Papers

Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow up study

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Abstract

Objective: To determine whether restricted growth in utero is associated with an increased risk of coronary heart disease among men in Finland, where rates of the disease are among the highest in the world.
Design: Follow up study.
Setting: Helsinki, Finland.
Subjects: 3302 men born in Helsinki University Central Hospital during 1924-33 who went to school in the city of Helsinki and were resident in Finland in 1971.
Main outcome measures: Standardised mortality ratios for coronary heart disease.
Results: Men who were thin at birth, with low placental weight, had high death rates from coronary heart disease. Men whose mothers had a high body mass index in pregnancy also had high death rates. In a multivariate analysis the hazard ratio for coronary heart disease was 1.37 (95% confidence interval 1.20 to 1.57) ($P < 0.0001$) for every standard deviation decrease in ponderal index at birth and 1.24 (1.10 to 1.39) ($P = 0.0004$) for every standard deviation increase in mother's body mass index. The effect of mother's body mass index was restricted to mothers of below average stature.
Conclusion: These findings suggest a new explanation for the epidemics of coronary heart disease that accompany Westernisation. Chronically malnourished women are short and light and their babies tend to be thin. The immediate effect of improved nutrition is that women become fat, which seems to increase the risk of coronary heart disease in the next generation. With continued improvements in nutrition, women become taller and heavier; their babies are adequately nourished; and maternal fatness no longer increases the risk of coronary heart disease, which therefore declines.

Introduction

A few decades ago Finland had exceptionally high rates of coronary heart disease.[1] Although rates have subsequently fallen, in keeping with trends in other western European countries, they remain high and around half of all deaths in the country are currently due to cardiovascular disease.[2] The geographical variation and temporal trends in mortality from coronary heart disease are not adequately explained by the lifestyles of Finnish men and women.

Coronary heart disease and its biological risk factors hypertension, non-insulin-dependent diabetes mellitus, and abnormalities in lipid metabolism and blood coagulation are associated with low birth weight.[3-7] In studies in which body length at birth was also available the associations with thinness and stunting at birth are stronger than with low birth weight alone. These associations are independent of adult obesity and social class and of lifestyle influences, including smoking and alcohol consumption. The early observations have been replicated in different populations, although there remain some inconsistencies—for example, the absence of an association between birth weight and blood pressure during adolescence.[4] The findings have led to the hypothesis that coronary heart disease is programmed in utero. The fetal origins hypothesis proposes that adaptations made by the fetus in response to undernutrition result in persisting changes in metabolism and organ structure that lead to disease.[3] This hypothesis is supported by experimental evidence in which offspring of undernourished pregnant animals show permanent changes, including raised blood pressure and abnormal glucose-insulin and lipid metabolism.[8-10]

Poor maternal and fetal health in Finland at the beginning of the century were reflected in exceptionally high infant death rates. To explore associations between poor fetal growth and coronary heart disease in Finland we studied a group of 3302 men who were born in Helsinki University Central Hospital, where detailed records have been kept on each birth for more than a century. These records allowed us to determine whether in utero influences contribute to the high rates of coronary heart disease in Finland and to examine the associations between a mother's height and weight and coronary heart disease in the next generation.

Subjects and methods

The birth records at Helsinki University Central Hospital contain data on the mothers as well as their newborn babies. Data on the mothers include age, parity, height, and date of the last menstrual period, together with body weight measured on admission in labour. Height was recorded to the nearest 0.5 cm and weight to the nearest 0.5 kg. Data on the newborn babies include birth weight, placental weight, length, and head circumference. Birth

See editorial by Scrimshaw

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weight and placental weight were rounded to the nearest 5 g and length and head circumference to the nearest 0.5 cm. Birth weight was recorded for all 2785 term babies, born after 37 completed weeks of gestation, on which most of our analyses are based. Placental weight was recorded for 2784, length for 2772, head circumference for 2781, mother's height for 2626, and mother's weight for 2610.

We studied a sample of men who were born at the hospital between 1924 and 1933, went to school in the city of Helsinki, and were still resident in Finland in 1971. School records for children attending schools in Helsinki are stored in the city archives. We identified 3593 men from the birth and school records and used the population register that covers the whole Finnish population to trace 3302 (92%) of them. The mean birth size of those who were traced and not traced was similar. Since 1971 all residents of Finland have been assigned a unique personal identification number. By using this number we identified all deaths among the men during 1971-95. Deaths in Finland are recorded in the national mortality register. The register was computerised in 1971 and causes of death were recorded according to ICD-8 (international classification of diseases, eighth revision) until 1986; thereafter ICD-9 was used until the end of 1995. The first three digits from the primary cause of death in ICD-8 and ICD-9 were used for identifying deaths from coronary heart disease (410-414). Using the father's occupation, which was on the birth records, we classed the men according to a social classification used by the Central Statistical Office. Overall, 2631 (85%) fathers were labourers.

The numbers of deaths from coronary heart disease were compared with those expected from Finnish national rates for men of corresponding age and year of birth. Death rates were expressed as standardised mortality ratios, the national average being 100. We examined the trends in standardised mortality ratios with maternal and neonatal measurements. Tests for trend were based on the corresponding log-linear model and on Cox's proportional hazards model.

Results

Table 1 shows the body size of the newborn babies and their mothers. A total of 982 of the 3302 men had died, 286 from coronary heart disease. The mean age at death from coronary heart disease was 57 years (range 37 to 70 years). The standardised mortality ratio was 85 (95% confidence interval 75 to 95) and was similar in the children of labourers (83) and the children of men in higher social classes (90).

Body size at birth

Table 2 shows that men with a low birth weight tended to have higher mortality from coronary heart disease, but the trend was not significant (P = 0.09). There was a similar non-significant trend in coronary heart disease with head circumference (P = 0.08) but no trend with birth length. There was no trend with the length of gestation, although men born after term (after 42 weeks of gestation) had the highest standardised mortality ratio (137).

Table 3 shows that there was a strong trend in coronary heart disease with ponderal index (birth weight/(length)^3). Men who were thin at birth (in the lowest quarter of the distribution of ponderal index) had death rates that were twice those of men who had a high ponderal index. The trend was not evident among the 358 men who were born prematurely—that is, before 37 completed weeks of gestation (table 3). A low ponderal index results either from failure of intrauterine growth or premature birth. We excluded premature babies from further analyses. Ponderal index was strongly related to placental weight. Table 4 shows that men who had a low placental weight had a low ponderal index at birth and raised death rates from coronary heart disease as adults.

Table 1 Neonatal and maternal characteristics of 3302 men born at Helsinki University Central Hospital, 1924-33

	Mean (SD)	Range
Newborn infant		
Birth weight (g) (n=3302)	3440 (510)	1560-5120
Head circumference (cm) (n=3297)	34.9 (1.4)	23.5-40
Birth length (cm) (n=3289)	50.2 (1.9)	39-57
Ponderal index (kg/m^3) (n=3289)	27.0 (2.5)	17.8-52.3
Placental weight (g) (n=3300)	634 (128)	240-1440
Length of gestation (days) (n=3143)	275 (15)	197-307
Mother*		
Height (m) (n=3076)	1.58 (0.06)	1.31-1.86
Weight in pregnancy (kg) (n=3058)	67.3 (9.1)	45-128
Body mass index in pregnancy (kg/m^2) (n=3035)	26.9 (3.2)	18.4-48.8
Age (years) (n=2921)	27.4 (5.7)	12-46

*Of 3301 women, 1426 (43%) were primiparous.

Table 2 Standardised mortality ratios for coronary heart disease according to birth weight

Birth weight (kg)	No of men	Standardised mortality ratio (No of deaths)
≤2.5	130	84 (11)
-3.0	504	83 (44)
-3.5	1211	99 (124)
-4.0	1052	76 (80)
>4.0	405	66 (27)
All	3302	85 (286)
P value for trend		0.09

Mother's body size

Mother's weight and body mass index in pregnancy were strongly and linearly related to the baby's ponderal index at birth. The ponderal index rose by 0.62 (0.52 to 0.73) for every 10 kg increase in mother's weight. Coronary heart disease was weakly associated with having a heavy mother (P = 0.1) and was unrelated to mother's height. It was, however, strongly related to the mother's body mass index in pregnancy (P = 0.008).

Table 3 Standardised mortality ratios for coronary heart disease according to ponderal index. Numbers in parentheses are numbers of deaths from coronary heart disease

Ponderal index (kg/m^3)	Born at term (n=2785)	Born preterm (n=358)	All (n=3143)
≤25	116 (59)	95 (12)	112 (71)
-27	105 (88)	61 (7)	99 (95)
-29	72 (64)	81 (6)	73 (70)
>29	56 (33)	76 (4)	57 (37)
All	86 (244)	79 (29)	85 (273)
P value for trend	<0.0001	0.7	<0.0001

Table 4 Ponderal index at birth and standardised mortality ratios for coronary heart disease according to placental weight among men born at term

Placental weight (kg)	No of men	Mean ponderal index (kg/m^3)	Standardised mortality ratio (No of deaths)
⩽ 0.5	591	25.6	111 (52)
-0.6	992	26.7	98 (85)
-0.7	951	27.3	76 (64)
> 0.7	753	28.3	67 (44)
All	3287	27.0	86 (245)
P value for trend		<0.0001	0.004

Table 5 shows that high body mass index among the mothers added to the effect of low ponderal index on death rates from coronary heart disease. The highest standardised mortality ratio (171) was in men who had the lowest ponderal index at birth and the highest maternal body mass index, whereas the lowest mortality ratio (38) was in men with the highest ponderal index and the lowest maternal body mass index. In a multivariate regression, with no other variables, the effects of ponderal index and mother's body mass index on the risk of coronary heart disease were both strongly significant. The hazard ratio for coronary heart disease was 1.37 (1.20 to 1.57) ($P<0.0001$) for every standard deviation decrease in ponderal index at birth and 1.24 (1.10 to 1.39) ($P=0.0004$) for every standard deviation increase in mother's body mass index. The effects were not influenced by maternal age and parity or by the duration of gestation.

In table 5 the men are stratified according to the mothers' height (above or below the mean of 1.58 m). Among men whose mothers were of below average height coronary heart disease was strongly related to both ponderal index and mother's body mass index ($P=<0.0001$ and 0.006, respectively). Among men whose mothers were of above average height mother's body mass index had no effect and only the effect of ponderal index remained ($P=0.004$).

Discussion

Our study was restricted to men who were born in Helsinki University Central Hospital, where about 60% of all births in the city occurred, and who went to school in Helsinki. The fathers of 85% of the men were classed as labourers. The men may be unrepresentative of all men living in Helsinki, although we know that in the early years of this century around 60% of men in the city were labourers.[11] This would only introduce a bias if the association between size at birth and coronary heart disease differed between those born in the hospital and outside it. We were able to trace 92% of the men in the sample. In the south of Finland, where our study took place, rates of coronary heart disease are lower than the national average, but they are nevertheless high in comparison with the rates among men in other European countries.

We found that men who were born at term and were thin at birth had high death rates from coronary heart disease (table 3). This is consistent with findings among men in Sheffield.[12] The association is remarkably strong, given the inevitable inaccuracies of measurements of body length at birth. Several studies have shown that thinness at birth is associated with insulin resistance in later life, which predisposes to coronary heart disease.[13 14] We found that thinness at birth was also associated with a low placental weight (table 4), which is again consistent with previous findings.[15]

Mother's body size

We examined for the first time the association between mother's body mass index and the risk of coronary heart disease in the next generation. Men whose mothers had a high body mass index in pregnancy had an increased risk of coronary heart disease. The highest death rates were therefore in men who were thin at birth and had a low placental weight but whose mothers had a high body mass index during pregnancy. The effects were large and highly significant. The effect of mother's body mass index was, however, restricted to mothers of below average stature. We do not know the processes by which high maternal body mass compounds the increased risk of coronary heart disease that is associated with thinness at birth and insulin resistance.

The mothers in our study were shorter and lighter than European women today. The mean height of 1.58 m and late pregnancy weight of 67 kg may be compared with values of 1.63 m and 78 kg in a recent study in the United Kingdom[16] and of 1.67 m in a recent study in Finland (P Jousilahti, personal communication). Mother's body mass index in late pregnancy reflects both weight gain during pregnancy and body mass index before pregnancy. Weight gain in pregnancy results from an increase in fat, uterine and breast tissue, and extracellular fluid, as well as from growth of the fetus and placenta. Body mass index in late pregnancy is highly correlated with body mass index before pregnancy, the coefficient in the study in the United Kingdom being 0.86 (K Godfrey et al, unpublished data). Body mass index in pregnancy is low in undernourished communities—21 kg/m^2 in a recent study in rural India (C Fall, unpublished data). We conclude that high body mass indices in mothers in our study reflected high energy intakes before and during pregnancy.

Table 5 Standardised mortality ratios for coronary heart disease according to ponderal index at birth and mother's body mass index at end of pregnancy. Numbers in parentheses are numbers of deaths

	Body mass index of mother (kg/m^2)					
Ponderal index of baby (kg/m^3)	⩽24	-26	-28	-30	>30	All
All mothers:						
⩽25	56 (6)	134 (20)	158 (17)	131 (7)	171 (7)	124 (57)
-27	88 (12)	87 (21)	123 (26)	104 (11)	131 (11)	104 (81)
-29	46 (5)	76 (17)	55 (13)	98 (12)	116 (16)	76 (63)
>29	38 (2)	61 (7)	45 (7)	68 (6)	72 (9)	58 (31)
All	62 (25)	89 (65)	89 (63)	97 (36)	111 (43)	89 (232)
Mother's height below mean (⩽1.58 m):						
⩽25	55 (3)	106 (9)	168 (12)	170 (5)	224 (6)	131 (35)
-27	55 (3)	70 (8)	146 (17)	113 (6)	134 (6)	104 (40)
-29	26 (1)	54 (6)	31 (4)	137 (10)	149 (11)	75 (32)
>29	0 (0)	63 (3)	26 (2)	55 (3)	75 (4)	48 (12)
All	43 (7)	73 (26)	88 (35)	114 (24)	136 (27)	90 (119)
Mother's height above mean (>1.58 m):						
⩽25	57 (3)	170 (11)	138 (5)	83 (2)	71 (1)	115 (22)
-27	110 (9)	102 (13)	94 (9)	96 (5)	126 (5)	103 (41)
-29	57 (4)	97 (11)	85 (9)	40 (2)	79 (5)	77 (31)
>29	55 (2)	59 (4)	66 (5)	86 (3)	70 (5)	66 (19)
All	75 (18)	105 (39)	89 (28)	75 (12)	85 (16)	89 (113)

Key messages

- Men who were thin at birth have high death rates from coronary heart disease
- If, in addition, their mothers were short and heavy they have even higher rates
- Women tend to be short and heavy in populations at an intermediate stage between chronic malnutrition and adequate nutrition
- This may explain why rates of coronary heart disease rise as nutrition improves in a population; rates then decline with continuing nutritional improvement

Coronary heart disease epidemic

The origins of the modern epidemic of coronary heart disease and its subsequent decline have not been adequately explained by changes in the lifestyle of middle aged men and women. The fetal origins hypothesis proposes that the disease "represents a stage of improving nutrition between chronic maternal malnutrition and nutrition at a plane that allows the mother to nourish her fetus adequately throughout gestation."[17] Table 5 provides the first direct support for this. In chronically malnourished populations mothers are short and thin; newborn babies tend to be thin; and rates of coronary heart disease are low (table 5). Thinness at birth in our study may reflect the effects of maternal undernutrition in previous generations in Finland because a mother who herself had a low birth weight tends to have babies with low placental weights and low ponderal indices, irrespective of her current height and weight.[15] The immediate consequence of improved nutrition is that mothers' weights increase, though they remain short in stature. Table 5 shows that this is associated with a steep increase in coronary heart disease. We speculate that increased maternal body mass leads to an increased fetal demand for nutrients that cannot be matched by increased supply because of the intergenerational constraints on placental growth. With continued improvements in nutrition in the population mothers become taller and heavier, constraints on placental growth diminish, and maternal fatness no longer increases the risk of coronary heart disease. Coronary heart disease therefore declines.

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When I use a word …
Wool gathering

We have all seen demented patients plucking at the bedclothes. This action has a name, two names actually: carphology and floccillation.

Carphology is Greek: κάρφοι (karphoi) is bits of twig, straw, or wool, such as birds collect to build a nest, and λέγω (lego) means "I gather" (so carphology is not a proper ology (*BMJ* 1997;314:28). Floccillation means much the same in Latin: floccus is a tuft of woolly hair, or by extension a trifle.

Wool gathering originally meant just that—gathering fragments of wool that had been torn off sheep by bushes—but it was not long before it took on a figurative meaning—to indulge in wandering fancies, to be dreamy or absent minded. Hence its application to demented plucking.

Nowadays hospital blankets are made of synthetic fibres, but at one time they would have been made of proper wool, so the literal and the figurative converge in these expressions.

Wool, in another Latin form lana, figures in pharmacology: digoxin is still extracted from *Digitalis lanata*, the woolly foxglove, some of whose glycoside constituents are known as lanatosides. And lanugo is the fine woolly coat that a baby wears.

Carminative, surprisingly, also has woolly connections. Carminare in Latin meant to card wool, from the tool used for doing it, carmen. Intestinal wind was thought to originate from humours whose tangles could be teased out by a carminative, just like a comb carding wool.

And there is more wool further down the intestine: villus, one form of vellus, wool or a long thin hair, is now used to mean one of the finger like protrusions of the intestinal mucosa. And a derivative, vellicare, also meant to pluck.

But perhaps you think this is all floccinaucinihilipilification—woolly nothings not worth bothering a hair about.

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