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Cardiovascular risk factors in extended family members and birthweight in offspring

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Abstract

Low birthweight has been related to an increased risk of adult cardiovascular disease (CVD). Transgenerational studies have been used to investigate likely mechanisms underlying this inverse association. However, previous studies mostly examined the association of offspring birthweight with CVD risk factors among parents. In this study, we investigated the association between offspring birthweight and individual CVD risk factors, an index of CVD risk factors, and education in their parents, aunts/uncles, and aunts'/uncles' partners. Birth data (Medical Birth Registry, Norway (MBRN) (1967–2012)) was linked to CVD risk factor data (the County Study, Age 40 Program, and Cohort Norway (CONOR)) for the parents, aunts/uncles, and their partners. For body mass index (BMI), resting heart rate (RHR), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG), and a risk factor index, the associations were examined by linear regression. For smoking and education, they were examined by logistic regression. Low birthweight was associated with an unfavorable risk factor profile in all familial relationships. For each kg increase in birthweight, the mean risk factor index decreased by −0.14 units (−0.15, −0.13) in mothers, −0.11 (−0.12, −0.10) in fathers, and −0.02 (−0.05, −0.00) to −0.07 (−0.09, −0.06) in aunts/uncles and their partners. The association in mothers was stronger than fathers, but it was also stronger in aunts/uncles than their partners. Profound associations between birthweight and CVD risk factors in extended family members were observed that go beyond the expected genetic similarities in pedigrees, suggesting that mechanisms like environmental factors, assortative mating, and genetic nurturing may explain these associations.

Introduction

Birthweight has in a number of studies been related to the adult risk of cardiovascular disease (CVD).[1–4] This could happen through metabolic and physiological changes during intrauterine life that program risk of disease in later life.[5,6] Alternatively, concerns have been raised that these observations are confounded by factors related to both birthweight and CVD such as socioeconomic environment and common genetic factors. In particular, the fetal insulin hypothesis proposes that genetic factors influencing fetal growth may also be involved in the development of chronic diseases later in life.[7]

Transgenerational studies have been used to investigate likely mechanisms underlying the inverse association of birthweight and adult risk of CVD. Studies investigating the association with parental CVD risk factors have reported that birthweight in offspring was inversely associated with insulin resistance, high blood pressure, body mass index (BMI), and unfavorable levels of lipids in both parents.[8–10] Multiple mechanisms such as shared genetic factors between mother and fetus, and intrauterine factors have been suggested in explaining these associations among mothers. The associations in fathers are quite important and propose a role of common genes as a father mainly influences his child's birthweight directly through inherited genes.[10] Shared environmental factors could also be important in paternal associations if the father's environment resembles the mother's environment.

Previous studies mostly examined the association between low offspring birthweight and CVD risk among parents. However, it has been difficult to assess the contribution of environmental versus genetic factors on the association as these factors are closely connected in nuclear families. Better understanding of genetic and environmental contributions to birthweight and CVD risk associations might be achieved by investigating offspring birthweight and CVD risk factors relationship in extended family members such as aunts/uncles and their partners, in addition to the biological parents. Children share 50% of genes, as well as a familial environment, with their parents but only 25% of genes, and a correlated environment, with aunts/

uncles. With partners of aunts/uncles, children are not expected to have any genetic relationship (0%), but a correlated environment is also likely here. Inclusion of aunts/uncles and their partners in the study would be helpful in identifying the contribution of genetic versus environmental factors because individuals are genetically linked with their parents and aunts/uncles, but not with the spouses of aunts/uncles. Any association with the partners would highlight the importance of familial environmental factors (clustered in the families) for the association between birthweight and later CVD.

We investigated the association between offspring birthweight (the exposure) and outcomes comprising CVD risk factors (BMI, resting heart rate (RHR), systolic blood pressure (SBP), total cholesterol (TC), triglycerides (TG), and smoking) and a CVD risk factor index among parents, aunts/uncles, and partners of aunts/uncles. To examine the importance of socioeconomic status, we also examined associations with education level in all familial relationships. We hypothesized, if common genes are causing the associations, that the associations would be of similar strength in mothers and fathers and half this strength among four groups of aunts/uncles. Any association with the partners of aunts/uncles would support the role of mechanisms giving rise to correlated environments such as assortative mating.

Methods

Study population

We linked birth data recorded in the Medical Birth Registry, Norway (MBRN) to CVD risk factor data for parents, four classes of aunts/uncles, and partners of aunts/uncles recorded in the three large Norwegian health surveys (the County Study, Age 40 Program, Cohort Norway (CONOR)). Each parent's eldest available full sibling (sharing both mother and father) was identified in the multigenerational database using personal identification numbers. Identification of parents has proved to be reliable for people born in and after 1940.[11] Therefore, for the identification of full siblings, we included participants (parents, aunts, and uncles) born in or after 1940.

Offspring with birthweight < 600 g and gestational age > 44 weeks were excluded from the sample before the identification of full siblings for each parent. Number of offspring (1967–2012) with both mother and father, where each parent had at least one sibling in the multigenerational database, was 1,532,202. Offspring were linked with their parents, aunts, and uncles in the health surveys within as well as outside of the trios. We further excluded offspring from the sample whose parents, aunts, and uncles had missing data on CVD risk factors: BMI, RHR, SBP, TG, TC, and smoking (Fig. 1 and Table S7). We could not compare similar-sized family relationships in our study as the important prerequisite was that they (parents, aunts/uncles, partners of aunts/uncles) participated in the health surveys (Fig. 1 and Table S2).

Furthermore, we identified partners of the included aunts/uncles from the multigenerational database (a subgroup). Aunts/uncles may have information on more than one partner in the database. We selected those who were partner at the time of aunt's/uncle's health survey examination. A total of 100,531 offspring were linked with partners of paternal aunts/uncles and 91,216 offspring were linked with partners of maternal aunts/uncles (Fig. 1).

The Medical Birth Registry, Norway (MBRN)

The Medical Birth Registry of Norway comprises information on each birth in Norway since 1967. For offspring, we included data on birthweight (kg; explanatory variable), gestational age (weeks), sex, and year of birth. Birthweight was analyzed as a continuous variable. For mothers, we included data on age at offspring birth and parity. Age at offspring birth was also calculated for fathers, aunts/uncles. and partners of aunts/uncles.

CVD risk factors

Three large cardiovascular health surveys; the Counties Study, the Age 40 Program, and CONOR were conducted in Norway during 1974–1988, 1985–1999, and 1994–2003, respectively. Information from the participants was collected through self-administered questionnaire, physical examination, and blood measurements. We included information on current smoking (yes/no) collected through a questionnaire. Data on clinical measurements such as SBP (mmHg), RHR (beats/minute), and BMI (kg/m^2) was also included in the study. Blood pressure and RHR were measured by an automatic device. Three readings were collected at 1-minute intervals and the mean value of the second and third measurements was recorded. Height was measured to the nearest centimeter and body weight was measured to the nearest half-kilogram with participants wearing light clothing without shoes. Serum lipid measurements (mmol/l), e.g. TC and TG were also recorded. In CONOR and the Age 40 Program, all biochemical measurements were done by the enzymatic methods. In the County Study, lipids were measured by nonenzymatic methods, but afterward converted to the enzymatic method by a correction factor.[12,13] Moreover, it should be considered that CVD risk factors in parents, aunts/uncles ,and in partners of aunts/uncles were measured after the birth of the children (Table 1 and Table S1).

Outcome variable

Our main outcome variable was a risk factor index. All included CVD risk factors (BMI, RHR, SBP, TC, TG, and smoking) were classified into two groups (coded as 0 and 1) according to cutoffs that are generally used to distinguish individuals into high and low risk of CVD.[14] The value 1 defines obesity (BMI ≥ 30 kg/m^2), elevated RHR (≥ 80 beats/min), high SBP (> 140 mmHg), high serum concentrations of TG (≥ 2 mmol/l), high TC (≥ 6 mmol/l), and current smoking. A risk factor index was constructed by adding up the scores (range 0–6). This risk factor score shows overall exposure to CVD risk factors, where a low score was believed to be favorable.

Education level of the parents, aunts/uncles, and partners (of aunts/uncles) was categorized according to the Norwegian Standard Classification of Education.[15] According to this classification, education in Norway is categorized as "≤ 9 years", "10–12 years", and "≥13 years". We compressed three categories into two (< 13 years and ≥ 13 years) to make a comparison between higher and lower education.

Statistical analyses

Stata software version 14 (Stata-Corp., LP, College Station, Texas, USA) was used for all the statistical analyses. Descriptive variables were summarized separately for mothers, fathers, each type of aunt/uncle, and their partners. Continuous variables were presented as means (*SD*). Categorical variables were described as

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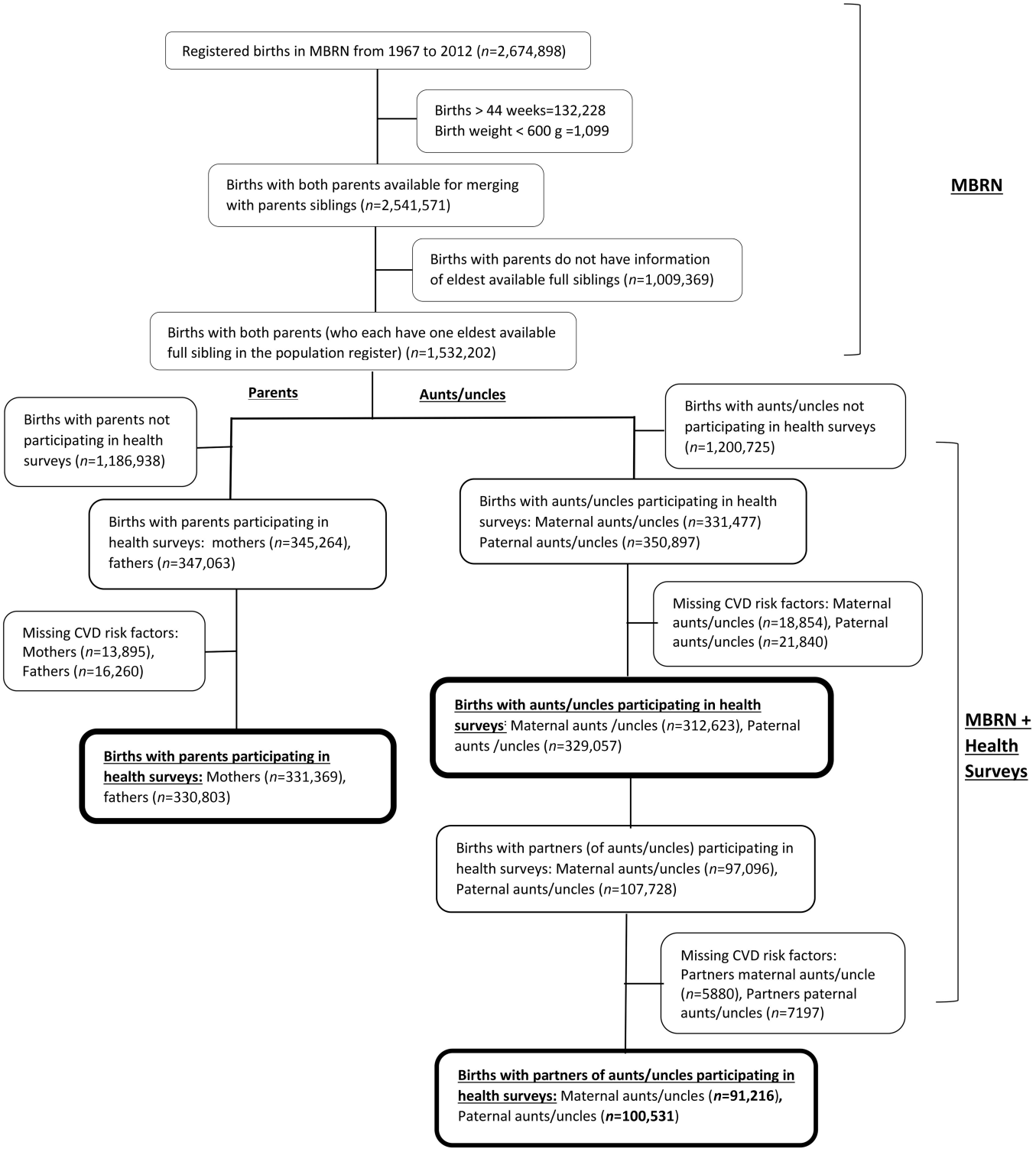

Fig. 1. Flowchart of the study population.

percentages (%). Pearson's correlation coefficient was used to assess correlation between CVD risk factors (BMI, RHR, SBP, DBP, TC, TG) in parents and their siblings.

The associations between offspring birthweight (kg) and each of the numeric risk factors (BMI, RHR, SBP, TC, and TG), and the risk factor index in parents, aunts/uncles, and partners of aunts/uncles were examined by linear regression models. For smoking and education level, the associations were examined using logistic regression models. The regressions were set up with birthweight as the exposure and risk factors as the outcome and each risk factor was analyzed in a separate model. The analyses were first adjusted for age of the outcome person (mothers, fathers, aunts/uncles, and partners of aunts/uncles) at risk factor measurement (Fig. 2/Table S5). Additionally, all analyses were adjusted for gestational age, offspring sex, and maternal parity (Fig. 3/Table S6). The associations for the risk factor index were compared between mothers and

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Table 1. Descriptive statistics in parents and aunts/uncles

	Mean (*SD*)					
	Mothers ($n = 331,369$)[a]	Fathers ($n = 330,803$)[a]	Maternal aunts ($n = 162,690$)[a]	Maternal uncles ($n = 149,933$)[a]	Paternal aunts ($n = 166,221$)[a]	Paternal uncles ($n = 162,836$)[a]
Age at risk factors measurement	40.3 (4.1)	40.8 (3.9)	40.8 (4.2)	41.1 (4.3)	40.7 (4.6)	40.9 (4.9)
Height (cm)	165.8 (5.7)	178.9 (6.4)	166.0 (5.7)	179.1 (6.3)	166.2 (5.8)	179.4 (6.4)
BMI (kg/m^2)	24.3 (3.8)	25.7 (3.3)	24.4 (3.9)	25.8 (3.2)	24.4 (4.0)	25.7 (3.2)
RHR (bpm)	76.7 (12.3)	72.5 (12.5)	76.5 (12.3)	72.2 (12.5)	76.6 (12.4)	72.0 (12.6)
SBP (mmHg)	125.0 (13.7)	135.0 (13.4)	125.6 (13.9)	135.2 (13.2)	125.8 (14.1)	135.2 (13.4)
TC (mmol/l)	5.44 (1.0)	5.80 (1.1)	5.42 (1.0)	5.7 (1.1)	5.46 (1.1)	5.81 (1.0)
TG (mmol/l)	1.34 (0.8)	2.11 (1.3)	1.32 (0.8)	2.10 (1.3)	1.34 (0.9)	2.09 (1.4)
	n (%)					
Education (≥ 13 years)	95,671 (28.8)	90,817 (27.5)	45,528 (29.3)	39,879 (27.5)	51,858 (29.1)	46,603 (28.3)
Obesity (BMI ≥ 30 kg/m^2)	26,829 (8.1)	28,544 (8.6)	14,133 (9.1)	14,253 (10.0)	16,764 (9.4)	16,247 (9.8)
RHR (≥ 80 bpm)	109,057 (33.0)	71,210 (21.6)	51,677 (33.5)	33,746 (23.5)	64,115 (36.2)	44,413 (27.0)
SBP (> 140 mmHg)	41,454 (12.5)	101,770 (30.9)	21,978 (14.2)	47,220 (32.9)	26,376 (14.8)	55,441 (33.6)
TC (≥ 6 mmol/l)	76,580 (23.1)	125,346 (38.0)	38,271 (24.8)	55,690 (39.0)	45,996 (25.2)	64,876 (39.5)
TG (≥ 2 mmol/l)	43,750 (13.2)	131,585 (39.6)	20,841 (13.5)	58,350 (40.7)	23,692 (13.3)	65,800 (40.0)
Current smokers	121,832 (36.7)	121,680 (37.0)	57,681 (37.1)	52,736 (36.8)	66,062 (37.6)	60,827 (37.3)

BMI, body mass index (weight (kg)/height (cm)); RHR, resting heart rate; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.
Values are presented as mean (*SD*) and percentages (%).
Comparable descriptive statistics for the partners of aunts and uncles may be found in Table S1.
[a]Number of offspring linked with parents, aunts/uncles, and partners of aunts and uncles who have information of CVD risk factors in the health surveys.

fathers, between aunts and uncles, and between aunts and uncles and their partners. The associations in parents were also compared for individual CVD risk factors. These comparisons were made using interaction terms in the models. Our data set comprised of single and multiple births. Several offspring were nested within the same parents, aunts, and uncles. This 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. The clustering was done on the identity of the outcome person.

Results

The descriptive information for the parents and all four classes of aunts/uncles is presented in Table 1. Mean age of mothers and fathers at birth of the offspring was 26.4 (5.9) and 30.0 (6.1) years, respectively. For all classes of aunts and uncles, the average age at offspring birth varied between 31.1 (8.0) and 33.5 (8.5) years. Mean age of parents, aunts/uncles, and partners of aunts/uncles at the time of risk factor measurement varied between 40.3 (4.1) and 41.4 (4.5) years (Table 1 and Table S1). Except for RHR, mean levels of CVD risk factors were higher in fathers and uncles (both classes) than in mothers and aunts (Table 1). Mean birthweight of the offspring was 3.52 (0.59) kg and mean gestational age at birth was 39.7 (2.0) weeks.

The prevalence of obesity was lower in parents than in aunts/uncles and their partners. Smoking prevalence was comparable among all relationships (parents, all classes of aunts/uncles, and partners of aunts/uncles) (Table 1 and Table S1). Hypertension and hypercholesterolemia were more common in paternal uncles whereas the proportion of hypertriglyceridemia was comparable in mothers and both groups of aunt, and in fathers and both groups of uncles. The pattern seems to be that these risk factors are much higher in men than women, and slightly higher in aunts/uncles and their partners than in mothers and fathers (Table 1 and Table S1).

In minimally adjusted linear regression analyses, an inverse association between offspring birth and the CVD risk index was observed among parents, all classes of aunts/uncles, and partners of aunts/uncles (Fig. 2/Table S5). For each kg increase in birthweight, the mean risk factor index decreased by −0.14 units (−0.15, −0.13) in mothers, −0.11 (−0.12, −0.10) in fathers, and −0.02 (−0.05, −0.00) to −0.07 (−0.09, −0.06) in aunts/uncles and their partners. The association in mothers was stronger compared to in fathers ($P < 0.001$). The association in maternal aunts was found to be stronger than in maternal uncles, and in paternal uncles, it was stronger than paternal aunts ($P < 0.001$). Moreover, the associations in the four combined groups of aunts/uncles were stronger than in their combined partners ($P < 0.001$). Regarding individual CVD risk factors (BMI, RHR, SBP, TC, and TG), the associations were observed among mothers, fathers, and all four groups of aunts/uncles (Fig. 2/Table S5). The associations were mostly negative, with lower birthweight being related to higher levels of CVD risk factors. However, associations with BMI were positive for all adults. The associations in mothers were stronger for most of the CVD risk factors except for TG, which was stronger in fathers ($P < 0.001$). For cholesterol, the associations were similar in both parents ($P = 0.750$).

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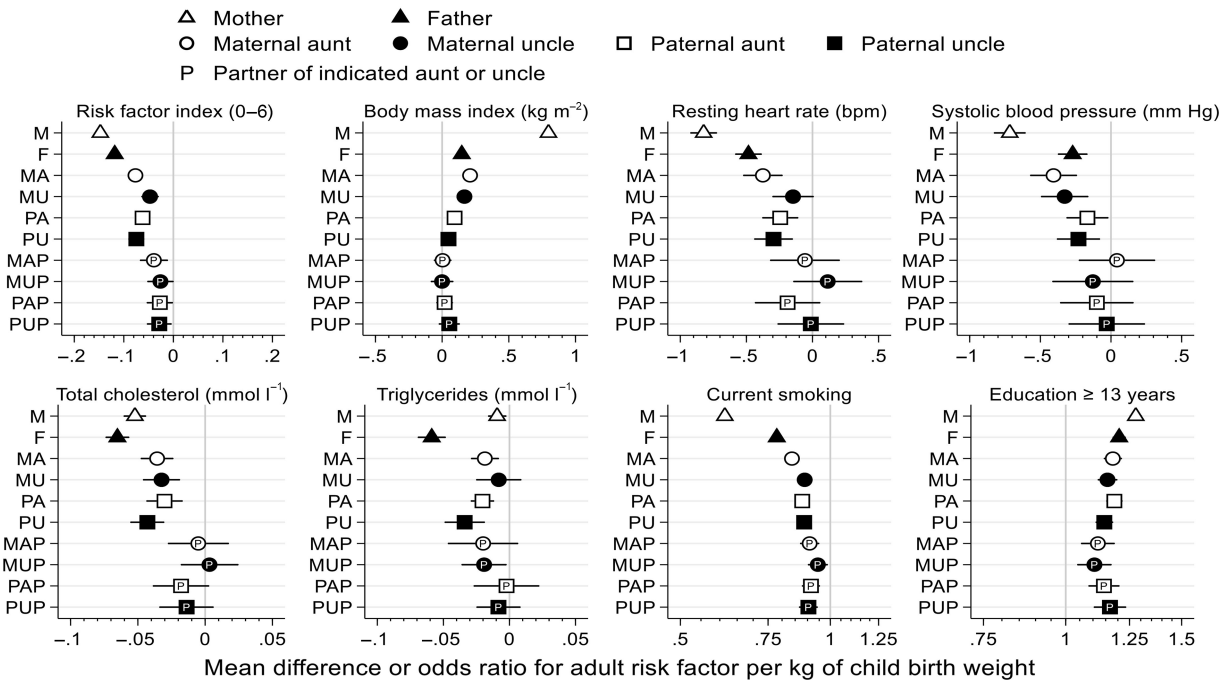

Fig. 2. Minimally adjusted associations between offspring birthweight and CVD risk factors in parents, aunts/uncles, and partners of aunts/uncles (Table S5).

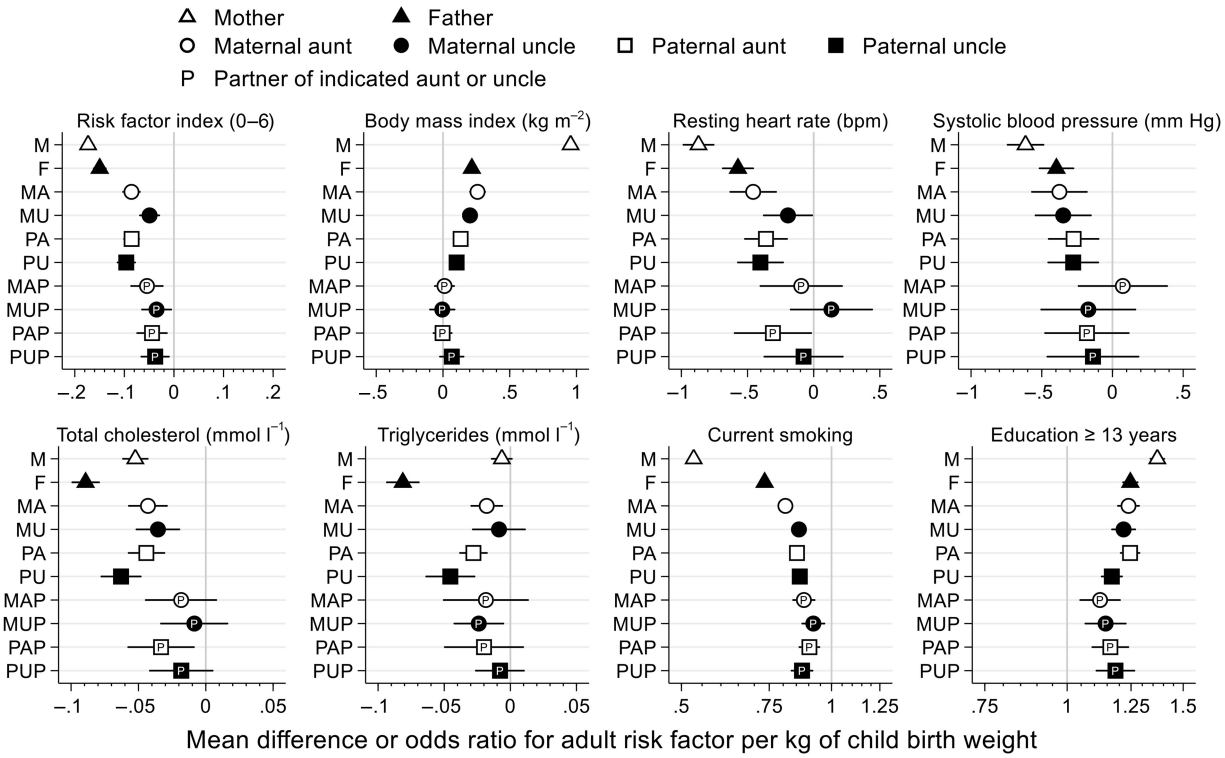

Fig. 3. Association between offspring birthweight and CVD risk factors in parents, aunts/uncles, and their partners after adjusting for age, offspring sex and gestational age, and maternal parity (Table S6).

Offspring birthweight was found to be associated with reduced smoking and higher education in parents, aunts/uncles, and their partners. The minimally adjusted odds ratios (ORs) for smoking in mothers and fathers were (0.61; 95% confidence interval (CI): 0.83, 0.92) and (0.78; 95% CI: 0.76, 0.79), respectively. For different groups of aunts/uncles, the ORs varied between (0.83; 95% CI: 0.81, 0.85) and (0.88; 95% CI: 0.86, 0.90). In the partners of aunts/uncles, they varied between (0.88; 95% CI: 0.83, 0.92) and (0.95; 95% CI: 0.83, 0.92).

All associations between birthweight and CVD risk factors were slightly attenuated after further adjustment for gestational age, offspring sex, and maternal parity (Fig. 3/Table S6). The correlations

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in CVD risk factors between mothers or fathers and their siblings varied between 0.15 (maternal DBP) and 0.28 (maternal TC) (Tables S3 and S4).

Discussion

In this population-based intergenerational study, we found that parents, aunts, and uncles of higher birthweight children had healthier CVD risk factor profiles, except for BMI. A similar but weaker trend was also observed for the partners of aunts/uncles. The associations in mothers were mostly stronger compared to fathers. However, for TG, the association in mothers was much weaker than the association in fathers. Furthermore, birthweight in offspring was found to be associated with smoking and a higher level of education among all familial relationships including partners (of aunts/uncles) suggesting multiple causal mechanisms are involved.

Comparison with existing literature

Our results support previous research reporting associations between offspring birthweight and CVD risk factors (blood pressure, BMI, and unfavorable levels of lipids) among both parents.[10] A number of studies have reported the association among mothers,[16–19] including two studies reporting an inverse association between offspring birthweight and SBP and insulin resistance in mothers.[9,20] Another study stated that low offspring birthweight was associated with higher levels of inflammatory and metabolic markers in their mothers, proposing that these women may be predisposed to upregulation of inflammation that has been associated with restricted fetal growth[21] and increased risk of CVD.[8,22] Moreover, a positive association between paternal BMI and infant birthweight has been reported in a previous study, which is in line with our results.[23] Contrary to this, a negative association between fathers' obesity and offspring birthweight has been reported in an intergenerational study. Some other studies have also reported higher BMI, higher glucose, and insulin resistance in fathers of SGA children compared to the fathers of their counterparts.[19,24,25]

We observed a negative association between offspring birthweight and CVD risk index in all four classes of aunts and uncles. Except for BMI, the associations for individual risk factors were generally consistent with these. Moreover, the associations with the risk factor index, smoking habits, and educational level were observed among partners of the aunts/uncles. According to our knowledge, the literature on the association between offspring birthweight and CVD risk in aunts/uncles and their partners is deficient. Therefore, a direct comparison of our results with previous data is not possible.

Interpretation

Offspring birthweight and CVD risk factors associations observed in parents and in aunts and uncles may have several explanations. The association in parents may potentially be explained by shared genes between children and their parents, a common environment shared by the parents, or a combination of both. Other environmental and social factors such as assortative mating may also contribute to the associations among parents.[26] Besides, a stronger association in mothers indicate the role of intrauterine factors. The associations in extended family members also support the role of genetic factors shared between aunts/uncles and their nieces/nephews. A correlated/shared environment between parents and their siblings can also contribute to these associations. The reason being that siblings usually share a similar lifestyle and dietary behaviors and these shared factors might affect both birthweight of the infant and CVD risk factors in the siblings. Moreover, it has been suggested that genetic and environmental factors are interconnected with each other. An offspring phenotype could be influenced by non-transmitted parental genetic alleles through environmentally mediated channels across generations.[26,27] This genetic nurturing/dynastic mechanism might be a possible explanation for the associations reported among parents and their siblings (aunts/uncles).

For smoking habits and educational level, the associations were also reported in the partners of aunts and uncles. As offspring are not expected to share genes inherited from the same lineage with the partners (of aunts/uncles), these associations indicate mechanisms other than the shared genes. Assortative mating on the basis of similar behavior and socioeconomic factors such as smoking and education, might create an apparent "environmental" effect and inflate the associations among partners of aunts/uncles.[28]

Strengths and weaknesses

The large sample size and population-based design are two main strengths of the study. In addition, offspring birth and pregnancy data were extracted from the Medical Birth Registry, which constitutes information on all births in Norway from 1967 onwards. Furthermore, it appears to be the first prospective intergenerational study investigating associations of offspring birthweight with measured CVD risk factors in aunts/uncles and their partners. However, the number of partners linked with offspring was much lower than the number of aunts/uncles. A possible reason for the low number of partners could be that we have selected those who were partners at the time of the health survey examination. Moreover, it should be considered that offspring were linked with their aunts and uncles in the health surveys within as well as outside of the trios. This could have an impact on our results. Hence, to check the validity of our results, we repeated our analyses in all familial relationships (parents, aunts/uncles) only in trios (Table S2). Results were found to be similar between the two analyses, suggesting that a possible selection bias is not influential in our study. Glucose levels and other lifestyle factors such as diet and physical activity could have given additional information on the mechanism behind offspring birthweight and CVD risk association but these factors were not measured. Genetic information from the parents, aunts/uncles, and partners was also not available in the study. Moreover, population surveys usually face the problem of missing data. This may have influenced the results of this study. However, participants for whom data were missing were listwise excluded. Presumably, it increases the validity of comparisons between different adults/different risk factors, because they were each analyzed using the same set of offspring. Finally, we have performed a high number of statistical tests, which increases the likelihood of Type I errors. This should be kept in mind when interpreting the results.

Conclusion

We observed an intergenerational association between offspring birthweight and CVD risk in parents and in four classes of aunts/uncles, proposing that these associations are attributable to genetic and environmental effects. The associations were also observed for smoking and educational level among partners of aunts/uncles. Our study revealed profound associations between

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offspring birthweight and CVD risk factors in extended family members and their partners that go beyond expected associations from known genetic similarities in pedigrees. This suggests that other mechanisms such as common environmental factors, assortative mating, and genetic nurturing may explain these associations.

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Ethical approval. Ethical approval of the study was acquired by the Regional Ethical Committee, Norway.

Conflict of interest. None.

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