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ORIGINAL ARTICLE

Cardiovascular diseases in grandparents and the risk of congenital heart diseases in grandchildren

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Hyperglycemia, dyslipidemia and hyperhomocysteinemia are associated with both adult cardiovascular disease (CVD) and having a child with a congenital heart disease (CHD). We investigated associations between CVD in grandparents and the risk of CHD in grandchildren. In a case–control family study, we obtained detailed questionnaire information on CVD and CHD in 247 families with a CHD child and 203 families without a CHD child. Grandparents with CVD or intermittent claudication (IC) were significantly associated with an increased risk for CHD in grandchildren [OR 1.39 (95% CI 1.03–1.89) and OR 2.77 (95% CI 1.02–7.56), respectively]. The risk of CHD grandchildren was particularly increased in paternal grandfathers with CVD [OR 1.85 (95% CI 1.01–3.37)]. Overall, having a grandparent with CVD increased the risk for CHD in the grandchild by 1.65 (95% CI 1.12–2.41). After adjustment for potential maternal confounders, this risk was 1.44 (95% CI 0.94–2.21). Having two or more grandparents with CVD was associated with an approximately threefold risk for CHD grandchildren [OR adjusted 2.72 (95% CI 1.08–6.89)]. Our data suggest that CVD and IC in grandparents are associated with an increased risk of having a CHD grandchild. These first findings may be explained by shared causality of derangements in metabolic pathways and are in line with the fetal origins of health and disease.

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Key words: cardiovascular disease, congenital heart disease, metabolic pathways, transgenerational

Introduction

The worldwide epidemic of cardiovascular diseases (CVD) remains the leading cause of death and represents 30% of all global deaths.[1] Moreover, an estimated 1 million children are born each year with congenital heart diseases (CHD) – the most common cause of death from congenital malformations worldwide.[2] To prevent both diseases in the future, risk factors have to be identified. Both animal and human studies show that common environmental exposures, including lifestyles, can derange metabolic pathways, in particular in combination with genetic susceptibilities during vulnerable periods in life and as such are implicated in the pathogenesis of both CVD and CHD.[3,4]

We have previously shown a significant association between maternal dyslipidemia and an increased risk of a child with CHD.[5] This finding is in line with other metabolic risk factors for CHD offspring, such as maternal hyperhomocysteinemia and hyperglycemia.[6,7] It is striking that the same metabolic derangements in later life are associated with adult CVD.[8,9]

Therefore, we hypothesize that CVD and CHD share variations in metabolic causal pathways, owing to interactions between poor lifestyles and genetic susceptibilities clustering in families. The underlying mechanism might be a derangement of epigenetic programming, which is substantiated by the observed transgenerational effects of exposure to famine.[10–12] A threefold increase in coronary heart disease and a more atherogenic lipid profile, especially in women, were found in the elderly whose mothers were undernourished early in pregnancy during the Dutch famine.[13,14] Shared metabolic variations of CVD and CHD can affect putative mechanisms of epigenetic (re)programming of the germ line (i.e. grandparents) and embryonic cardiac tissue (i.e. grandchild), thereby mediating the risk for both diseases.

The relatively low prevalence of CHD, that is, 4–8 per 1000 live births makes a prospective preconceptional cohort study unfeasible. Therefore, we conducted a case–control family study to investigate associations between CVD in grandparents and the risk of CHD offspring.

Methods

Study population

This study was part of the HAVEN study, a case–control family study designed to investigate environmental and genetic determinants in the pathogenesis and prevention of CHD, and has been described in detail before.[5,7]

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In addition to this study, grandparents of 806 participating families were invited to participate in the current study, of which 552 families (68%) responded (Fig. 1). Of these families, 91 families (11%) did not want to participate and before the analyses we excluded 11 families (1%) without any living grandparent. This resulted in 450 (56%) families for further analyses. Of these 450 families with 1800 grandparents, 250 (14%) did not respond and 1550 (86%) responded by returning the questionnaire. A total of 214 grandparents from the latter group were deceased and therefore excluded, which leaves 1336 grandparents for further analyses.

Questionnaires

All participating grandparents filled out a detailed paper questionnaire at home on general characteristics and their own medical history as well as that of their parents, that is, great-grandparents. Questions on medical history were derived from questionnaires used on patients with heterozygous familial hypercholesterolemia.[15] From these questionnaires, we extracted date of birth, medical history, medical surgery, medication use, special diet, smoking, and family medical history of CVD and CVD-related diseases.

The medical history of grandparents comprised self-reported CVD, defined as any acute, chronic, ischemic, pulmonary, or other form of heart and vascular diseases, based on the National Health Interview Survey of the Centers for Disease Control and Prevention.[16] Information on the CVD-related diseases such as hypertension, intermittent claudication (IC), cerebrovascular accident (CVA), thrombosis and pulmonary embolism was obtained and analyzed separately. The medical history of great-grandparents comprised information on CVD only. To validate the diagnosis, the year of diagnosis and treatment – that is, medication use, special diet and/or surgery – was reported. Medication use was reported as the name of the drug, date of prescription, amount prescribed and dose regimen. All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) Classification System of the WHO Collaborating Center for Drug Statistics Methodology. The use of a special diet was defined as cholesterol and/or fat-limited diet, low-sodium diet, a weight-reducing diet or other special diet. In addition, information was collected on the period in which the special diet was used and whether it was prescribed by a dietitian or doctor. Smoking was reported as the year when people started smoking, the amount and kind of tobacco products smoked per day, and the moment of quitting smoking. A smoker was defined as someone who smoked currently or had a history of smoking. When a first- or second-degree family member was deceased, the cause and age of death were reported.

We did not obtain data on CVD and CVD-related diseases in mothers and fathers of the case and control children, because they were too young to have already experienced these diseases. Other details on mothers, fathers and children were obtained as described previously.[7,17] Periconceptional folic-acid supplement use was defined as the daily intake of at least 400 µg in the entire periconceptional period, which was defined as 4 weeks before conception until 8 weeks after conception. Total plasma homocysteine and total serum cholesterol concentrations of venous blood samples from the mothers were obtained and published previously.[5]

Statistical analyses

We compared case and control families using the Student's *t*-test and Mann–Whitney *U*-test for continuous variables, and the χ^2-test for categorical variables. When the number of observations for analysis was less than five, we used Fisher's exact test.

We used univariable logistic regression analyses to study the associations between different risk factors including CVD in grandparents, and the risk of CHD in grandchildren. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated.

A stratified analysis for the two maternal and two paternal grandparents was performed to investigate a significant grandparent-of-origin effect. Confounding of maternal factors was investigated using multivariable logistic regression analyses. We adjusted for the following potential maternal confounders: age at conception of the index child, educational level, total homocysteine and total cholesterol concentrations, and periconceptional folic-acid supplement use. We also adjusted for CHD in the parents of the child.

Furthermore, we investigated whether the risk of CHD in grandchildren increased with more CVD-affected grandparents using univariable and multivariable logistic regression analyses. In these analyses, we adjusted for the same maternal confounders and additionally for the number of grandparents that were ascertained per child.

A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics 20.0 for Windows software (IBM, Armonk, NY, USA).

Results

A total of 247 case and 203 control families were included for analysis (Fig. 1). General characteristics of the children and their parents are summarized in Table 1. CHD phenotypes of the case children comprised perimembranous ventricular septal defect ($n = 60$), transposition of the great arteries ($n = 48$), pulmonary valve stenosis ($n = 42$), coarctation of the aorta ($n = 28$), tetralogy of Fallot ($n = 24$), atrioventricular septal defect ($n = 20$), hypoplastic left heart syndrome ($n = 11$), aortic valve stenosis ($n = 6$) and miscellaneous ($n = 8$). Case children showed a significantly lower birth weight adjusted for gestational age compared with control children. Case and control mothers were significantly different for age at birth of the index child and CHD in the family. Case and control fathers were significantly different for educational level.

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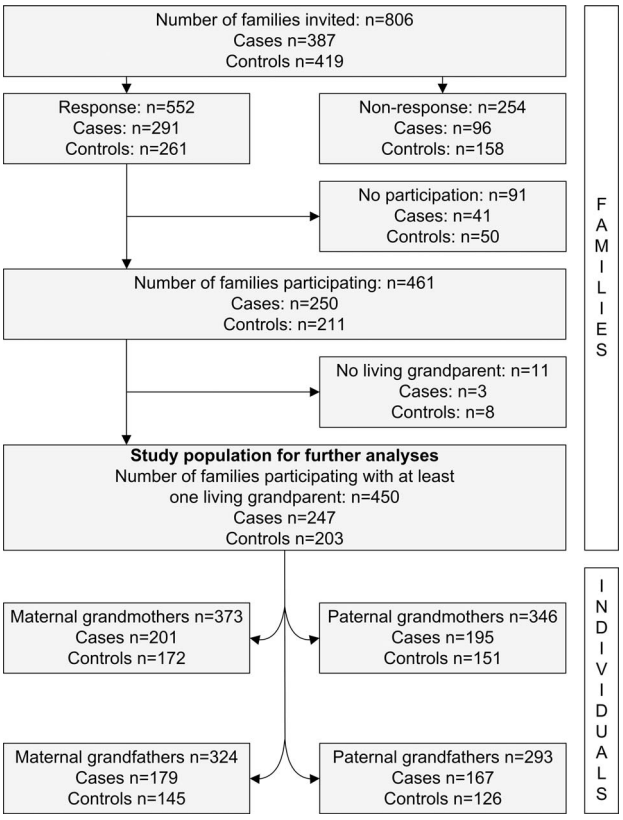

Fig. 1. Flowchart of the HAVEN study population.

The risk factors of living grandparents are presented in Table 2. The number of grandparents participating per child did not differ statistically significantly between case and control families ($P = 0.711$; Supplementary Table S1). CVD and IC were more common in the grandparents of CHD children (17% *v.* 13%, $P = 0.034$ and 2% *v.* 1%, $P = 0.038$, respectively). Grandparents with either CVD or IC were significantly associated with an increased risk for CHD grandchildren, OR 1.39 (95% CI 1.03–1.89) and OR 2.77 (95% CI 1.02–7.56), respectively. The prevalence of CVD in the parents of these grandparents, that is, great-grandparents, was not significantly different between the case and control families.

Table 3 shows the results of the stratified analysis for the four different grandparents. We observed a significant association between smoking in maternal grandmothers and the risk of a CHD grandchild [OR 1.73 (95% CI 1.02–2.93)]. CVD in paternal grandfathers was associated with an increased risk for a CHD grandchild [OR 1.85 (95% CI 1.01–3.37)]. No significant associations were observed in the stratified analysis for great-grandparents.

There was a 1.6-fold higher CHD risk [OR 1.65 (95% CI 1.12–2.41)] when at least one of the grandparents of the child suffered from CVD. When we adjusted the association for potential maternal confounders, the OR attenuated to 1.44 (95% CI 0.94–2.21).

Stratification for the number of CVD-affected grandparents showed that children with one grandparent with CVD had a 1.5-fold increased CHD risk [OR 1.51 (95% CI 1.01–2.26), case/control children $n = 93/62$], and with two or more CVD-affected grandparents a more than 2.5-fold increased CHD risk [OR 2.58 (95% CI 1.15–5.78), case/control children $n = 23/9$]. Adjustment for maternal confounders and the number of grandparents ascertained per child attenuated the association between CHD risk and one grandparent affected by CVD [OR 1.29 (95% CI 0.83–2.02)]. The association between CHD risk and two or more grandparents affected by CVD became stronger [OR adjusted 2.72 (95% CI 1.08–6.89)].

Because data were self-reported, we cross-checked CVD diagnoses in both case and control grandparents with treatment data (Supplementary Table S2). Of the grandparents with CVD, 81–100% used medication from the ATC group C (cardiovascular system) or underwent CVD-related interventions/surgery or followed a special diet for their CVD.

Discussion

This case–control family study suggests that both CVD and IC in grandparents are associated with an increased risk for CHD in grandchildren. Especially having two or more grandparents with CVD increases the risk for CHD in grandchildren. These findings support our hypothesis that CVD and CHD share common metabolic or other pathways. The heritability of lifestyle factors in the same way as genetic factors affecting these metabolic pathways should be considered with respect to both the high prevalence of poor nutrition, smoking and other lifestyles in the general population, and the relatively small numbers of genetic variations identified for CVD and CHD.[18–20] Of interest in this regard is also the established association between maternal grandmother smoking and CHD in the grandchild. However, additional adjustment for maternal or grandparental and particularly grandmaternal smoking did not significantly affect the results (Supplementary Table S3). Smoking is a proxy measure for socioeconomic status, which is clustering in families and as such should also be considered as a risk factor for both CVD and CHD. Adjustment for maternal educational level as a proxy for socioeconomic status did not attenuate the risk for CHD in grandchildren. However, this does not rule out the contribution of poor lifestyles in families to the risk for both CVD and CHD.

Our results show the highest CHD risk in grandchildren in which the paternal grandfather suffered from CVD. This observation is in line with studies showing that the paternal diet can affect cholesterol and lipid metabolism in the offspring.[21] However, underdiagnosis of CVD in women is an issue to be considered, in particular in grandmothers.

Besides lifestyle risk factors, it should be emphasized that other environmental factors may also be involved, such as psychological stresses and pollution, especially those linked to the socioeconomic status. After fertilization, the somatic cell

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Table 1. *General characteristics of case families of a child with CHD and control families of a healthy child*

	Cases (n = 247)	Controls (n = 203)	P-value
Characteristics of children			
Age – months (S.D.)	16.6 (3.3)	15.9 (2.0)	0.088
Male gender	147 (60)	117 (58)	0.687
Birth weight adjusted for GA (median, min–max)	3390 (865–5100)	3520 (2235–5180)	0.000
Ethnicity			0.492
Dutch native	213 (86)	180 (89)	
European others	19 (8)	10 (5)	
Non-European	15 (6)	13 (6)	
Characteristics of mothers			
Age at birth of index child – years (S.D.)	35.1 (4.3)	34.0 (4.2)	0.019
Educational level			0.052
Low	45 (18)	22 (11)	
Intermediate	104 (42)	103 (51)	
High	98 (40)	78 (38)	
CHD[a]	4 (2)	0 (0)	0.131
CHD family history[b]	36 (15)	11 (5)	0.002
Periconceptional			
Folic-acid supplement use[c]	42 (17)	37 (18)	0.734
Smoking	42 (17)	33 (16)	0.832
Total homocysteine, mean (S.D.; n = 384)	10.5 (4.4)	9.8 (3.1)	0.056
Total cholesterol, mean (S.D.; n = 384)	4.9 (0.9)	4.8 (0.9)	0.138
Characteristics of fathers			
Age at birth of index child – years (S.D.)	37.4 (4.3)	36.9 (4.7)	0.264
Educational level			0.034
Low	58 (23)	35 (17)	
Intermediate	81 (33)	90 (44)	
High	108 (44)	78 (38)	
CHD[a]	2 (1)	0 (0)	0.504
CHD family history[b]	27 (11)	14 (7)	0.139
Smoking	75 (30)	69 (34)	0.408

GA, gestational age; CHD, congenital heart disease.

Values are means or numbers (percentages) unless otherwise specified.

[a]Congenital heart disease defined as perimembranous ventricular septal defect, transposition of the great arteries, pulmonary valve stenosis, coarctation of the aorta, tetralogy of Fallot, atrioventricular septal defect, hypoplastic left heart syndrome, aortic valve stenosis.

[b]Any congenital heart disease of family members in the first, second or third degree.

[c]Adequate periconceptional folic-acid supplement use 4 weeks before conception until 8 weeks after conception.

line is reprogrammed among others into the cardiac tissues, which will form the embryonic heart.[22] After that, the cardiac cells will be fixed in tissue-specific patterns of gene expression through subsequent generations of cell division. During this critical window, epigenetic alterations in the programming of embryonic growth and/or specific cardiovascular growth genes caused by poor environmental exposures may contribute to CHD and increase the susceptibility of developing CVD in later life. The cardiovascular system consists of many different cell types from which both CVD and CHD originate. All differentiated cell types have their own unique epigenetic mark, which reflects not only the developmental history and previous environmental exposures, supported by our observed association with maternal grandmother smoking, but also its phenotype.[22] In this context, the concept of the fetal origins of CVD is an attractive hypothesis.[23] This is in line with findings in patients with CHD showing both a higher susceptibility to develop ischemic heart disease and a higher prevalence of CVD risk factors.[24] However, this study is a first epidemiological attempt to determine an association between CVD and CHD and should be interpreted with caution. Nevertheless, potentially modifiable risk factors, such as nutrition and smoking, are of great importance and should be further investigated.

Within families, ethnic and cultural factors determine environment. In our study population, 94% of the families are from European origin (87% Dutch natives, 6% European others). Therefore, our results are unlikely to be caused by differences in ethnicity or culture. However, within families, classic genetic factors cannot be ignored. Familial transgenerational risks are not only determined by shared environment but also by shared alleles. Therefore, familial transgenerational risks are the result of a combined effect of susceptibility genes,

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Table 2. *Risk factors of grandparents for having a CHD grandchild*

	Case grandparents (n = 742)	Control grandparents (n = 594)	Missing data case/control grandparents n (%)	OR (95% CI)
Grandparents (n = 1336)				
Age – years (range)	65 (46–88)	64 (47–85)	11/5 (1/1)	1.01 (1.00–1.03)
Gender				
Male	346 (47)	270 (45)	0/0 (0/0)	1.04 (0.84–1.29)
CVD	127 (17)	77 (13)	5/2 (1/0)	1.39 (1.03–1.89)
Hypertension	217 (29)	177 (30)	5/2 (1/0)	0.98 (0.77–1.24)
IC	17 (2)	5 (1)	5/2 (1/0)	2.77 (1.02–7.56)
CVA	26 (4)	15 (3)	5/2 (1/0)	1.41 (0.74–2.68)
Thrombosis/pulmonary embolism	20 (3)	18 (3)	5/2 (1/0)	0.89 (0.47–1.70)
Smoking	133 (18)	90 (15)	6/2 (1/0)	1.23 (0.92–1.65)
Great-grandparents				
Great-grandfather CVD (n = 1237)	267 (39)	207 (37)	59/40 (9/7)	1.08 (0.85–1.36)
Great-grandmother CVD (n = 1260)	206 (30)	148 (26)	45/31 (6/5)	1.18 (0.92–1.51)

CVD, cardiovascular disease; IC, intermittent claudication; CVA, cerebrovascular accident.
Values are means or numbers (percentages) unless otherwise specified. ORs are unadjusted.

that is, risk alleles, and environmental risk factors clustering in families.[25] It cannot be excluded that within the case families some major alleles are being selected with a dominant inheritance, which increases risks within these families compared with the general population. Therefore, a genetic contribution by the transfer of risk alleles should be considered as well.

It has been shown that maternal environmental factors during early pregnancy modify the risk for CHD in the offspring. A well-known example is the periconceptional use of a folic-acid supplement to reduce the risk of having a child with CHD.[3,26] After adjustment in our analyses for several maternal factors, the risk for CHD in the child still remained significant for the highest risk group. Therefore, it is not very likely that the association between CVD and CHD is owing to confounding of the investigated maternal factors. However, residual confounding of unobserved risk factors cannot be completely excluded. We selected as potential confounders a subset of maternal environmental factors, although it can be assumed that paternal risk factors contribute as well.[27] Owing to small sample sizes in the high-risk groups, and the potential of overadjustment, we had to limit the number of potential confounders. Moreover, there are several contradictory studies on CHD risk factors and especially paternal risk factors, which make a valid selection of true confounders very difficult.

The questions about self-reported CVD diagnoses are based on the National Health Interview Survey of the Centers for Disease Control and Prevention. These data were cross-checked using self-reported CVD treatment information. Of all the grandparents with CVD, 81–100% used medication from the ATC group C (cardiovascular system), a special diet related to CVD, and/or underwent a CVD-related intervention/surgery (Supplementary Table S2). CVD was significantly correlated with these medical data (data not shown). The use of medication could not be confirmed with pharmacy data. However, because of the good agreement of self-reported CVD and medical data, we do not expect recall bias between case and control grandparents.

We did not study CVD in parents because they were too young to have already experienced CVD (Table 1). Our results are based on 1336 grandparents of 450 children, which is a complete data set for 74% grandparents with a comparable number of cases and controls (Supplementary Table S1). This means that data of 464 grandparents were not analyzed, that is, 250 alive or deceased non-responders and 214 excluded deceased grandparents. The strength of the study is that, in the excluded group of deceased grandparents, the distribution of cases and controls were comparable (cases n = 124 and controls n = 90, P = 0.511), as well as the number of CVD-related deaths (cases n = 34 and controls n = 23, P = 0.761). Data on other diseases in this group were incomplete (49%) and therefore not further analyzed. A sensitivity analysis restricted only to children with data on all four grandparents attenuated the ORs to close to 1.0, although with wide confidence intervals because of small sample sizes. Another strength of our study is that the participants were not aware of the diseases of interest as an extensive questionnaire on multiple diseases was completed. Therefore, we conclude that it is not very likely that selection and recall bias have confounded our results, although bias because of missing grandparents cannot be ruled out.

Here we show that families in which grandparents are affected by CVD and IC have an increased risk for having grandchildren with CHD. These interesting findings may stimulate further research into modifiable environmental risk

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Table 3. *Risk factors of grandparents stratified for maternal and paternal grandmothers, and maternal and paternal grandfathers (n = 1336) for having a CHD grandchild*

	Maternal grandmothers			Maternal grandfathers			Paternal grandmothers			Paternal grandfathers		
	Case (*n* = 201)	Control (*n* = 172)	OR (95% CI)	Case (*n* = 179)	Control (*n* = 145)	OR (95% CI)	Case (*n* = 195)	Control (*n* = 151)	OR (95% CI)	Case (*n* = 167)	Control (*n* = 126)	OR (95% CI)
Age – years (range)	63 (50–84)	62 (49–80)	1.02 (0.98–1.05)	65 (46–83)	65 (54–84)	1.01 (0.97–1.04)	66 (50–87)	65 (47–85)	1.02 (0.99–1.05)	66 (49–88)	66 (52–82)	1.00 (0.97–1.04)
CVD	26 (13)	13 (8)	1.82 (0.90–3.66)	43 (24)	31 (22)	1.17 (0.69–1.98)	17 (9)	14 (9)	0.94 (0.45–1.97)	41 (25)	19 (15)	1.85 (1.01–3.37)
Hypertension	53 (26)	53 (31)	0.80 (0.51–1.26)	52 (29)	38 (26)	1.16 (0.71–1.90)	62 (32)	45 (30)	1.11 (0.70–1.76)	50 (30)	41 (33)	0.89 (0.54–1.47)
IC	1 (0)	0 (0)	na	7 (4)	1 (1)	5.89 (0.72–48.43)	6 (3)	2 (1)	2.38 (0.47–11.95)	3 (2)	2 (2)	1.14 (0.19–6.92)
CVA	7 (3)	2 (1)	3.07 (0.63–15.0)	6 (3)	3 (2)	1.65 (0.41–6.71)	9 (5)	6 (4)	1.18 (0.41–3.38)	4 (2)	4 (3)	0.75 (0.18–3.07)
Thrombosis/pulmonary embolism	6 (3)	8 (5)	0.63 (0.21–1.86)	6 (3)	5 (3)	0.98 (0.29–3.26)	6 (3)	2 (1)	2.38 (0.47–11.95)	2 (1)	3 (2)	0.50 (0.08–3.03)
Smoking	47 (24)	26 (15)	1.73 (1.02–2.93)	38 (21)	24 (17)	1.38 (0.78–2.43)	20 (10)	21 (14)	0.71 (0.37–1.36)	28 (17)	19 (15)	1.14 (0.60–2.15)
Great-grandparents												
Great-grandfather CVD	81 (44)	75 (48)	0.86 (0.56–1.32)	74 (44)	48 (35)	1.41 (0.89–2.25)	58 (34)	51 (36)	0.92 (0.57–1.46)	54 (34)	33 (28)	1.35 (0.80–2.27)
Great-grandmother CVD	63 (34)	47 (28)	1.29 (0.81–2.03)	41 (25)	39 (28)	0.83 (0.50–1.39)	60 (32)	41 (29)	1.18 (0.73–1.89)	42 (27)	21 (18)	1.65 (0.91–2.98)

CHD, congenital heart disease; CVD, cardiovascular disease; IC, intermittent claudication; CVA, cerebrovascular accident; na, not applicable.
Because of missing values, numbers in the table may not add up. Values are means or numbers (percentages). ORs are unadjusted.

factors of underlying common metabolic pathways to prevent both CHD and CVD in future generations.

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Conflict of Interest

None.

Ethical Standards

The study protocol was approved by the Central Committee for Human Research (CCMO) in The Hague, The Netherlands, and by the Institutional Review Boards (Medical Ethics Committees) of all participating hospitals. All parents and grandparents gave their written informed consent. Mothers and their partner gave written informed consent on behalf of their participating child.

Supplementary material

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/S2040174414000026

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