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The role of family factors in the association between early adulthood BMI and risk of cardiovascular disease. An intergenerational study of BMI in early adulthood and cardiovascular mortality in parents, aunts and uncles

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Abstract

Background—High body mass index (BMI) in childhood and adolescence is related to cardiovascular disease (CVD). Causality is not established because common genetic or early life socioeconomic factors (family factors) may explain this relationship. We aimed to study the role of family factors in the association between BMI and CVD by investigating if early adulthood BMI in conscripts and CVD mortality in their parents/aunts/uncles are related.

Methods—Data from the Armed Forces Personnel Database (including height and weight among conscripts) were linked with data from the Norwegian Population Registry, generational data from the Norwegian Family Based Life Course Study, the National Educational Registry and the Cause of Death Registry using unique personal identification numbers. The study sample (N=369 464) was Norwegian males born 1967-1993, who could be linked to both parents and at least one

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Competing interests
None declared.

Author contributions
ØN and MK conceived the idea of the article, MK did the statistical analyses and drafted the article and all authors have critically revised the manuscript and contributed in the final stage of writing.

Ethics
The study was approved by the Norwegian Regional Committees for Medical and Health Research Ethics (REK) (2012/827). Written informed consent was obtained from participants in the Age 40 Program and CONOR. Participants in the Counties studies gave written permission for their results to be sent to their physician. Permission to be absolved from this professional secrecy has been granted and concession to handle this personal health information has been given by the authorities. The health studies have been conducted in full accordance with the World Medical Association Declaration of Helsinki

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maternal and one paternal aunt or uncle. Subsamples were identified as conscripts whose parents/aunts/uncles had data on cardiovascular risk factors available from Norwegian health surveys. Cox proportional hazards regression models were used to estimate hazard ratios (HR) of CVD mortality in the parental generation according to BMI categories of conscripts.

Results—Parents of conscripts with obesity or overweight had a higher hazard of CVD death (fathers HR obese: 1.99 (1.79,2.21), overweight: 1.33 (1.24,1.42) mothers HR obese: 1.65 (1.32,2.07), overweight: 1.23 (1.07,1.42)) than parents of normal- or underweight conscripts. Aunts and uncles of conscripts with obesity and overweight had an elevated hazard of CVD death, but less so than parents. Adjustment for CVD risk factors attenuated the results in parents, aunts and uncles.

Conclusions—Family factors may impact the relationship between early adulthood overweight and CVD in parents. These can be genes with impact on BMI over generations and genes with a pleiotropic effect on both obesity and CVD, as well as shared environment over generations.

Introduction

Obesity in childhood and adolescence is related to cardiovascular disease (CVD) later in life (1, 2). This has raised concern regarding increasing levels of early life obesity and its long-lasting impact for future population health. Efforts have been made to develop strategies to prevent potential long-term consequences of early life obesity (3). There is, however, limited evidence from empirical studies in support of a causal relationship between early life obesity and later CVD risk within individuals. Several alternative mechanisms may confound this relationship. One possible confounder is socioeconomic factors, as people with a disadvantaged socio-economic position (SEP), during childhood and/or in adulthood, have an increased risk of both obesity and CVD (4–6). A genetic predisposition to obesity may increase risk of CVD through BMI, but there is also evidence of genes influencing the risk of both obesity and CVD independently (7). However, a recent Mendelian randomization study using genetically predicted early life body size and measured BMI in adulthood suggests that much of the effect of early life obesity on later disease is through the persistence of a greater body weight into adulthood (8).

One approach has been to investigate the importance of family factors (shared environment and genes) in the association between early life obesity and later CVD. This has previously been done by comparing the relationship between offspring obesity and CVD mortality in mothers and fathers. Stronger associations in mothers point to mother-specific factors in general, including mother`s education and her contribution to nutrition and lifestyle in the shared environment (9, 10), and in particular to intra-uterine factors (11). Even considering the strength of the parent-offspring design, it is still difficult to disentangle the mechanisms because within a nuclear family both shared environmental and shared genetic factors are closely intertwined. An advancement of the parent-offspring design for this purpose is to investigate CVD mortality in extended family members with known genetic relatedness and less influence of the shared environment than in the nuclear family. If the association is wholly genetically determined and shared environmental influence in extended family members is negligible, we would expect to find associations between conscript obesity and CVD mortality in parental siblings to be 50% of the association between conscript obesity

and CVD mortality in parents. We would also expect that this association would not be explained by established cardiovascular risk factors with a strong environmental component, such as smoking, although smoking may also act as a mediator in the relationship by obesity increasing the risk of smoking which in turn increases the risk of CVD (12).

Furthermore, a short adult height is associated with risk of CVD (13, 14). Height is largely genetically determined (14). An association between offspring height and CVD in the parental generation would therefore indicate a genetic basis for intergenerational links of CVD, although there may be some environmental confounding from early life, for example from an effect of inadequate nutrition on height (15).

The aim of the present study was to investigate the role of family factors in the association between BMI and CVD by comparing the size of the associations between early adulthood BMI in conscripts and CVD mortality in their parents, aunts and uncles.

Methods

Study population

The target population was Norwegian males born between 1967 and 1993 (N=1 177 684). In Norway, men enrolled for military service, usually between 18 and 20 years of age, are obliged to complete conscript examinations, including objective measurements of height and weight. At the time of data collection, about 90 % of Norwegian men were enrolled. Those not undergoing this appraisal include those who were physically and mentally disabled, those who had a criminal record or those being abroad at the normal conscript age. Military service was voluntary for women in Norway at the time of the data collection. From men in the conscript register, we included those who could be linked to both parents and at least one maternal and one paternal aunt or uncle (N= 399 202). Data from the Armed Forces Personnel Data Base (1985-2012) were linked with data from the Norwegian Population Registry, generational data from the Norwegian Family Based Life Course Study (NFLC), National Educational Registry and the Cause of Death Registry using the unique national personal identification numbers. Due to their low number (5.5% of conscripts), women were excluded. Parents' siblings (aunts and uncles of conscripts) were identified in the NFLC, defined as full sibling if they shared both mother and father (99%), and half-sibling if they shared mother or father only (1%). When a parent had more than one sibling, the oldest available was included. However, each parent and aunt/uncle could appear multiple times in the sample, as each mother and father may have multiple children, and aunts/uncles may be aunts/uncles to children of more than one sibling. After exclusion of those without suitable data (Figure 1), the main analyses used a study sample of 369 464 male conscripts. The proportion of conscripts having a sibling in the sample was 43%, and each mother had an average of 1.7 conscripts in the sample. Five percent of the sample were born before 1970.

Subsamples constituted parents (mother N=97 966, father N=93 723), aunts (maternal aunts N=39 752, paternal aunts N=42 900) and uncles (maternal uncles 37 263, paternal uncles N=39 363)) with objectively measured information on cardiovascular risk factors. These data were available from several national and regional Norwegian cardiovascular health surveys: The Counties Study, the Age 40 Program and Cohort of Norway (CONOR). In the

Counties studies (1985-88) all men and women aged 35-49 years living in three different counties in Norway were invited (16). In the Age 40 Program (1985-99) inhabitants aged 40-44 years in all Norwegian counties, except Oslo, were invited (17). Cohort of Norway (CONOR) (1994-2003) is based on data from health surveys from all over Norway, with participants aged 20-103 years (18). The attendance rate of the surveys was 86%, 70% and 58% respectively (18–20). The subsamples were analyzed separately

Variables

BMI in conscripts was calculated from measurements of weight and height (kg/m^2) and classified into underweight (BMI<18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obesity (BMI≥30 kg/m^2). BMI in parents and aunts/uncles was from health surveys and classified in the same manner. Data on CVD mortality and year of censoring for those who died from other causes were obtained from the Norwegian Cause of Death Registry with CVD defined as codes 390-459 in ICD-9 and codes I00-I99 in ICD-10.

A person's highest attained educational level was classified as "≤ 9 years", "10-12 years/started or completed upper secondary school" or "≥13 years/university college or university education". Education was adjusted for in analyses as a proxy for socioeconomic position.

Non-fasting serum total cholesterol (TC, mmol/L) was measured initially by a non-enzymatic, and later an enzymatic, method. Non-enzymatic values were converted by a correction factor (21). Blood pressure (BP, mmHg) was measured by automatic oscillometric devices, and defined by the average of the last two available measures. Resting heart rate was recorded (beats/minute). BMI was calculated from measurements of weight and height (kilogram/meter^2). Self-reported smoking status ("daily smoker" or "not daily smoker") and current treatment of hypertension were recorded.

Statistical analyses and analytical approaches

Cox proportional hazards regression models, with age as underlying time, were used to estimate hazard ratios (HR) of mortality from CVD in the parental generation according to BMI categories of conscripts, and per BMI unit (22) Hazard ratios were also estimated per 10 cm increase in conscript height. Differences between mothers and fathers and between aunts and uncles in associations between BMI in conscripts and CVD mortality in the parental generation were assessed by including a product term between BMI and a relation term (within-parents and within- aunts/uncles). Parents, aunts and uncles were followed from the age of 40 to the age of death (from any cause), emigration or end of follow-up (31.12.2014) with the event defined as death from CVD. The proportional hazards assumption was examined by a log-log plot and supplemented by a global test of a zero slope in the association between age and the scaled Schoenfeld residuals. Familial clustering was taken into account by computing robust standard errors through the "vce (cluster)" command in Stata. This command effectively adjusts the standard error for within- parent and within-aunts/uncles correlation. If family clustering were not taken into account, the standard errors would be smaller. The clustering was done on the identity of the outcome person.

Analyses were adjusted for offspring year of birth (model 1), and in model 2 additionally for educational length in the outcome person (mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle). A third model with additional adjustment for cardiovascular risk factors (total cholesterol, blood pressure, heart rate, current treatment for hypertension, smoking, BMI) in the outcome person was carried out in subsamples including those with these data available. To check for differences between this subsample and the whole sample, models 1 and 2 were also run in these subsamples. Sensitivity analyses were carried out with follow-up from 20 years (including those who died or emigrated before the age of 40). Correlation of BMI/height between conscripts and parents, aunts and uncles was assessed using Pearson's correlation coefficient.

Results

The number of conscripts included was 369 464 (mean age 18.4), with 265 236 different mothers and 262 153 different fathers. Mean BMI among conscripts were 22.8 kg/m^2. Mean age of CVD death was 57.0 (SD 8.0) years among fathers, 55.3 (7.4) among mothers, 58.5 (8.3) among paternal uncles and 58.0 (8.0) among paternal aunts, 57.6 (8.4) among maternal uncles and 57.3 (8.1) among maternal aunts. Mean age (years) at end of follow-up was 61.8 (6.9) years among fathers, 57.9 (6.8) among mothers, 61.8 (7.7) among paternal uncles and 61.8 (SD 7.5) among paternal aunts, 60.0 (8.1) among maternal uncles and 59.9 (7.8) among maternal aunts. The proportion of fathers and mothers reaching the age of 65 in 2014 was 40 % and 20 %, respectively. The respective proportions of paternal and maternal aunts/uncles were 41 % and 33 %. The total follow-up time was 7 408 004 years for fathers and 6 630 748 years for mothers. Number of CVD deaths was 1680 (0.5%) among mothers, 6801 (2.0%) among fathers, 1324 (0.8%) among maternal aunts, 4799 (2.5%) among maternal uncles, 1600 (0.9%) among paternal aunts and 5594 (2.9%) among paternal uncles (Table 1).

Parents of a conscript with overweight or obesity had a higher hazard ratio of CVD death than parents of a normal or underweight conscript (Table 2). Adjustment for education somewhat attenuated the results. There was some evidence (P=0.08) that the association was stronger in fathers (obesity HR 1.99 (1.79, 2.22)) than in mothers (1.65 (1.32, 2.07)). The strength of the association between conscript obesity and maternal CVD mortality was only slightly higher than in uncles. The weakest associations were seen among aunts. In a subsample including only those with information on CVD risk factors available, associations between conscript overweight or obesity and parental generation CVD mortality were weaker than in the full sample, but still strongest among fathers. Adjustment for CVD risk factors in addition to education further attenuated the results, both in parents and aunts/uncles, although the hazard ratio was still clearly elevated in the fathers and uncles of obese conscripts.

The hazard for CVD mortality increased with higher conscript BMI (Table 3). The association was strongest among fathers (HR 1.05 (1.04, 1.06) per BMI unit), and of similar magnitude among mothers and uncles.

Height in conscripts was relatively strongly correlated with height in mothers (0.50) and fathers (0.49). As expected, this was about twice as strong as in aunts and uncles (maternal

uncles (0.28), maternal aunts (0.27) and paternal aunts and uncles (0.26)). Compared to height, BMI in conscripts was more weakly correlated to BMI in mothers (0.25), fathers (0.24), paternal aunts and uncles (0.10) and maternal aunts and uncles (0.11).The hazard of CVD mortality decreased with increasing conscript height among parents (Model 1 HR 0.83 (0.80, 0.87) per 10 cm in fathers, 0.80 (0.73, 0.87) in mothers), and to a smaller degree among paternal aunts and uncles. Before adjustment for education, an association between conscript height and CVD mortality among maternal uncles was also seen (Table 4). Adjustment for CVD risk factors attenuated the HR among both mothers and fathers.

We did sensitivity analyses with follow-up from the age of 20 years (including those who died or emigrated before the age of 40), with no meaningful differences in results. There was no strong evidence of departure from proportional hazards (all p-values >0.1).

Discussion

We found an association between conscript BMI and CVD mortality in parents and aunts/uncles, of which much was explained by cardiovascular risk factors in the parental generation. The association was stronger among fathers than among mothers, aunts and uncles. The association between conscript height and CVD mortality was stronger among parents than aunts/uncles, and similar in mothers and fathers.

Both genes and environment of a relative can influence BMI in offspring, and the same genes or environment may be associated with CVD in the relative. The impact on conscript BMI of parental genes will be stronger than that of genes in aunts and uncles, and the difference is even greater regarding environment (23). Differences between mothers and fathers could reflect their different influences on the environment important for conscript BMI, and also maternal-specific factors, including the intrauterine environment (11,24). Furthermore, fathers had about four times as high rates of CVD mortality as mothers.

Associations between offspring BMI and CVD mortality in aunts and uncles indicate a genetic link. It could also relate to environmental factors, as parents and their siblings shared a childhood home environment, and this environment may be correlated with that of the conscript. A stronger association among fathers than in aunts/uncles points towards both a genetic basis for the relationship and the importance of a shared early life environment. The attenuation of associations after adjustment for education and CVD risk factors emphasize the influence of environmental factors, although risk factors may have a genetic component. We cannot claim to disentangle shared environment and genes in our study. Family members beyond the closest nuclear family may share environment, and one potential mechanism recently described is when alleles in parents not transmitted to offspring might give an environmental influence on offspring. Similar mechanisms might operate in extended family members and give rise to the observed associations in education (25). Our findings of associations in all family members, which seem to some extent to be explained by CVD risk factors, is consistent with this mechanism. In a recent study investigating the role of such dynastic effects in mendelian randomization, genetic instruments for BMI was related to blood pressure and diabetes. The investigators did not find much difference between conventional mendelian randomization estimates and when including sibling-fixed effect but

strong attenuation between BMI and education, suggesting this mechanism may operate through behavioral pathways (26).

The associations between conscript height and CVD mortality in their parents, aunts and uncles reflected the expected pattern of a genetic effect, in that the paternal and maternal associations were equally strong, and about twice the strength of the associations in aunts and uncles. This contrasts with the observed associations between BMI and CVD mortality, pointing towards a greater environmental influence in the associations with conscript BMI.

One previous study, based on Norwegian register data and similar health surveys as the present article, investigated the association between offspring birthweight and CVD mortality in parents, aunts and uncles (24). The authors reported in accordance with the present study associations among both parents, aunts and uncles, and stronger associations among both mothers and fathers than among aunts/uncles.

A number of studies on associations between birth weight and parental CVD have reported stronger mother-offspring than father-offspring associations (11), highlighting mechanisms such as maternal health and health behavior influencing the intrauterine environment of the fetus and dual action of maternal genes, affecting the fetus by both gene inheritance and by affecting the intrauterine environment. Our study indicates that any effects of intrauterine experiences giving stronger associations among mothers are attenuated by early adulthood. In the Norwegian Mother and Child cohort (MoBa), the maternal influence had diminished and become equal to the paternal by the age of three years in offspring (27).

Our sample consisted of male offspring only, due to relying on data from military conscription. We could hypothesize that same-sex associations are stronger than opposite sex associations, and that fathers and sons, after early childhood when height is established, have more similarities in lifestyle than mothers and sons. However, this is not in line with findings from Sweden (28), but in line with several other studies showing stronger same-sex correlations than mother-son or father-daughter associations for anthropometric measurements, blood pressure and cholesterol (29–31). A tendency of stronger associations among uncles than aunts was also seen for obesity.

Follow-up was right-censored at an average age of 58 years for mothers, 60 years for maternal aunts/uncles and 62 years for fathers and paternal aunts/uncles. This, along with the typically earlier development of heart disease in men, probably contributed to the higher number of CVD deaths we found among men. It might also contribute to the stronger association with offspring BMI observed among fathers than among mothers, if earlier cases tend to be more unusual CVD types with other underlying causes not related to adiposity. However, we found no evidence for the non-proportional hazards which such a mechanism would indicate. Furthermore, associations with conscript BMI appeared to depend more on the sex of an uncle/aunt than on which parent they were related to (and thus their age at censoring). Nonetheless, a replication of this analysis with the parental generation followed up to old age would be interesting.

We used data from nationwide registers, providing a large sample size and comprehensive population coverage. Further, we had objectively measured weight and height, and the

possibility to link offspring to parents and their siblings. Paternal misclassification is a possible source of bias (18), but the similar correlation of height among mothers and fathers indicates that this is not a substantial bias in our study. A limitation is that we were only able to investigate men who attended conscription examinations. A high proportion of participants was in the normal weight category, and there was a low proportion with obesity and this may have implications for generalizability. A low proportion of obesity could also be related to the use of historical data (32). Our selection of aunts and uncles means that they are presumably somewhat older than parents and fathers were a little older than mothers.

Conclusion

Our study showed associations between higher offspring BMI and an increased hazard of CVD mortality among parents, uncles and aunts. The association was partly explained by education and cardiovascular risk factors in the parental generation. This indicates an important role of shared family factors on the association between offspring obesity and CVD.

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Data sharing statement

Data are owned by Norwegian Institute of Public Health (NIPH) and cannot be shared. Application has to be sent to NIPH after approval of study from Norwegian Regional Committees for Medical and Health Research Ethics

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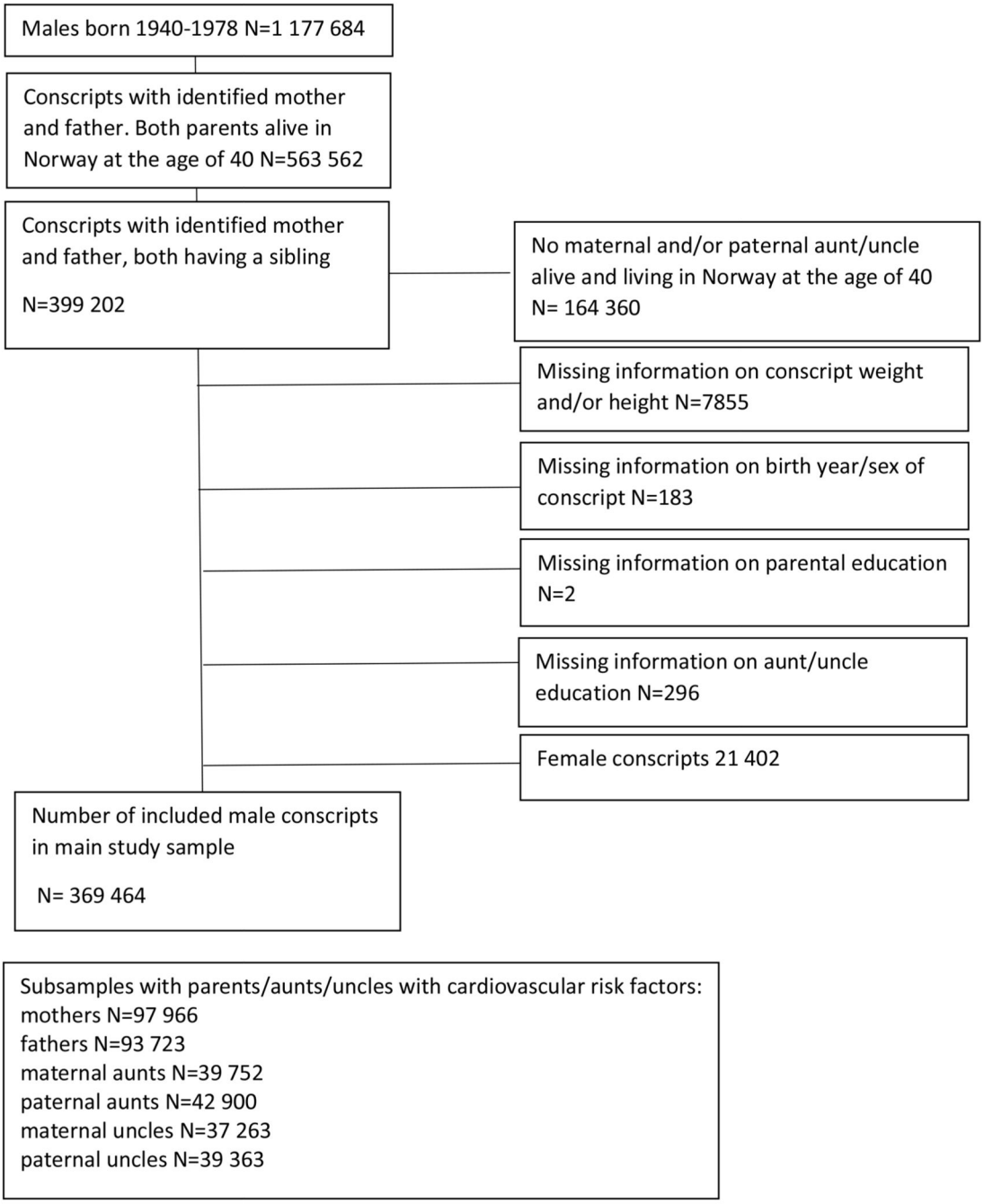

Figure 1. Flow chart depicting the study population of individuals included in the study

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Table 1
Characteristics of sample according to offspring body mass index category

	Conscript weight category				
	Underweight N=20 728 (5.6%)	**Normal N=273 621 (74.1%)**	**Overweight N=56 763 (15.4%)**	**Obesity N=18 352 (5.0%)**	**Total N= 369 464**
Mother (N=264 236)* Education ≤nine years (%)	26.5	23.0	26.3	32.1	24.1
Mortality from CVD, N (%)	93 (0.5)	1236 (0.5)	259 (0.5)	90 (0.5)	1680 (0.5)
Father (N=262 153) Education ≤nine years (%)	21.1	19.5	23.3	29.0	20.6
Mortality from CVD, N (%)	351 (1.7)	4887 (1.9)	1119 (2.0)	444 (2.4)	6801 (2.0)
Maternal aunt (N=114 201) Education ≤nine years (%)	24.1	22.3	25.1	28.7	23.1
Mortality from CVD, N (%)	59 (0.7)	972 (0.7)	230 (0.9)	63 (0.7)	1324 (0.8)
Maternal uncle (N=124 301) Education ≤nine years (%)	23.1	21.1	22.9	26.5	21.7
Mortality from CVD, N (%)	247 (2.3)	3543 (2.5)	746 (2.5)	263 (2.7)	4799 (2.5)
Paternal aunt (N=121 740) Education ≤nine years (%)	22.7	22.2	24.5	29.1	22.9
Mortality from CVD, N (%)	106 (1.1)	1142 (0.9)	270 (1.0)	82 (0.9)	1600 (0.9)
Paternal uncle (N=132 660) Education ≤nine years (%)	21.8	21.1	23.6	27.4	21.8
Mortality from CVD, N (%)	308 (2.8)	4079 (2.9)	886 (3.0)	321 (3.3)	5594 (2.9)

N is the number of unique observations; each relative was counted only once in these percentages even if they were included for multiple conscripts

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Table 2

Hazard ratio (HR) of CVD mortality in the parental generation by categories of conscripts' body mass index. The reference category was normal and underweight combined.

	HR (95% Confidence Interval)					
	Model 1		Model 2		Model 3	
	Overweight	Obesity	Overweight	Obesity	Overweight	Obesity
Main study sample, N=369 464						
Mother	1.23 (1.07, 1.42)	1.65 (1.32, 2.07)	1.16 (1.01, 1.33)	1.43 (1.14, 1.79)	-	-
Maternal aunt	1.30 (1.12, 1.58)	1.25 (0.95, 1.64)	1.24 (1.06, 1.44)	1.13 (0.86, 1.48)	-	-
Maternal uncle	1.15 (1.07, 1.25)	1.42 (1.23, 1.62)	1.12 (1.03, 1.22)	1.31 (1.14, 1.51)	-	-
Father	1.33 (1.24, 1.42)	1.99 (1.79, 2.22)	1.26 (1.18, 1.35)	1.79 (1.61, 1.99)	-	-
Paternal aunt	1.24 (1.08, 1.43)	1.27 (1.00, 1.62)	1.17 (1.04, 1.38)	1.17 (0.92, 1.48)	-	-
Paternal uncle	1.14 (1.06, 1.23)	1.42 (1.26, 1.60)	1.10 (1.02, 1.18)	1.31 (1.16, 1.48)	-	-
Subsample with cardiovascular risk factors available *						
Mother	1.18 (0.93, 1.49)	1.09 (0.71, 1.66)	1.13 (0.89, 1.42)	0.98 (0.64, 1.51)	0.95 (0.75, 1.21)	0.69 (0.45, 1.07)
Maternal aunt	1.31 (0.98, 1.73)	1.00 (0.58, 1.72)	1.24 (0.93, 1.65)	0.92 (0.53, 1.59)	1.15 (0.86, 1.52)	0.82 (0.48, 1.41)
Maternal uncle	1.09 (0.91, 1.30)	1.73 (1.33, 2.26)	1.06 (0.89, 1.26)	1.63 (1.25, 2.12)	1.00 (0.84, 1.20)	1.44 (1.11, 1.87)
Father	1.28 (1.14, 1.45)	1.91 (1.58, 2.31)	1.23 (1.09, 1.38)	1.74 (1.44, 2.11)	1.08 (0.96, 1.22)	1.35 (1.11, 1.64)
Paternal aunt	1.08 (0.83, 1.41)	1.36 (0.91, 2.04)	1.04 (0.79, 1.35)	1.26 (0.84, 1.88)	0.96 (0.74, 1.26)	1.07 (0.71, 1.60)
Paternal uncle	1.12 (0.96, 1.30)	1.59 (1.27, 1.99)	1.08 (0.93, 1.25)	1.48 (1.18, 1.84)	0.98 (0.85, 1.14)	1.26 (1.06, 1.58)

Model 1: Adjusted for year of birth

Model 2: Additionally adjusted for educational length of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively

Model 3: Additionally adjusted for cardiovascular risk factors (BMI, blood pressure, total cholesterol, heart rate, current treatment for hypertension, smoking) of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively

Difference in HR (Model 1) between mothers and fathers p=0.13, maternal uncles and aunts: p=0.83 paternal uncles and aunts: p=0.90

* N (subsample) mother (97 966) father (93 723) maternal aunt (39 752) maternal uncle (37 263) paternal aunt (42 900) paternal uncle (39 363)

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Table 3

Hazard ratio (HR) of CVD mortality in the parental generation per unit (kg/m^2) increase in conscript body mass index

	HR (95% Confidence Interval)		
	Model 1	**Model 2**	**Model 3**
	Main study sample, N=369 464		
Mother	1.03 (1.02, 1.05)	1.02 (1.01, 1.04)	-
Maternal aunt	1.03 (1.01, 1.05)	1.03 (1.01, 1.04)	-
Maternal uncle	1.02 (1.02, 1.03)	1.02 (1.01, 1.03)	-
Father	1.05 (1.04, 1.06)	1.04 (1.03, 1.05)	-
Paternal aunt	1.02 (1.00, 1.03)	1.01 (1.00, 1.02)	-
Paternal uncle	1.02 (1.02, 1.03)	1.02 (1.01, 1.02)	-
Subsample with cardiovascular risk factors available *			
Mother	1.02 (1.00, 1.05)	1.02 (0.99, 1.04)	0.99 (0.96, 1.01)
Maternal aunt	1.01 (0.99, 1.04)	1.01 (0.98, 1.04)	1.00 (0.97, 1.02)
Maternal uncle	1.02 (1.01, 1.04)	1.02 (1.00, 1.03)	1.00 (0.99, 1.02)
Father	1.05 (1.04, 1.06)	1.04 (1.03, 1.06)	1.02 (1.01, 1.04)
Paternal aunt	1.02 (1.00, 1.05)	1.02 (0.99, 1.05)	1.01 (0.98, 1.04)
Paternal uncle	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)

Model 1: Adjusted for year of birth
Model 2: Additionally adjusted for educational length of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively
Model 3: Additionally adjusted for cardiovascular risk factors (BMI, blood pressure, total cholesterol, heart rate, current treatment for hypertension, smoking) of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively
Difference in HR (Model 1) between mothers and fathers p=0.07, maternal uncles and aunts: p=0.34, paternal uncles and aunts p=0.86

* N (subsample) mother (97 966) father (93 723) maternal aunt (39 752) maternal uncle (37 263) paternal aunt (42 900) paternal uncle (39 363)

Table 4

Hazard ratio (HR) of CVD mortality in the parental generation by conscript's height (per 10 cm)

	HR (95% Confidence Interval)		
	Model 1	**Model 2**	**Model 3**
Main study sample, N=369 464			
Mother	0.80 (0.73, 0.87)	0.86 (0.78, 0.94)	
Maternal aunt	0.97 (0.88, 1.07)	1.04 (0.94, 1.14)	
Maternal uncle	0.93 (0.88, 0.98)	0.97 (0.92, 1.02)	
Father	0.83 (0.80, 0.87)	0.87 (0.84, 0.91)	
Paternal aunt	0.86 (0.79, 0.94)	0.90 (0.83, 0.98)	
Paternal uncle	0.92 (0.87, 0.96)	0.95 (0.90, 0.99)	
Subsample with cardiovascular risk factors available *			
Mother	0.86 (0.68, 0.93)	0.85 (0.73, 0.99)	0.91 (0.78, 1.06)
Maternal aunt	0.99 (0.82, 1.19)	1.05 (0.87, 1.27)	1.12 (0.93, 1.36)
Maternal uncle	1.02 (0.91, 1.14)	1.05 (0.94, 1.18)	1.09 (0.98, 1.22)
Father	0.87 (0.81, 0.94)	0.90 (0.84, 0.98)	0.95 (0.88, 1.03)
Paternal aunt	0.85 (0.73, 1.00)	0.89 (0.76, 1.05)	0.92 (0.78, 1.07)
Paternal uncle	0.98 (0.89, 1.09)	1.01 (0.91, 1.11)	1.05 (0.95, 1.16)

Model 1: Adjusted for year of birth
Model 2: Additionally adjusted for educational length of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively
Model 3: Additionally adjusted for cardiovascular risk factors (BMI, blood pressure, total cholesterol, heart rate, current treatment for hypertension, smoking) of mother, father, maternal aunt, maternal uncle, paternal aunt or paternal uncle respectively
Difference in HR between mothers and fathers: p= not calculated due to collinearity, maternal uncles and aunts: p=0.46, paternal uncles and aunts: p=0.46

* N (subsample) mother (97 966) father (93 723) maternal aunt (39 752) maternal uncle (37 263) paternal aunt (42 900) paternal uncle (39 363)