthweight correspond with the results of that analysis. In a large mortality follow-up of men and women born in Helsinki between 1924 and 1944, however, short birth length was associated with higher cardiovascular mortality later in life.

Genetic and environmental factors appear to influence measures of birth size differently, and there is evidence that head size at birth is closely related to genetic factors. Early gestational growth, which is highly influenced by genes, may be particularly important for head size. Based on the results of a study of more than 100,000 families and a large cohort study, it was concluded that environmental factors were less important for the variation in head circumference than for birthweight. Thus, genetic factors that promote intrauterine head growth may also be associated with lower risk of heart disease in adulthood. Since head circumference is correlated with brain volume, it is possible that infants born with relatively large heads could benefit from the lower cardiovascular mortality that has been associated with high cognitive ability. Although extreme growth restriction is associated with reduced cognitive performance later in life, some studies have shown...
that head circumference at birth may not be associated with childhood intelligence.\textsuperscript{29,30}

**Influence of maternal height**

The association of head size at birth with CHD mortality was modified by the height of the mother. For people whose mother was relatively tall (tallest third), we found two distinctly different patterns. First, people in the lowest third of head circumference, who had a tall mother, were at the highest risk of death from CHD. The lack of coherence (small head but tall mother) suggests that these people had failed to reach their growth potential \textit{in utero} and most likely had suffered from intrauterine growth restriction.\textsuperscript{31} The higher risk of death from heart disease in this group may support the hypothesis that intrauterine growth restriction causes fetal adaptations that in the long term contribute to increase the risk of heart disease.\textsuperscript{32} Alternatively, it has been suggested that the higher risk associated with being small at birth could be attributed to accelerated post-natal growth.\textsuperscript{33}

In particular, small infants with tall parents tend to experience accelerated growth in early childhood,\textsuperscript{34} and catch-up growth, both in weight and height, may be associated with higher body mass, fat mass and cardiovascular risk.\textsuperscript{33,35}

People in the highest third of both head circumference and maternal height were at the lowest risk of death from CHD. A large baby of a tall mother could be the result of a combination of a close to optimal environmental and genetic conditions for intrauterine growth, that in itself has been suggested to be protective against future heart disease.\textsuperscript{36} Given the tallness of the mother, the healthy offspring would probably end up tall, and could therefore also benefit from the inverse association of adult height with risk of heart disease.\textsuperscript{37}

**Influence of adult body mass**

We found that the inverse association of head circumference at birth was particularly strong for those who were in the top third of adult body mass as adults. Thus, people with head circumference in the lowest third at birth, whose adult body mass indicated overweight or obesity (highest third), had the highest risk of death from CHD. This finding is in agreement with other studies in suggesting that small birth size combined with high weight gain later in life is associated with higher risk of CHD.\textsuperscript{10,38} More specifically, other studies have also suggested an interaction effect between birth size (indicated by birthweight) and adult body mass in predicting adult heart disease.\textsuperscript{8,9}

This may suggest that the inverse association of birth size with adult heart disease could be restricted to people who are overweight in adulthood. These findings appear to be compatible with the original hypothesis that early deprivation followed by later affluence is associated with higher risk of heart disease.\textsuperscript{39} Our results suggest that people with relatively slow head growth \textit{in utero} may be particularly susceptible to detrimental effects of later weight gain.

**Conclusion**

In this prospective study of Norwegian men and women, the strong inverse association of head circumference at birth with deaths from CHD in adulthood was modified by maternal height and by adult body mass. Our findings suggest that combined effects of genetic factors related to growth (growth potential and fetal growth) and non-genetic influences (intrauterine growth restriction and later weight gain) acting throughout the life course could mediate the effects of birth size on adult heart disease.

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**Conflict of interest**: None declared.

**References**


