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The association between birthweight and grandparental type 2 diabetes and cardiovascular disease in a multiethnic population

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Original Article

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Abstract

Intergenerational links of chronic disease have been suggested, as birthweight (BW) is associated with cardiovascular disease (CVD) and type 2 diabetes (T2D) in both parents and grandparents. However, most studies investigating these relationships have used relatively homogenous, white, majority populations. This study aimed to investigate the association between BW and CVD and T2D in a multiethnic population, that is, where the parents and grandparents often developed in a different environment from that where the child was born. Participants were women from a population-based cohort study of pregnant women (STORK Groruddalen), attending Child Health Clinics for antenatal care in three administrative city districts in Oslo, Norway, 2008–2010. Information about socioeconomic and lifestyle factors were collected among mothers and fathers. Parents reported history of CVD or T2D among grandparents. In logistic regressions, higher BW *z*-scores were associated with lower odds of T2D among maternal (OR 0.71 (95% CI 0.53, 0.97) and paternal (0.68 (0.49, 0.94) grandmothers after adjustments for parental and grandmothers' characteristics. BW was not associated with CVD, but the association in maternal grandfathers was borderline significant. Our results indicate intergenerational transmission of chronic diseases like T2D in a multiethnic population.

Background

Low birthweight (BW) is associated with an increased risk of chronic diseases later in life.[1] Several family studies have suggested intergenerational links of chronic diseases, as BWs of children are associated with cardiovascular disease (CVD) and diabetes in parents[2] as well as grandparents.[3–6] Proposed mechanisms of intergenerational links of chronic diseases include genetic or epigenetic factors influencing fetal growth and adult health, fetal nutrition programming future health[7] and/or confounding by socioeconomic factors and shared lifestyle and health behavior passed on through generations.

Most studies report stronger associations between offspring BW and parental morbidity in mothers than in fathers.[2] This could be due to maternal health-related behaviors or poor maternal health, leading to both reduced offspring BW and increased risk of disease in mothers, but also genetic factors influencing maternal health outcomes and the offspring in utero. Stronger associations between BW and morbidity in mothers than fathers could be related to imprinted genes from the mother if the gene is related to both offspring BW and maternal disease risk. With imprinted genes only one of two copies are active, either the one from the mother or the one from the father. Mothers suffering from gestational diabetes mellitus (GDM) are more likely than others to deliver a large for gestational age baby, and to develop type 2 diabetes (T2D) later in life, thus potentially making associations between BW and T2D in mothers U-shaped.[5] However, other studies have reported similar associations between offspring BW and risk of CVD in both parents, pointing towards mechanisms acting similarly in both parents, including genes related to fetal growth and adult chronic diseases, as well as environmental factors shared by the parents.[2] Many of the mechanisms possibly explaining the relationship between BW and chronic diseases in parents may as well relate to grandparents, including genetic factors related to BW and development of disease and effects of shared environment and of maternal constraint. Maternal constraint is a process in which maternal and uteroplacental factors limit the growth of the fetus. In this context, important reasons for constraint could be small size of the mother or the mother having an inadequate diet. These factors in the grandmothers could

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be related to BW and size of mothers, and also to risk of chronic disease. The long-term impact of such constraints could change over generations, with changes in availability of food and in energy demands, and with people living longer. In addition, there is an interplay between genes and environment where the genes of close relatives may influence a person's environment, and in turn health, without having inherited the genes as such (genetic nurture).[8]

Of note, previous studies in the field have mainly been carried out among primarily white, majority populations with a low prevalence of T2D. However, the population in Oslo is multiethnic, as in many European cities today, with a considerable proportion of immigrants from low- and middle-income countries, with a high prevalence of CVD and T2D,[9–11] and with a differential exposure to fetal growth restraining factors across generations. Mean BW is lower among most immigrant groups originating from low- and middle-income countries compared with European host populations[12] Furthermore, with a relatively high social mobility, children born in Norway today were conceived and will grow up in a very different environment than their grandparents, in particular those with an ethnic minority background. Hence, if we do not observe intergenerational links in this population, shared environment or health-related behavior across generations might be an explanation for the previously observed associations. The STORK Groruddalen is a population-based cohort study of pregnant women with a multiethnic, socioeconomically diverse sample and extensive data on health, life course socioeconomic factors and lifestyle of mothers, including gestational diabetes, and health among fathers and grandparents. This gives us the opportunity to investigate intergenerational links of chronic disease, controlling for important potential confounders. The objective of the present study was to investigate the association between offspring BW and a history of CVD or T2D in grandparents in a multiethnic sample in Oslo, Norway. As ethnic minority populations (in Europe) have been exposed to rapid epidemiological transitions through changes in socioeconomic status and migration over a few generations, the study might contribute to more knowledge about the early-life environment and health across generations.

Methods

The STORK Groruddalen is a population-based cohort study of healthy pregnant women attending Child Health Clinics for antenatal care in three administrative city districts in Oslo, Norway, between May 2008 and May 2010. The details of the study are published elsewhere.[13] Eligible women (1) lived in the study districts, (2) planned to give birth in one of the study hospitals, (3) were <20 weeks pregnant, (4) could communicate in Norwegian or any of the eight study languages (Arabic, English, Sorani, Somali, Tamil, Turkish, Urdu, and Vietnamese), and (5) were able to give an informed written consent for participation. Exclusion criteria were suffering from T2D or other diseases necessitating intensive hospital follow-up during pregnancy.

During the first visit (between gestational week 8 and 20), data on socioeconomic factors, ethnicity and migration, parity, medical history, actual pregnancy and modifiable factors, including smoking and physical activity were collected, using an interviewer-administered questionnaire. Mothers were given a questionnaire for the father to fill out at home, about demographic factors, family, and medical history, to be returned by the second visit. At the second visit (in gestational week 28), data on diet were also collected. Body weight was measured using a body fat analyzer, in light clothing (Tanita-weight BC 418 MA. Tanita, Tokyo, Japan). Maternal fasting blood samples were taken, an oral glucose tolerance test was performed, and a diagnosis of GDM was based on these measurements. Glucose was analyzed on site in EDTA blood samples (HemoCue, Angelholm, Sweden).

Variables

Grandparents

A history of CVD or T2D in grandparents of the offspring was reported by study participants (mothers and fathers of offspring) at the second visit. Participants were asked "Do you know whether one or several of your closest relatives (parents, siblings, children) have suffered from CVD (heart attack, angina, stroke) before the age of 55 years (men) or 65 years (women)?" (yes/no) "Do you know whether one or several of your closest relatives (parents, siblings, children) suffer or have suffered from diabetes?" Diabetes was recorded as no, type 1, type 2, and unknown type, and categorized into "no" (no and type 1) and "yes" (type 2 and unknown type).

Mother

Maternal age at inclusion was calculated based on date of birth. Maternal parity was categorized into "nulliparous" or "parous". Marital status was recorded as "married or co-habiting" or "not married/co-habiting". Maternal socioeconomic position (SEP) was a score derived from a principal components analysis of 11 sociodemographic variables.[14] The variables contributing most to this score were individual-level data about education, occupational class and employment status, and household variables as own or renting tenure, and rooms per person in the household. The score was normally distributed (mean = 0, median = 0.1, SD = 1 range:−2.91–2.59). Ethnic origin was defined as country of birth of the participant, or the participant's mother's country of birth if that was outside of Europe or North America, and grouped into "Norway", "other Western countries", "South Asia", "East Asia", "Middle East" (including North Africa/Central Asia), "Sub-Saharan Africa" (mainly Somalia), and "Central/South America". In some analyses, participants were grouped into "Western countries" (including Norway and other Western countries) and "Asia/Africa/Central and South America)". Smoking during pregnancy was recorded as "no" "sometimes" and "daily", and the two latter were collapsed to "yes". Data on maternal grandmother's smoking during pregnancy are based on self-report from the mother (she was given the opportunity to ask her mother before answering this part of the questionnaire). The mother's SEP score in childhood, also reflecting the maternal grandfather's and grandmother's SEP when the mother was 10 years old, was constructed by principal component analyses. Information about the highest family occupational class, rooms per person in the household, and family ownership of a car were entered to the analyses.[14] A food frequency questionnaire was designed for the study with the aim to reflect the habitual diet 2 weeks prior to the study, and with a focus on food items considered especially important for modifying risk of T2D and obesity. Four dietary patterns were derived from these data, using cluster analyses (Ward's method).[15] These four clusters were merged into two ("healthy" and "unhealthy") and used to adjust for dietary intake in the present study. Pre-pregnant regular physical activity, according to national guidelines, was captured as a self-reported history of physical activity prior to the pregnancy, and categorized into "yes" and "no".[16] The maternal GDM diagnosis was based on the WHO 1999 criteria; fasting glucose ≥ 7.0 mmol/l and/or 2-h

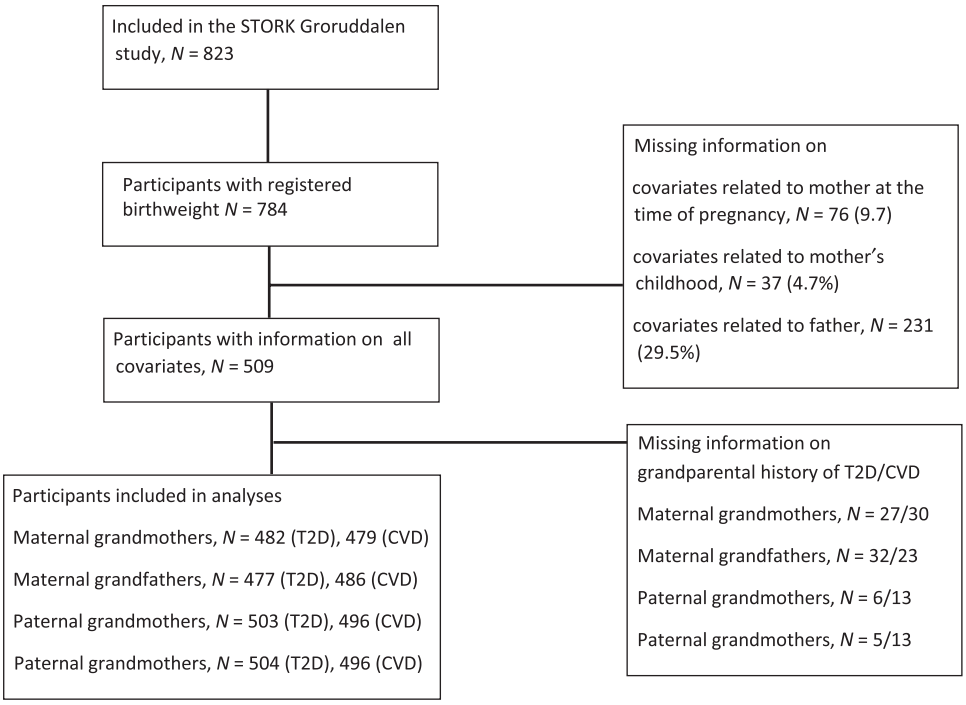

Fig. 1. Flowchart STORK Groruddalen. T2D, Type 2 diabetes; CVD, Cardiovascular disease.

plasma glucose ≥ 7.8 mmol/l.[17] Preeclampsia was defined according to the International Society for the Study of Hypertension in Pregnancy and Norwegian antenatal guidelines as blood pressure ≥140/90 mmHg and 24-h proteinuria ≥0.3 g.[18] History of preeclampsia was available from maternal records at the two maternity units.

Father

We used information about self-reported smoking (similar categories as for mother, current smoking), and body weight. We also had information on father's country of origin, but as most fathers (86%) belonged to the same ethnic group as their partner, we did not use this information in the analyses.

Offspring

Data on offspring BW and length were available from routine records at maternity units. Offspring BW (per *z*-score, according to gestational age- and sex-specific Norwegian national references), length (per cm), and ponderal index (kg/m^3) were analyzed as continuous variables. Analyses were also carried out with BW in quintiles.

Statistical methods

Logistic regressions with odds ratio (OR) were used to estimate associations between a history of CVD or T2D among grandparents according to BW of offspring (*z*-score). Analyses were first carried out without adjustments, and in Model 1: adjusted for GDM, preeclampsia, mother's weight at first visit, diet and physical activity and adult SEP, Model 2: additionally adjusted for maternal childhood SEP and grandmother's smoking during her pregnancy with the mother, and Model 3: additionally adjusted for paternal smoking and weight. Similar logistic regressions were carried out using offspring length at birth (cm) and ponderal index as exposure. As a sensitivity analysis, we reran the analyses for BW *z*-score including only those who reported not to smoke during pregnancy ($N = 402$, 16% missing) and by Western versus Asian/African/Central and South American background. We also run Model 1 without excluding those with missing data on paternal variables. Finally, we analyzed associations by quartiles of BW to check for U-shaped tendencies.

Analyses were carried out using IBM SPSS Statistics 25.

Results

Of those invited, the response rate was 73.9% and a total of 823 women participated in the study. Of these, 8 women were lost to follow-up, 20 women experienced fetal loss, and 11 had a twin pregnancy, leaving a sample of 784 women with a registered offspring BW. Of these, 9.7% of participants had incomplete information on covariates related to the mother at the time of pregnancy (mainly GDM and diet), 4.7% on covariates related to the mother's childhood, and 29.5% on covariates from the father, giving 509 participants with a complete set of covariates on mothers and fathers for analyses (Fig. 1). Of these 509, the number of grandparents with reported status of T2D or CVD varied between 477 and 504.

Mean gestational length was 39.4 weeks, and mean BW 3451 g (Table 1). Mean BW by grandparental history of CVD and T2D is shown in Supplementary Table C. The majority of mothers were married or co-habiting, and mean age at inclusion was 30.2 years (Table 1). Almost half of the women were from Norway or other Western countries, 23% originated from South Asia, 13% from the Middle East (including Central Asia and North Africa), while the rest came from other parts of the world. Few ethnic minority women were born in Norway. The current pregnancy was the first for almost half of the women. GDM was present in 13% of the women, and preeclampsia in 6%. One-third (31%) of fathers smoked, while 6% of mothers smoked during pregnancy, of which the majority were ethnic Europeans. A larger proportion of mothers had smoked 3 months prior to pregnancy (17%).

Table 1. Characteristics of mothers and fathers in the STORK Groruddalen study 2008–2010. $N = 509$

Offspring	
Sex, *n* (%)	
Female	253 (49.7)
Male	256 (50.3)
Gestational age, week (SD)	39.4 (1.6)
Birthweight gram, (SD)	3451 (537)
Length at birth, cm (SD)	49.8 (2.3)
Ponderal Index, kg/m^3(SD)	27.8 (2.7)
Mother	
Age at inclusion, years (SD)	30.2 (4.8)
Married or co-habiting, *n* (%)	494 (96.9)
Ethnicity, *n* (%)	
Norway	230 (45.2)
Other Western countries	13 (2.6)
Eastern Europe	27 (5.3)
South Asia	116 (22.8)
East Asia	28 (5.5)
Middle East/Central Asia/North Africa	66 (13.0)
Sub Saharan Africa	23 (4.5)
South/Central America	6 (1.2)
Length of residency, *n* (%)	
Norwegian ethnicity/other European, raised in Norway	229 (45.0)
Born in Norway to immigrant parents	22 (4.3)
>20 years	37 (7.3)
10–19 years	61 (12.0)
5–9 years	78 (15.3)
2–4 years	54 (10.6)
<2 years	28 (5.5)
Parity (%)	
Nulliparous	233 (45.8)
Parous	276 (54.2)
Gestational diabetes*, *n* (%) ($N = 742$)	66 (13.0)
Preeclampsia, *n* (%)	28 (5.5)
Weight at visit 1, mean (SD)	68.0 (13.9)
Smoking during pregnancy, *n* (%)	24 (5.6)
Smoking 3 months prior to pregnancy	88 (17.4)
Not regularly physically active before pregnancy, *n* (%)	303 (59.5)
Father	
Weight, mean (SD)	83.8 (13.7)
Smoking (%)	160 (31.4)

*Fasting glucose ≥ 7.0 mmol/l, 2-h glucose ≥ 7.8 mmol/l.

The history of T2D and CVD among grandparents is shown in Table 2. The prevalence of T2D varied between 10% among paternal grandfathers and 13% among maternal grandmothers. A history of CVD was reported in 7% of paternal grandmothers, 8% of maternal grandmothers, 16% of maternal grandfathers, and 18% of paternal grandfathers. The prevalence of reported T2D was especially high among grandparents of Asian/African/Central and South American origin, and the CVD prevalence was also higher among maternal grandparents from these regions. Among the offspring, 50% had no grandparents with a history of T2D or CVD, 32% had one grandparent with either T2D or CVD, and 13% had two grandparents with one of these diseases (or one grandparent with both). The others (5%) had three or four grandparents with a history of one or both diseases. A few grandparents had a history of both T2D and CVD (4 paternal grandmothers, 10 maternal grandmothers, 18 paternal grandfathers, and 20 maternal grandfathers)

In logistic regressions, a higher BW *z*-score was associated with lower odds of T2D among maternal (OR 0.71 (95% CI 0.53, 0.97) and paternal (0.68 (0.49, 0.94) grandmothers after adjustments for maternal, paternal, and grandmother's characteristics (Table 3). We found no associations between BW and CVD, but the association among maternal grandfathers was borderline significant.

As a sensitivity analyses, we reran the analyses including only those not smoking during pregnancy and found similar results (Supplementary Table A). We also ran the same analyses for participants with background from Western countries (high-income countries) and those from Asia/Africa/Central and South America (mainly representing low- and middle-income countries). The results confirmed a similar association between offspring BW *z*-score and T2D in grandmothers in both groups, although not significant, probably due to a small sample size. Further, running the logistic regression Model 1 for maternal grandparents not excluding participants with missing on paternal data and covariates did not alter the estimates notably. Only slightly weaker estimates were seen for associations between BW *z*-score and grandmothers' T2D. Offspring length at birth (not shown) and ponderal index (Supplementary Table B) were generally not associated with T2D or CVD among grandparents. We found no tendency of U-shaped associations when analysing by quartiles of BW.

Discussion

In a multiethnic cohort from Oslo, we found inverse associations between offspring BW and reported T2D in both maternal and paternal grandmothers, but not in grandfathers. We found no associations between BW and CVD in grandparents, or between offspring length or ponderal index and grandparents' CVD or T2D.

Relation to other studies

Previous studies examining associations between offspring BW and risk of T2D[4,5] and CVD[19] in grandparents are few and heterogeneous, both in methods, outcomes, number of participants, and results. Further, mechanisms involved in the associations are potentially different for T2D and CVD.

McCarron *et al.*[5] investigated the association between BW and a history of T2D among grandparents in a white UK population with a low prevalence of T2D, and reported an increase in OR of T2D with high BW among maternal grandparents, in contrast to our findings. Among paternal grandparents, however, an inverted U-shape was found for the associations among grandmothers, and also among grandfathers before adjustments. The lowest risk of T2D was seen among the grandparents of offspring with the highest BW, in line with our results. The estimates changed only

Table 2. Number and proportion of grandparents with reported history of type 2 diabetes (T2D) or cardiovascular disease (CVD) in the STORK Groruddalen study 2008–2010. $N = 509$

Total	Maternal grandmother	Maternal grandfather	Paternal grandmother	Paternal grandfather
Grandparents with diabetes status available, *n* (%)	503 (98.8)	504 (99.0)	482 (94.7)	477 (93.7)
T2D, *n* (%)	67 (13.3)	57 (11.2)	57 (11.8)	46 (9.6)
Grandparents with CVD status available, *n* (%)	496 (97.5)	496 (97.5)	479 (94.1)	486 (95.5)
CVD, *n* (%)	41 (8.2)	86 (16.1)	32 (6.7)	86 (17.7)
Western countries				
Grandparents with diabetes status available, *n* (%)	269 (99.6)	268 (99.3)	263 (97.4)	262 (97.0)
T2D, *n* (%)	16 (5.9)	17 (6.3)	14 (5.3)	13 (5.0)
Grandparents with CVD status available, *n* (%)	262 (97.0)	264 (97.8)	263 (97.4)	262 (97.0)
CVD, *n* (%)	16 (6.1)	35 (13.2)	18 (6.8)	45 (17.2)
Non-Western countries				
Grandparents with diabetes status available, *n* (%)	234 (97.9)	236 (98.7)	219 (91.6)	215 (90.0)
T2D, *n* (%)	51 (21.3)	40 (16.9)	43 (9.6)	32 (14.9)
Grandparents with CVD status available, *n* (%)	234 (97.9)	232 (97.1)	216 (90.4)	224 (93.7)
CVD, *n* (%)	25 (10.7)	45 (19.4)	14 (6.5)	40 (17.9)

Table 3. Odds Ratio (OR) of diabetes type 2 (T2D) and cardiovascular disease (CVD) in grandparents with 1 *z*-score change in offspring birthweight in the STORK Groruddalen study, 2008–2010

	Model 1	Model 2	Model 3	Model 4
Maternal grandmother				
T2D	0.74 (0.56 0.97)	0.68 (0.50 0.91)	0.69 (0.51 0.94)	0.71 (0.52 0.97)
CVD	1.06 (0.77 1.46)	1.01 (0.72 1.44)	1.02 (0.72 1.45)	1.03 (0.72 1.47)
Maternal grandfather				
T2D	0.81 (0.61 1.07)	0.73 (0.58 1.06)	0.80 (0.59 1.09)	0.77 (0.56 1.05)
CVD	0.85 (0.66 1.08)	0.78 (0.59 1.02)	0.78 (0.59 1.01)	0.78 (0.60 1.02)
Paternal grandmother				
T2D	0.73 (0.55 0.98)	0.65 (0.47 0.90)	0.68 (0.49 0.94)	0.68 (0.49 0.95)
CVD	1.01 (0.71 1.44)	1.03 (0.70 1.53)	1.05 (0.71 1.55)	1.01 (0.68 1.50)
Paternal grandfather				
T2D	0.89 (0.65 1.22)	0.87 (0.61 1.20)	0.89 (0.64 1.25)	0.84 (0.60 1.18)
CVD	0.99 (0.79 1.25)	1.03 (0.80 1.33)	1.04 (0.81 1.33)	1.01 (0.78 1.30)

Model 1: Crude (*z*-score adjusted for gestational age and offspring sex).
Model 2: Adjusted for maternal weight, adult socioeconomic position, gestational diabetes and preeclampsia, diet and physical activity.
Model 3: Model 2+ maternal socioeconomic position in childhood, and maternal grandmother's smoking.
Model 4: Model 3+ father's smoking and current weight.
$N = 477$–504, according to number of grandparents with reported medical history.

marginally after adjustment for grandparental smoking in McCarron's study, as we also observed in our study. Shrivastava *et al.*[4] reported, in accordance with our findings, inverse associations between BW and both maternal grandparents with T2D, and more strongly so among maternal grandmothers than grandfathers. They also reported inverse associations between offspring BW and stroke in maternal grandmothers. Further, Smith *et al.*[19] reported inverse associations between BW and CVD among maternal grandparents. We observed no associations between BW and CVD in maternal grandparents, but the estimates among maternal grandfathers might indicate an association, if observed in a larger sample.

Several studies have investigated associations between BW and grandparental mortality. Næss *et al.*[6] reported inverse associations between offspring BW and CVD mortality in all four grandparents, with stronger associations among maternal grandmothers than grandfathers. Manor *et al.*[3] reported similar associations between paternal grandmothers. However, a different set of factors may be related to morbidity and mortality. Moreover, T2D is rarely the primary cause of death, but contribute to premature deaths from CVD. As our study addressed pregnant women, most grandparents were not yet in the oldest segment of the population, in which mortality is most prevalent.

Mechanisms

The inverse association between a child's BW and T2D in grandmothers is consistent with genetic factors influencing both BW and disease. The inverse association between a child's BW and T2D in grandmothers is consistent with genetic factors influencing both BW and disease. The influence of genetic factors may be direct, although if so, in our study we would then expect similar associations in grandfathers as in grandmothers. However, the influence of maternal genetic factors may also work through indirect effects on the intrauterine environment, or the environment after birth (genetic nurture). Further, the early-life environment may lead to epigenetic changes that is associated with risk of chronic disease, although there is limited evidence that these changes can be transferred across several generations. Genome-wide association studies have identified several loci related to both BW and T2D.[20] There is evidence for genetic factors influencing insulin function in mothers and thus BW of the offspring,[21] as well as maternal blood pressure and offspring BW.[22]

Another plausible factor in this relationship over generations is supply-driven maternal constraint caused by, for example, an inadequate intake of nutrients before and during pregnancy or small maternal size.

Shared environment, including socioeconomic factors and health behavior such as smoking, across generations could contribute to an intergenerational link of chronic disease. Such influences could come from the mother, the father, and the grandparents, and also be related to assortative mating. Associations between T2D and BW were in the same direction for all four grandparents, albeit stronger among grandmothers than grandfathers. Although we adjusted for several environmental factors, the observed associations may still represent effects of shared environment and behavior in families over generations. However, if so, the stronger associations in grandmothers could either suggest that mothers are more important for transfer of, for example, dietary habits and health behavior than fathers, or that these environmental factors influence the intrauterine environment. Among participants from the ethnic minority population, the grandmothers developed in a very different environment from that where her grandchild is born, and it is therefore interesting that we observed an association also in this group. In a large Norwegian sample, an inverse association between BW and CVD mortality was found among all four grandparents, and most of the inverse association was explained by maternal smoking.[6] As very few women smoked during pregnancy in our study, in particular ethnic minority women, we could not adjust for smoking in our analyses. However, analyses excluding smokers and those who did not report on smoking did not substantially alter our results. Moreover, adjusting for grandmother's smoking during her pregnancy and paternal smoking did not alter the results. Thus, maternal smoking is not likely to be a key factor in our sample. Previous research have shown U-shaped associations between BW and T2D in mothers and grandmothers,[5] pointing towards intrauterine mechanisms where maternal hyperglycemia increases both BW and later risk of T2D.[22] We did not find support for a U-shaped association between BW and grandparental T2D in our sample (checked with BW *z*-score in quartiles). Adjusting for GDM had little impact on the estimates.

Strengths and limitations

We investigated intergenerational links of CVD and T2D in an ethnically diverse, population-based sample. The response rate into the study was 74%, and the respondents' ethnic background and parity reflected the population in the area, and maternal age at inclusion reflected mean age in pregnant women in Norway.[13] Still, we cannot rule out that factors such as health and language skills could possibly be related to nonattendance, and therefore may have biased our results. Strengths of the study include extensive data on health, SEP, and lifestyle in mothers, fathers, and grandparents, as well as BW and other data on offspring and mother from hospital records. Fathers had a lower response rate than mothers, and as we included data on paternal characteristics and information of disease in paternal grandparents given by the father, our sample is smaller than the full sample of mothers. Running the logistic regression Model 1 for maternal grandparents without excluding participants with missing on paternal data or covariates did not alter the estimates notably. Further, there were no differences in mothers' SEP or in the proportion of maternal grandparents with T2D or CVD between those with and without missing paternal data. The highest proportion of excluded participants originated from Asia/Africa/Central and South America (46% vs 29% from Western background). Sensitivity analyses showed little differences in estimates between those with a Western and an Asian/African/Central and South American background. Mothers with known diabetes were excluded from the study. Mothers with pregestational diabetes tend to give birth to large for gestational age babies and have an increased likelihood of having a parent with diabetes, and possibly also CVD.[5] Thus, although few mothers were excluded because of diabetes, exclusion of these mothers could have led to a slight underestimation of results. We had a relatively small sample size, limiting the power for subgroup analyses.

A history of T2D or CVD in grandparents was based on recall from their adult children. Not all children are aware of, or remember, a history of disease in their parents. Thus, it may be that not all cases of T2D or CVD are reported. An acute CVD event in a close relative will probably cause more concern and therefore be more easily recalled than the slow onset T2D, and any underreporting will probably be more likely for T2D than CVD. It is, however, unlikely that underreporting of a history of disease during pregnancy is related to BW of the baby, and it would probably not influence our results. Participants were asked to recall CVD events before the age of 55 (women) or 65 (men) years, which means we have only included premature CVD events. If we had followed participants for a longer time period with updated information about their parents, we would most likely have included more CVD events. This could have led to stronger associations, but perhaps also to weaker associations, as risk for CVD increases with age regardless of grandchild's BW. The risk of T2D and CVD differs between immigrant groups, with an especially high prevalence among South Asians.[10] One-fourth of the women in our study were of South Asian origin. Numbers were too small to investigate the associations in this group separately. However, sensitivity analyses indicated a similar association between offspring BW and T2D in grandmothers among participants from Asia/Africa/Central and South America (mainly low- and middle-income countries) and Western countries (high-income countries). This is interesting, as these two groups are likely to represent very different environmental exposures, and thus constraining factors, and changes in exposures, across the last two generations.

Conclusion

Our results indicate intergenerational transmission of chronic diseases like T2D in a multiethnic population, in which smoking

do not seem to be important. Studies with larger sample size and the possibility to investigate associations in distinct ethnic groups, as well as with genetic and epigenetic data and clinical measurement of CVD/T2D in family members, are warranted to further investigate the relative importance of genes, intrauterine effects, and shared family environment in the development of chronic diseases in minority groups.

Supplementary materials. For supplementary material for this article, please visit https://doi.org/10.1017/S2040174419000758

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Conflict of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the Helsinki Declaration of 1975, as revised in 2008, and The Norwegian Data Inspectorate has approved the study protocol. The Regional Ethics Committee has approved the work of this paper. The Norwegian Directorate of Health approved the storage of biological material. Participation was based on written consent from mothers and fathers.

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