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Strength of family history in predicting levels of blood pressure, plasma glucose and cholesterol

THESE

préparée sous la direction du Docteur Murielle Bochud, Privat-Docent et Professeur assistante
avec la co-direction du Professeur Fred Paccaud, Directeur de l'Institut de médecine sociale et préventive

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Strength of family history in predicting levels of blood pressure, plasma glucose and cholesterol

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Directrice de l'Ecole doctorale

Rapport de synthèse

Strength of family history predicting levels of blood pressure, plasma glucose and cholesterol
Valeur de l'anamnèse familiale pour la prédiction du niveau de tension artérielle, de la glycémie à jeun et du cholestérol.

L'histoire familiale reflète non seulement la susceptibilité génétique d'un individu à certaines maladies mais également ses comportements et habitudes, notamment partagées au sein d'une famille. L'hypertension artérielle, le diabète et l'hypercholestérolémie sont des facteurs de risque cardio-vasculaire modifiables hautement prévalent. L'association entre l'histoire familiale d'hypertension artérielle ou de diabète et le risque accru de développer de l'hypertension artérielle ou du diabète, respectivement, a été préalablement établie. Par contre, le lien entre l'histoire familiale de facteurs de risque cardio-vasculaire et les traits continus correspondants n'avaient jamais été mis clairement en évidence. De même, la signification d'une histoire familiale inconnue n'avait jusqu'alors pas été décrite.

Ce travail, effectué dans le cadre de l'étude Colaus (Cohorte Lausannoise), une cohorte regroupant un échantillon composé de 6102 participants âgés de 35 à 75 ans sélectionnés au hasard dans la population lausannoise, a permis de décrire en détail la relation entre l'histoire familiale des facteurs de risque cardio-vasculaires et les trait correspondants dans la population étudiée.

Les différentes analyses statistiques ont permis de mettre en évidence une relation forte entre l'histoire familiale d'hypertension artérielle, de diabète ainsi que de l'hypercholestérolémie et leurs traits dichotomique et continu correspondants. Les anamnèses des frères et sœurs avaient des valeurs prédictives positives plus élevées que les anamnèses parentales. Ceci signifie que les programmes de dépistage ne prenant en compte que l'histoire familiale des frères et sœurs seraient probablement plus efficaces que ceux qui comportent l'évaluation des anamnèses paternelle et maternelle.

Plus de 40% des participants ignoraient l'histoire familiale d'hypertension d'au moins un des membres de leur famille. Ceux-ci avaient des valeurs de tension artérielle systolique plus élevées que ceux dont l'histoire familiale était négative, permettant de souligner la valeur prédictive du fait de ne pas connaître l'histoire familiale d'hypertension artérielle. Ces résultats montrent également que, lors d'analyses de la relation entre l'anamnèse familiale de facteurs de risque cardiovasculaires et leurs traits correspondants, les participants donnant des réponses négatives doivent être distingués de ceux qui ne connaissent pas leur anamnèse familiale.

Les résultats de cette étude confirment la place centrale qu'occupe l'anamnèse familiale dans l'évaluation du risque cardio-vasculaire auprès de la population générale. L'importance de cet outil prédictif simple et bon marché ne va cesser d'augmenter avec la disponibilité croissante d'information génétique détaillée pour les maladies cardiovasculaires communes.

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Strength of Family History in Predicting Levels of Blood Pressure, Plasma Glucose and Cholesterol

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Key Words
Cardiovascular risk · Diabetes · Dyslipidemia · Family history · Hypercholesterolemia · Hypertension · Population-based study

Abstract
Objective: Limited information is available on the quantitative relationship between family history and the corresponding underlying traits. We analyzed these associations for blood pressure, fasting blood glucose, and cholesterol levels. ***Methods:*** Data were obtained from 6,102 Caucasian participants (2,903 men and 3,199 women) aged 35–75 years using a population-based cross-sectional survey in Switzerland. Cardiovascular disease risk factors were measured, and the corresponding family history was self-reported using a structured questionnaire. ***Results:*** The prevalence of a positive family history (in first-degree relatives) was 39.6% for hypertension, 22.3% for diabetes, and 29.0% for hypercholesterolemia. Family history was not known for at least one family member in 41.8% of participants for hypertension, 14.4% for diabetes, and 50.2% for hypercholesterolemia. A positive family history was strongly associated with higher levels of the corresponding trait, but not with the other traits. Participants who reported not to know their family history of hypertension had a higher systolic blood pressure than participants with a negative history. Sibling histories had higher positive predictive values than parental histories. The ability to discriminate, calibrate, and reclassify was best for the family history of hypertension. ***Conclusions:*** Family history of hypertension, diabetes, and hypercholesterolemia was strongly associated with the corresponding dichotomized and continuous phenotypes.

Family history not only captures genetic susceptibility to a specific disease but also behaviors and life styles that are shared across members of the same family. Hypertension, diabetes mellitus, and hypercholesterolemia are highly prevalent modifiable cardiovascular risk factors that are known to aggregate in families [1–3]. A positive family history of hypertension or diabetes is an independent risk factor for hypertension [4] or diabetes [3, 5–8], respectively. Whether a positive family history of hypercholesterolemia is able to capture any familial aggregation and hence represents an independent risk factor for the disease is more controversial, as it has been reported in some studies [3, 9, 10] but not in others [11, 12].

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Although numerous studies have analyzed the risk of cardiovascular disease associated with a positive family history of risk factors, considerably less data are available on the relationship between a positive family history and the corresponding level of the continuous trait [10, 13]. This is especially true for hypercholesterolemia in adults, with little population-based data available on family history [10, 14]. In addition, data on the cardiovascular risk of subjects who report not to know their family history of hypertension, diabetes, and/or hypercholesterolemia are scarce [13, 15, 16].

We took advantage of the CoLaus study to explore in more detail the relationship between family history and related traits. The CoLaus study is a population-based study aiming at unraveling the genetic determinants of cardiovascular risk factors [17]. We analyzed (1) the relationship between the family history of hypertension, diabetes, or hypercholesterolemia and the corresponding continuous phenotype in a large population-based study, (2) whether knowledge of a specific family history was associated with the corresponding phenotype and hence with cardiovascular risk, and (3) whether personal awareness of hypertension, diabetes, or hypercholesterolemia changed these associations.

Subjects and Methods

Study Population

Recruitment began in June 2003 and ended in May 2006. The complete list of Lausanne inhabitants aged 35–75 years (n = 56,694) was provided by the population registry of the city. A simple non-stratified random sample of 35% of the overall population was drawn. Inclusion criteria were: (a) written informed consent, (b) aged 35–75 years, (c) available examination and blood sample, and (d) Caucasian descent. Of the 6,188 participants, we excluded 86 subjects because they were adopted (n = 62), or because of missing blood pressure (n = 6), laboratory (n = 11), questionnaire (n = 5), and anthropometric (n = 2) data, leaving 6,102 for the main analyses. The study was approved by the Ethics Committee of the Faculty of Biology and Medicine of Lausanne. In Switzerland health insurance is mandatory, and access to health care is universal. Therefore, every inhabitant has easy access to cardiovascular screening. In Lausanne the screening guidelines are based on the US Preventive Services Task Force guidelines [18].

Questionnaire Data

Trained health professionals used a standardized questionnaire on socio-demographic characteristics and family history. Subjects were asked questions about hypertension, diabetes, and hypercholesterolemia in their father, mother, and siblings. The following questions were asked: 'Is your father still alive?', 'Does (did) your father have hypertension?', 'If yes, at what age was hypertension diagnosed?', 'Does (did) your father have diabetes?', 'Does (did) your father have elevated cholesterol levels?'. Possible answers were 'yes', 'no', and 'don't know'. The same questions were asked for the mother's history. 'Do you have siblings?', 'If yes, how many siblings do you have?', 'How many of your siblings suffer from hypertension? Diabetes? Hypercholesterolemia?'. A 'don't know' answer could be provided. For awareness, the following questions were asked: 'Did a medical doctor ever tell you that you have elevated blood pressure (hypertension)?', 'Were you ever told that you have diabetes? Hypercholesterolemia?'. Definitions of hypertension, diabetes, or hypercholesterolemia were not provided to participants. None of the subjects who reported not to have diabetes or hypertension reported to be treated for hypertension or diabetes. We included the 44 participants who reported not to have hypercholesterolemia but were treated with statins in the group of persons unaware of being affected.

Assessment Process and Data Collection

Participants attended the outpatient clinic of the University Hospital of Lausanne (CHUV) in the morning after an overnight fast. For the purpose of the present analysis, smoking was defined as present if a participant reported to be a current smoker at the time of examination; alcohol consumption was defined as present for participants reporting to drink alcohol at least once a day. Body mass index (BMI) was defined as weight divided by height in meter squared. Blood pressure and heart rate were measured 3 times on the left arm after at least 10 minutes rest in the seated position using a clinically validated automatic oscillometric device (Omron HEM-907, Matsusaka, Japan) [19] with an appropriately sized cuff. The average of the 2nd and 3rd readings was used for analyses. Hypertension was defined as a mean systolic blood pressure $\geq$140 mm Hg and/or a diastolic blood pressure $\geq$90 mm Hg and/or presence of anti-hypertensive drug treatment. A venous blood sample was collected from each participant under fasting conditions. Blood tubes were centrifuged at 1,500 rpm for 10 min at 4°C within 2 h of admission. The CHUV Clinical Laboratory, which is ISO 9001 certified and regularly checked by the Swiss Centre for Quality Control, conducted all measurements in a Modular P apparatus (Roche Diagnostics, Switzerland). Glucose and blood lipids were measured using standard laboratory methods. Diabetes was defined as a fasting blood glucose $\geq$126 mg/dl or presence of any antidiabetic drug (including insulin). Two definitions were used for hypercholesterolemia. The first was defined as a fasting blood cholesterol $\geq$242 mg/dl or under lipid lowering treatment. The second definition took into account fasting LDL-cholesterol values $\geq$161 mg/dl or $\geq$101 mg/dl in participants at high risk of cardiovascular diseases (i.e., a history of myocardial infarction, stroke, coronary artery disease, or diabetes) or under lipid lowering treatment.

Statistical Analyses

Statistical analyses were performed using Stata 9.2 (Stata Corp., College Station, USA). Quantitative data were expressed as mean $\pm$ standard deviation or as median and interquartile range. We conducted multiple linear regressions using (1) systolic blood pressure, (2) fasting blood glucose, and (3) fasting serum cholesterol levels as the dependent variables. For all traits, the values of the dependent variables and the residuals of the regression models were approximately normally distributed. For age- and sex-adjusted models we used F tests to compare adjusted means between groups. For full models, age, sex, education level, smoking status, alcohol consumption, weight, height, and treatment (coded as 0/1

for the absence/presence of current antihypertensive drugs for hypertension, lipid lowering drugs for hypercholesterolemia, and antidiabetic drugs for diabetes) were added as covariates in the models. We conducted regression diagnostics to assess non-linearity and heteroscedasticity. We tested for collinearity using the 'collin' function in Stata. We did not systematically test all two-way interactions but conducted separate analyses by sex. In addition, we assessed whether any of the family history was associated with systolic and diastolic blood pressure, fasting glucose, and total cholesterol using multiple linear regressions (e.g., whether a positive family history of hypertension was associated with higher fasting blood glucose, etc.). To assess the influence of outlier observations, we conducted sensitivity analyzes using continuous traits winsorized at percentiles 1 and 99 (i.e., replacing values lying away from percentiles 1 or 99 by percentiles 1 or 99, respectively). Family history of cardiovascular risk factors in siblings was considered as 'don't know' when the history of at least one sibling was unknown. We also conducted separate analyses for men and women, for treated and untreated subjects, and used a definition for a family history of hypertension that took into account the age of diagnosis of hypertension in the parent. After excluding 'don't know' responses, we conducted multiple logistic regressions adjusted for age, sex, educational level, BMI, smoking, and alcohol consumption to measure the association between a positive family history and the risk of the corresponding dichotomized risk factor. We also conducted these latter analyses using the combined negative and 'don't know' responses as a reference group. We also estimated the ability of family history (1) to discriminate the dichotomized risk factor using area under the curve (AUC), (2) to calibrate the risk factor using the Hosmer-Lemeshow test, and (3) to reclassify the dichotomized risk factor using the net reclassification index [20]. Separate linear and logistic regression analyses including only participants who were unaware of their own disease status (i.e., hypertension, diabetes, and/or hypercholesterolemia) were also conducted. After excluding 'don't know' responses, we also calculated the sensitivity, specificity, and positive and negative predictive values of the family history to predict the corresponding disease in participants, including exact binomial confidence intervals.

Results

Participants' Characteristics

Participants' characteristics are listed in table 1. Differences between men and women were statistically significant for all variables except for total cholesterol levels ($p = 0.09$) and personal history of stroke ($p = 0.10$). Women had lower education levels and were less frequently treated for hypertension, diabetes, and/or dyslipidemia than men. Men had higher levels of systolic and diastolic blood pressure, fasting blood glucose and triglyceride, and a lower HDL-cholesterol level than women, whereas total cholesterol levels were similar in men and women. The prevalence of hypertension, diabetes, and hypercholesterolemia (1st and 2nd definitions, see Subjects and Methods) was 35.7%, 6.2%, 33.8%, and 22.9%, respectively.

Prevalence of Positive and Unreported ('Don't Know') Family History

36% of the fathers and 56% of the mothers of the participants were reported to be alive at the time of the interview. The prevalence of a positive family history (father, mother, and/or siblings) was 39.6% for hypertension, 22.3% for diabetes, and 29.0% for hypercholesterolemia. The prevalence of a positive paternal, maternal, and sibling history was 16.5%, 23.9%, and 12.9% for hypertension, 9.0%, 10.5%, and 6.5% for diabetes, and 13.9%, 12.7%, and 10.0% for hypercholesterolemia, respectively (table 2). The prevalence of 'don't know' responses for at least one family member was 41.8% for hypertension, 14.4% for diabetes, and 50.2% for hypercholesterolemia. The paternal, maternal, and sibling history was reported not to be known by 30.3%, 19.1%, and 16.5% of the participants for hypertension, 8.7%, 4.5%, and 5.7% for diabetes, and 38.2%, 29.6%, and 22.0% for hypercholesterolemia, respectively (table 2).

Association of a Positive Family History with Corresponding Cardiovascular Risk Factors

Age- and sex-adjusted systolic blood pressure was higher in participants with a positive family history of hypertension than in participants with a negative or unreported history. Similar observations were made for fasting blood glucose and family history of diabetes, as well as for fasting total cholesterol levels and family history of hypercholesterolemia (table 2). Results were similar for diastolic blood pressure (data not shown). In multiple linear regressions adjusting for age, sex, treatment, BMI, educational level, smoking, and alcohol consumption a positive family history was also independently associated with the corresponding trait (i.e., blood pressure, fasting blood glucose, and cholesterol) (data not shown). The systematic associations of a positive family history with increased cardiovascular risk factor were specific to the corresponding trait (i.e., family history of hypertension was associated with increased blood pressure but not with increased fasting blood glucose or cholesterol).

Association of Unreported Family History with Corresponding Cardiovascular Risk Factors

Participants unable to report on their family history (father, mother, or siblings) of hypertension had a higher systolic blood pressure than those with a negative history (table 2). The same association was observed for fasting glucose levels and a missing history of diabetes, although it did not reach statistical significance in siblings. Par-

Table 1. Participants' characteristics overall and by sex

	Total (n = 6,102)	Men (n = 2,903)	Women (n = 3,199)
Age (years)	53.0 ± 10.9	52.6 ± 10.9	53.5 ± 10.7
Education level (%)			
Less than high school	20.7	17.4	23.8
Apprenticeship	36.9	37.9	36.0
High school /GED	23.8	22.7	24.8
More than high school	18.5	22.0	15.4
Antihypertensive treatment (%)	18.1	19.9	16.5
Antidiabetic treatment (%)	3.7	5.5	2.0
Lipid lowering treatment (%)	11.5	14.2	9.0
Current smoker (%)	26.7	29.1	24.9
Daily alcohol drinker (%)	25.4	36.0	15.7
Weight (kg)	73.6 ± 15.0	81.5 ± 13.2	66.4 ± 12.8
Height (cm)	168.6 ± 9.3	175.0 ± 7.3	162.8 ± 6.7
Body mass index (kg/m^2)	25.8 ± 4.5	26.6 ± 4.0	25.1 ± 4.8
Hypertension (%)	35.7	42.0	30.1
Diabetes (%)	6.2	9.3	8.1
Hypercholesterolemia 1 (%)[a]	33.8	35.1	32.6
Hypercholesterolemia 2 (%)[b]	22.9	26.9	19.4
SBP (mm Hg)	128.2 ± 17.9	132.1 ± 16.6	124.7 ± 18.3
DBP (mm Hg)	79.3 ± 10.8	81.3 ± 10.7	77.5 ± 10.6
Glucose (mg/dl)	99.9 ± 20.5	104.0 ± 21.8	96.1 ± 18.4
Total cholesterol (mg/dl)	218.0 ± 40.2	216.8 ± 40.6	218.8 ± 39.8
HDL-cholesterol (mg/dl)	63.6 ± 17.2	56.2 ± 14.0	70.6 ± 16.8
Triglycerides (mg/dl)	123.7 ± 105.0	147.7 ± 136.2	103.2 ± 57.9
Personal history			
Acute myocardial infarction (n)	97	75	22
Stroke (n)	70	39	31

Data are means ± SD, unless stated otherwise. Differences between men and women were statistically significant for all variables except for total cholesterol levels (p = 0.09) and personal history of stroke (p = 0.10). SBP = Systolic blood pressure; DBP = diastolic blood pressure

[a] Hypercholesterolemia was defined as a fasting blood cholesterol ≥242 mg/dl or under lipid lowering treatment.

[b] Hypercholesterolemia was defined as a fasting LDL-cholesterol ≥161 mg/dl or ≥101 mg/dl in participants at high risk of cardiovascular diseases (i.e., a history of myocardial infarction, stroke, coronary artery disease, or diabetes) or under lipid lowering treatment.

ticipants with an unreported family history of hypercholesterolemia had cholesterol levels similar to those of participants with a negative family history.

Association of the Number of Positive Family Histories with Cardiovascular Risk Factors

After adjusting for age, sex, educational level, BMI, smoking, alcohol consumption, and treatment, mean systolic blood pressure, fasting glucose, and cholesterol levels linearly increased with an increasing number of first-degree relatives with a positive history of hypertension, diabetes, or hypercholesterolemia, respectively (fig. 1). The three risk factors were significantly higher with every added positive family history ($p < 0.001$). Participants who did not know their family history (n = 2,917) were excluded from these analyses in order to compare positive with negative responses only.

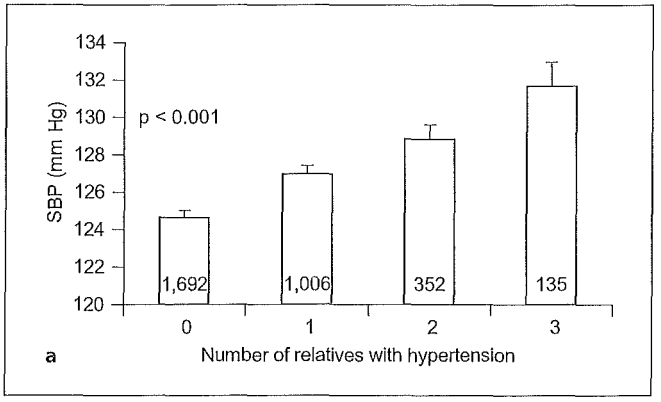
Association of the Number of Unreported Family Histories with Continuous Cardiovascular Risk Factors

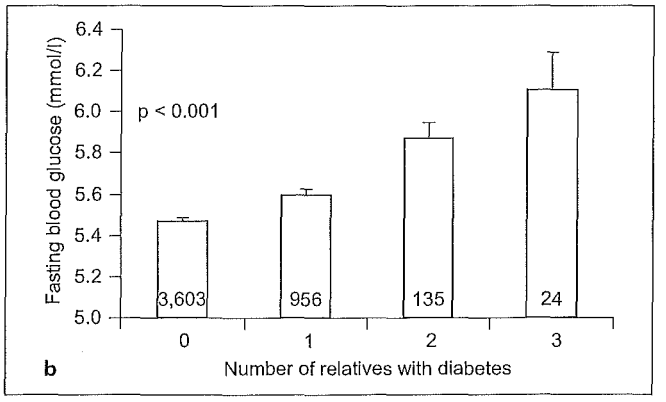
The same approach was used to determine differences in mean systolic blood pressure, glucose, and cholesterol level when considering the number of 'don't know' re-

Table 2. Age- and sex-adjusted systolic blood pressure, fasting glucose, and total cholesterol levels by family history status

	Father			Mother			Siblings		
	no	don't know	yes	no	don't know	yes	no	don't know	yes
History of hypertension									
n (%)	3,250 (53.3)	1,848 (30.3)	1,004 (16.5)	3,479 (57.0)	1,167 (19.1)	1,456 (23.9)	3,825 (70.5)	897 (16.5)	702 (12.9)
Age (years)	52.0 ± 0.2	56.1 ± 0.2[a]	50.7 ± 0.3[b, c]	52.0 ± 0.2	57.2 ± 0.2[a]	52.3 ± 0.3[c]	51.1 ± 0.2	56.5 ± 0.3[a]	57.4 ± 0.4[b]
SBP (mm Hg)	127.1 ± 0.3	128.8 ± 0.4[a]	131.0 ± 0.5[b, c]	127.0 ± 0.3	129.1 ± 0.5[a]	130.6 ± 0.4[b, c]	127.1 ± 0.3	129.1 ± 0.5[a]	132.4 ± 0.6[b, c]
Glucose (mmol/l)	5.52 ± 0.02	5.60 ± 0.03[a]	5.50 ± 0.03	5.52 ± 0.02	5.61 ± 0.03[a]	5.56 ± 0.03	5.53 ± 0.02	5.57 ± 0.04	5.59 ± 0.04
Cholesterol (mmol/l)	5.59 ± 0.02	5.60 ± 0.02	5.54 ± 0.03	5.57 ± 0.02	5.60 ± 0.03	5.60 ± 0.3	5.58 ± 0.02	5.60 ± 0.03	5.50 ± 0.04[c]
History of diabetes									
n (%)	5,025 (82.4)	530 (8.7)	547 (9.0)	5,189 (85.0)	275 (4.5)	638 (10.5)	4,763 (87.8)	308 (5.7)	353 (6.5)
Age (years)	52.9 ± 0.2	56.9 ± 0.5[a]	50.5 ± 0.5[b, c]	52.7 ± 0.1	58.2 ± 0.6[a]	53.7 ± 0.4[b, c]	52.1 ± 0.2	57.6 ± 0.6[a]	58.3 ± 0.6[b]
SBP (mm Hg)	128.1 ± 0.2	129.3 ± 0.7	128.7 ± 0.7	128.0 ± 0.2	130.0 ± 0.9[a]	129.2 ± 0.6	127.8 ± 0.2	130.0 ± 0.9[a]	130.0 ± 0.8[b]
Glucose (mmol/l)	5.51 ± 0.02	5.68 ± 0.05[a]	5.76 ± 0.05[b]	5.50 ± 0.02	5.65 ± 0.07[a]	5.86 ± 0.04[b, c]	5.50 ± 0.02	5.61 ± 0.06	6.06 ± 0.06[b, c]
Cholesterol (mmol/l)	5.59 ± 0.01	5.59 ± 0.04	5.55 ± 0.04	5.59 ± 0.01	5.47 ± 0.06	5.63 ± 0.04[c]	5.57 ± 0.01	5.49 ± 0.06	5.63 ± 0.05
History of hypercholesterolemia									
n (%)	2,924 (47.9)	2,329 (38.2)	849 (13.9)	3,524 (57.8)	1,804 (29.6)	774 (12.7)	3,684 (67.9)	1,195 (22.0)	545 (10.0)
Age (years)	52.3 ± 0.2	55.9 ± 0.2[a]	47.6 ± 0.4[b, c]	52.2 ± 0.2	56.1 ± 0.2[a]	49.4 ± 0.4[b, c]	51.3 ± 0.2	56.5 ± 0.3[a]	55.0 ± 0.4[b, c]
SBP (mm Hg)	127.6 ± 0.3	128.8 ± 0.3[a]	129.1 ± 0.5[b]	127.7 ± 0.3	129.3 ± 0.4[a]	128.4 ± 0.6	127.7 ± 0.3	129.5 ± 0.5[a]	128.1 ± 0.7
Glucose (mmol/l)	5.54 ± 0.02	5.56 ± 0.02	5.55 ± 0.04	5.52 ± 0.02	5.58 ± 0.03	5.62 ± 0.04[b]	5.53 ± 0.02	5.58 ± 0.03	5.60 ± 0.05
Cholesterol (mmol/l)	5.56 ± 0.02	5.57 ± 0.02	5.72 ± 0.04[b, c]	5.56 ± 0.02	5.59 ± 0.02	5.68 ± 0.04[b, c]	5.55 ± 0.02	5.57 ± 0.03	5.74 ± 0.04[b, c]

Data are means ± SE. SBP = Systolic blood pressure.
[a] $p < 0.05$ for the difference between 'don't know' and 'no' responses.
[b] $p < 0.05$ for the difference between 'yes' and 'no' responses.
[c] $p < 0.05$ for the difference between 'yes' and 'don't know' responses.





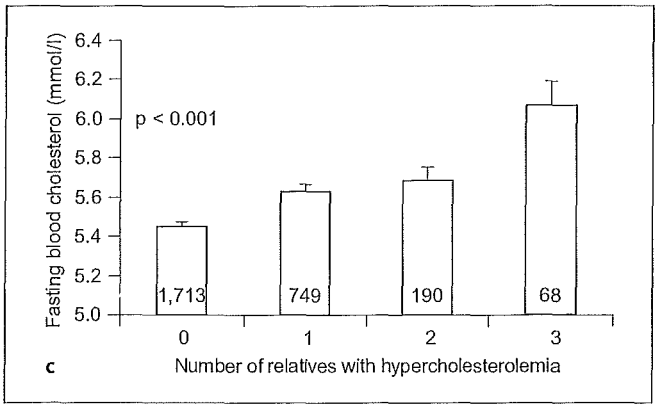


Fig. 1. Quantitative relationships between the number of relatives with a positive history of hypertension (**a**), diabetes (**b**), and hypercholesterolemia (**c**) and the corresponding underlying trait. Traits are adjusted for age, sex, BMI, alcohol consumption, smoking, treatment, and education level. 'Don't know' responses were excluded.

Table 3. Risk of hypertension, diabetes, or hypercholesterolemia associated with a positive family history

	Unadjusted		Age- and sex-adjusted		Fully adjusted 1		Fully adjusted 2	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Hypertension (n)	(3,196)		(3,196)		(3,185)		(5,424)	
Father history	1.41	1.19–1.68	1.91	1.58–2.33	2.16	1.75–2.66	1.61	1.30–2.02
Mother history	1.63	1.39–1.93	2.12	1.76–2.55	2.10	1.72–2.55	1.45	1.19–1.76
Sibling history	3.38	2.76–4.14	2.85	2.28–3.56	2.73	2.15–3.47	1.54	1.20–1.97
Number of relatives								
0	1.00		1.00		1.00		1.00	
1	1.37	1.15–1.62	1.79	1.48–2.18	1.94	1.58–2.39	1.40	1.16–1.68
2	2.25	1.77–2.85	2.98	2.28–3.90	3.08	2.31–4.10	1.51	1.10–2.07
3	5.79	3.99–8.40	6.92	4.58–10.46	6.79	4.40–10.49	2.95	1.83–4.79
Diabetes (n)	(4,722)		(4,722)		(4,718)		(5,424)	
Father history	2.14	1.51–3.02	2.77	1.93–3.98	2.80	1.91–4.10	2.03	1.40–2.94
Mother history	2.68	1.95–3.67	2.85	2.05–3.97	2.70	1.90–3.83	2.63	1.93–3.58
Sibling history	4.59	3.28–6.41	4.00	2.81–5.70	3.34	2.29–4.85	2.83	2.01–3.97
Number of relatives								
0	1.00		1.00		1.00		1.00	
1	2.74	2.05–3.65	3.01	2.23–4.07	2.95	2.16–4.05	2.45	1.86–3.23
2	5.30	3.22–8.74	5.36	3.15–9.12	3.92	2.23–6.90	3.09	1.84–5.18
3	17.26	7.41–40.24	20.25	8.37–48.98	18.22	7.26–45.73	17.06	7.69–37.86
Hypercholesterolemia (n)	(2,727)		(2,727)		(2,720)		(5,424)	
Father history	1.20	0.99–1.46	1.80	1.45–2.22	1.93	1.55–2.40	1.51	1.24–1.84
Mother history	1.08	0.86–1.34	1.40	1.11–1.77	1.39	1.10–1.77	1.16	0.94–1.43
Sibling history	2.12	1.66–2.72	2.11	1.62–2.74	1.96	1.50–2.56	1.42	1.14–1.78
Number of relatives								
0	1.00		1.00		1.00		1.00	
1	1.13	0.94–1.36	1.59	1.30–1.96	1.66	1.35–2.05	1.27	1.18–1.51
2	1.39	1.01–1.91	1.98	1.41–2.76	1.92	1.36–2.70	1.54	1.13–2.09
3	3.73	2.78–6.12	5.06	3.02–8.50	4.97	2.92–8.45	2.77	1.66–4.64

OR = Odds ratio; 95% CI = 95% confidence interval.

Data are results from multiple logistic regression models using either negative histories (fully adjusted 1) or negative and 'don't know' histories (fully adjusted 2, n = 5,424) as the reference group. Fully adjusted models included the use of age, sex, education level, body mass index, smoking, and alcohol consumption as covariates.

sponses, using the same multivariable adjustment (fig. 2). Positive responses were excluded in order to compare negative with 'don't know' responses only, reducing the sample size to 3,803 participants. Systolic blood pressure was higher with every additional 'don't know' response, with statistically significant ($p < 0.05$) differences between 0 and 2, and 0 and 3 unreported histories. No such association was found with the other risk factors.

Association of a Positive Family History with the Risk of the Dichotomized Cardiovascular Risk Factors

A positive history of hypertension in the father, the mother, or siblings increased the risk of hypertension by approximately 50% in fully adjusted models (table 3). With a corresponding family history, the risk of diabetes increased by about 150%. By contrast, a maternal history of hypercholesterolemia was not associated with increased risk of hypercholesterolemia in the subject. Using an alternate definition of hypercholesterolemia by taking only LDL-cholesterol values into account did not change those results significantly but tended to weaken the associations between family history and hypercholesterolemia. There was a trend toward increased risk of hypertension, diabetes, and hypercholesterolemia with an increasing number of first-degree relatives with a positive history. This trend was the strongest for diabetes. For each trait, the odds ratios were not attenuated and sometimes strengthened with the fully adjusted model. Asso-

Table 4. Sensitivity, specificity, and predictive values of family history for the risk of the corresponding disease

	n	'Don't know' responses	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV, % (95% CI)	NPV, % (95% CI)
Hypertension						
Father history	4,244	excluded	33.4 (30.5–36.3)	79.5 (78.1–80.9)	34.8 (31.8–37.8)	78.5 (77.0–79.9)
	6,084	included	21.8 (19.8–23.9)	85.4 (84.3–86.4)	34.8 (31.8–37.8)	75.3 (74.1–76.5)
Mother history	4,921	excluded	40.8 (38.1–43.6)	74.3 (72.9–75.8)	35.1 (32.7–37.6)	78.7 (77.3–80.0)
	6,084	included	31.8 (29.5–34.2)	79.0 (77.8–80.2)	35.1 (32.7–37.6)	76.4 (75.2–77.6)
Sibling history	4,514	excluded	31.3 (28.6–34.2)	89.7 (88.7–90.7)	50.4 (46.6–54.1)	79.7 (78.4–81.0)
	5,409	included	24.9 (22.7–27.2)	91.3 (90.4–92.1)	50.4 (46.6–54.1)	77.4 (76.2–78.6)
Diabetes						
Father history	5,458	excluded	16.8 (12.3–22.1)	90.4 (89.6–91.2)	7.6 (5.5–10.2)	95.9 (95.3–96.4)
	5,967	included	13.5 (9.9–17.8)	91.2 (90.4–91.9)	7.6 (5.5–10.2)	95.2 (94.5–95.7)
Mother history	5,711	excluded	24.5 (19.5–30.0)	89.7 (88.8–90.5)	10.7 (8.4–13.3)	95.9 (95.3–96.5)
	5,967	included	22.0 (17.5–27.1)	90.1 (89.3–90.8)	10.7 (8.4–13.3)	95.6 (95.0–96.1)
Sibling history	5,011	excluded	25.6 (20.2–31.7)	94.0 (93.2–94.6)	17.2 (13.4–21.6)	96.3 (95.7–96.8)
	5,310	included	22.4 (17.5–27.9)	94.3 (93.6–94.9)	17.2 (13.4–21.6)	95.8 (95.2–96.3)
Hypercholesterolemia						
Father history	3,631	excluded	29.4 (26.3–32.8)	79.7 (78.2–81.2)	28.6 (25.5–31.8)	80.4 (78.9–81.8)
	5,798	included	15.9 (14.1–17.9)	86.7 (85.7–87.7)	28.6 (25.5–31.8)	75.5 (74.5–76.7)
Mother history	4,130	excluded	26.5 (23.7–29.5)	84.6 (83.3–85.8)	33.7 (30.3–37.3)	79.6 (78.2–80.9)
	5,798	included	17.2 (15.3–19.3)	88.7 (87.7–89.6)	33.7 (30.3–37.3)	76.2 (75.0–77.4)
Sibling history	4,019	excluded	23.8 (21.1–26.7)	90.1 (89.0–91.1)	41.4 (37.2–45.8)	80.0 (78.7–81.3)
	5,154	included	17.1 (15.1–19.3)	92.1 (91.2–92.9)	41.4 (37.2–45.8)	77.1 (75.9–78.3)

'Don't know' responses were either excluded or coded as negative responses (included) in the analyses.
95% CI = 95% confidence intervals calculated using an exact binomial distribution; PPV = positive predictive value; NPV = negative predictive value.

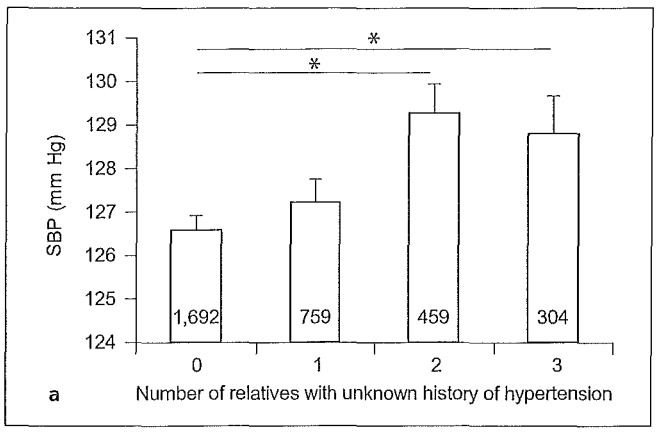
ciations obtained using the combination of negative and 'don't know' histories as the reference group were substantially weaker than those excluding 'don't know' responses (last column of table 3).

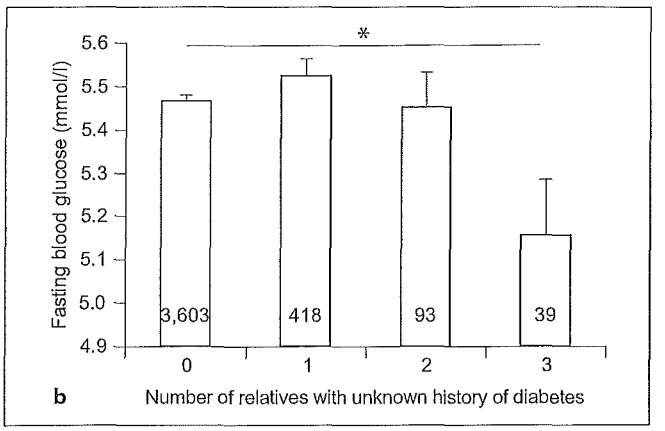
Ability of Family History to Predict the Risk of the Corresponding Disease

For hypertension, diabetes, and hypercholesterolemia, a negative sibling history was more specific to exclude the presence of the underlying disease in the participant than either paternal or maternal history (table 4). Analogously, a positive sibling history was better in predicting disease in the participant than either paternal or maternal histories. The positive predictive value was highest for the family history of hypertension, in particular for sibling history, and lowest for the family history of diabetes. Combining 'don't know' with negative responses resulted in lower sensitivities and higher specificities of family history to predict the corresponding disease whereas it did not alter positive predictive values and only slightly modified negative predictive values.

Ability of Family History to Discriminate, Calibrate, and Reclassify the Dichotomized Cardiovascular Risk Factors

The inclusion of family history of hypertension, diabetes, or hypercholesterolemia in a model including only age and sex as covariates always significantly improved the AUCs to predict the corresponding dichotomized risk factor for hypertension and diabetes, except for the mother's history of hypercholesterolemia (table 5). Taking 'don't know' responses into account always led to similar or better AUCs than considering 'don't know' as negative responses. The calibration of the models including family history were not always good as reflected by low Hosmer-Lemeshow p values (table 5), in particular for the family history of hypercholesterolemia. Adding family history to age and sex led to improved reclassification of hypertension status, whether or not 'don't know' responses were included in the models (table 5). This was only observed for sibling and overall family history for hypercholesterolemia. Family history of diabetes had little to no ability to reclassify diabetes status.





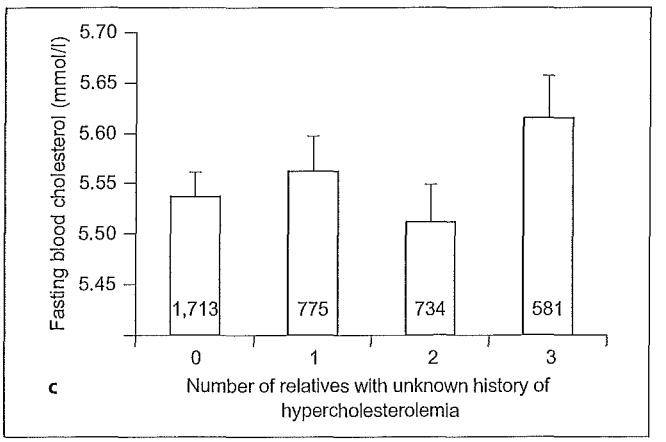


Fig. 2. Quantitative relationships between the number of relatives with unknown history of hypertension (**a**), diabetes (**b**), and hypercholesterolemia (**c**) and the corresponding underlying trait. Traits are adjusted for age, sex, BMI, alcohol consumption, smoking, treatment, and education level. Positive responses were excluded. *Statistically significant ($p < 0.05$) differences between 0 and 2 and between 0 and 3 unreported histories.

Sensitivity Analyses

Analyses conducted using winsorized continuous phenotypes led to similar results, i.e., differing by 50% or less of a standard error for systolic blood pressure and cholesterol and by 17–183% of a standard error for fasting glucose without changing our conclusions. Results were similar when analyses were stratified by sex or treatment status or when a family history of hypertension was considered as positive only if hypertension was reported to have been diagnosed before the age of 60 years. We conducted the same analyses in the subgroups of participants who were unaware of having a specific condition [hypertension (n = 4,481), diabetes (n = 5,663), and/or hypercholesterolemia (n = 4,346)], as these participants would represent the target population for selected screening. Among the participants unaware of being affected, the associations between family history and the corresponding trait were in the same direction as those observed in the entire sample but were weaker. Subjects with a positive family history had higher levels of the corresponding trait than those with a negative history (systolic blood pressure with and without paternal history of hypertension was 124.8 ± 0.4 mm Hg vs. 123.1 ± 0.3 mm Hg, $p < 0.05$, whereas with or without maternal history of hypertension it was 125.3 ± 0.5 mm Hg vs. 122.9 ± 0.3 mm Hg, $p < 0.05$). The associations were statistically significant ($p < 0.05$), except for those with a positive paternal history of hypercholesterolemia. Participants who were unaware of their family history of hypertension had higher systolic blood pressure levels than those who reported a negative family history, but this was only statistically significant for paternal (124.8 ± 0.4 mm Hg vs. 123.1 ± 0.3 mm Hg, $p < 0.05$) and maternal (125.3 ± 0.5 mm Hg vs. 122.9 ± 0.3 mm Hg, $p < 0.05$) histories. Similar conclusions can be made for the associations between family history and the risk of disease (hypertension, diabetes, hypercholesterolemia) in participants who were unaware of being affected (with or without excluding 'don't know' responses). In order to asses a recall bias concerning family history of cardiovascular risk factors, we conducted

Table 5. Discrimination, calibration, and reclassification ability of family history to predict the risk of hypertension, diabetes, or hypercholesterolemia

	Including DK responses		Coding DK responses as 'no'		Comparison	
Hypertension						
Discrimination and calibration	AUC	HL p value	AUC	HL p value	p value[b]	
Age, sex	0.763	0.26	0.763			
+ father history	0.769[a]	0.21	0.768[a]	0.27	0.27	
+ mother history	0.772[a]	0.44	0.772[a]	0.50	0.50	
+ sibling history	0.774[a]	0.05	0.773[a]	0.22	0.22	
+ parents and sibling history	0.783[a]	0.13	0.781[a]	0.07	0.07	
Reclassification						
Full model	NRI	p value	NRI	p value	NRI[c]	p value[c]
+ father history	0.016	0.03	0.013	0.03	0.002	0.65
+ mother history	0.029	0.0003	0.023	0.005	0.007	0.11
+ sibling history	0.024	0.006	0.018	0.03	0.006	0.16
+ parents and sibling history	0.047	<0.0001	0.040	<0.0001	0.005	0.39
Diabetes						
Discrimination and calibration	AUC	HL p value	AUC	HL p value	p value[b]	
Age, sex	0.755	0.20	0.755	0.20		
+ father history	0.766[a]	0.13	0.758	0.13	0.04	
+ mother history	0.774[a]	0.15	0.772[a]	0.03	0.32	
+ sibling history	0.779[a]	0.04	0.776[a]	0.003	0.26	
+ parents and sibling history	0.798[a]	0.07	0.790[a]	0.04	0.02	
Reclassification						
Full model	NRI	p value	NRI	p value	NRI[c]	p value[c]
+ father history	0		0			
+ mother history	0		0			
+ sibling history	0.002	0.59	0.002	0.59		
+ parents and sibling history	0.009	0.12	0.008	0.15		
Hypercholesterolemia						
Discrimination and calibration	AUC	HL p value	AUC	HL p value	p value[b]	
Age, sex	0.687	<0.0001	0.687	<0.0001		
+ father history	0.692[a]	<0.0001	0.691	<0.0001	0.32	
+ mother history	0.689	<0.0001	0.688	<0.0001	0.34	
+ sibling history	0.695[a]	<0.0001	0.694[a]	<0.0001	0.49	
+ parents and sibling history	0.698[a]	0.0001	0.698[a]	0.0005	0.37	
Reclassification						
Full model	NRI	p value	NRI	p value	NRI[c]	p value[c]
+ father history	0.005	0.34	0.007	0.16	−0.001	0.78
+ mother history	0.010	0.06	0.004	0.44	0.006	0.09
+ sibling history	0.018	0.02	0.015	0.05	0.004	0.44
+ parents and sibling history	0.029	0.001	0.021	0.01	0.008	0.11

DK = 'Don't know' response; AUC = area under the curve (test of discrimination); HL p value = p value from a Hosmer-Lemeshow goodness of fit test of calibration; NRI = net reclassification index.

For reclassification a full model including family history was compared to a reduced model including only age and sex.

[a] $p < 0.05$ for the comparison of the AUC including family history and the AUC including only age and sex as covariates.

[b] p value for the comparison of AUC including 'don't know' responses as a separate category versus considered them as negative responses.

[c] NRI and p value for the comparison of including 'don't know' responses as a separate category versus considering them as negative responses.

sensitivity analyses in which an interaction term between family history and a reported cardiovascular event (either stroke or acute myocardial infarction) in the father or in the mother was added. None of the interaction terms was significant, which suggests that the risk of dichotomized phenotype (i.e., hypertension, diabetes, hypercholesterolemia) associated with corresponding parental history did not significantly differ according to the presence or absence of reported cardiovascular events in the parents.

Discussion

We found that a positive family history of hypertension, diabetes, and hypercholesterolemia was strongly associated with higher levels of blood pressure, fasting glucose, and cholesterol, respectively. These associations were 'dose-dependent' in that the larger the number of affected first-degree relatives, the higher the corresponding trait. Most studies on the family history of these phenotypes have reported the associated risk of hypertension, diabetes, or hypercholesterolemia, but few have analyzed the independent effect size of a positive family history on the continuous underlying phenotype. From a standpoint of preventive medicine, our results suggest that family histories of hypertension, diabetes, and hypercholesterolemia should be used as a tool to detect subjects at high cardiovascular risk in the general adult population, increasing the effectiveness of screening in the general population [21].

Tozawa et al. [22] also found a significant linear relationship between the number of first-degree relatives with a positive family history of hypertension and the participant's blood pressure level. Wada et al. [3] reported a similar relationship for diabetes and hyperglycemia but not for high blood pressure and dyslipidemia. This discrepancy with our results and those of Tozawa et al. [22] may come from the facts that (1) Wada et al. [3] did not consider separately 'don't know' and negative answers for the family histories and (2) the sample population size was smaller, with lower BMI and younger age. Our results confirm those obtained by Lauer et al. [10] who found significantly higher total cholesterol levels in young adults with a positive family history of high cholesterol as compared to those with a negative history. Our results are also consistent with results of prospective studies showing that parental blood pressure levels predict those in the offspring [4, 23], that parental hypercholesterolemia predicts elevated total cholesterol levels in the offspring [24], or that a positive family history of diabetes predicts the incidence of impaired glucose tolerance and diabetes during follow-up [25–27].

Few population-based studies have analyzed the sibling history of hypertension [3, 22], diabetes [3], and/or hypercholesterolemia [3]. In the present study, sibling history was as strongly associated with the risk of the corresponding dichotomized phenotype and with the underlying continuous phenotype as were the parental histories. Furthermore, the contribution of sibling history was independent of that of parental histories. In the Framingham Offspring study, sibling history of cardiovascular disease was more strongly associated with increased risk of incident cardiovascular disease during follow-up than parental history of cardiovascular disease [28]. We found sibling histories to have higher positive predictive values than either paternal or maternal histories in predicting the risk of the underlying dichotomized phenotype. We found large differences in risk observed between the unadjusted and fully adjusted models for sibling history for each trait, which underlines the key role of confounding factors (e.g., age and educational level) when analyzing the risk associated with a positive sibling history. Our data suggest that screening programs focused only on sibling family history may be more efficient than those taking paternal and maternal histories into account, and such programs should therefore be further evaluated.

Participants were unable to report on their family history of hypertension (41.8%) or hypercholesterolemia (50.2%) much more frequently than on their family history of diabetes (14.4%). Thorand et al. [15] found a higher prevalence of 'don't know' responses for maternal (8.8%) and paternal history (17.3%) of diabetes than we did (4.5% and 8.7%, respectively). In our study, 'don't know' responses were strongly associated with parent's gender, older age, and lower education level of the participants. The increase in the prevalence of 'don't know' responses with age [15, 16], the role of the education level [16], and the higher prevalence of 'don't know' responses for paternal as compared to maternal histories [15, 16, 29] have been previously reported.

In the present study, unreported family history of hypertension was associated with higher systolic blood pressure levels, even after adjustment for age, educational level, and other potential confounders. This was not true for the family history of diabetes and hypercholesterolemia. To our knowledge, this finding has never been described before. Also, we found that including 'don't know' responses in the models usually led to better dis-

crimination, but without significantly improving the ability to reclassify participants as having the dichotomized phenotype. Our results show that 'don't know' responses and negative family history of hypertension should be analyzed separately. Subjects who are unable to report on their family history of hypertension have a cardiovascular risk profile that matches more closely those with a positive family history than those with a negative family history. A potential explanation is that 'hypertension' is less clearly perceived as a disease than diabetes. Given the high prevalence of hypertension (36%), the 'don't know' responses will inevitably encompass many positive histories. Family history of hypercholesterolemia shares many common features with high blood pressure (high prevalence and high proportion of 'don't know' responses) and lies somewhere between hypertension and diabetes.

Another reason to separately consider 'don't know' responses is illustrated by the family history of diabetes. Whenever 'don't know' responses are ignored (i.e., classified as negative responses), the maternal history of diabetes is about twice as common as the paternal history [30–33]; by contrast, studies that took 'don't know' responses into account, such as this study, found a much lower difference between maternal and paternal history of diabetes [15, 16]. Failure to account for 'don't know' responses creates a reporting bias that leads to an overestimation of excess maternal transmission of diabetes [15, 16].

This study suffers from some limitations. First, it is cross-sectional, and we cannot show to what extent family history predicts longitudinal changes in cardiovascular risk factors and future cardiovascular risk. Second, we rely on self-reported family history, which is subject to misclassification. The estimate of the prevalence of hypertension among fathers was very low, which suggests that hypertension in fathers was underestimated. This further underlines the usefulness of sibling history. Also, we did not provide a definition for family history. However, family history of hypertension, diabetes, and hypercholesterolemia was found to be very accurate when validated against confirmed medical evidence [14]. Third, the less striking association between family history of hypercholesterolemia and elevated cholesterol levels can, at least partly, be explained by an overdiagnosis in this study because of the inclusion of treated patients in the group with elevated cholesterol levels. Many participants receiving lipid lowering drugs had lipid levels which would not qualify for our definition of dyslipidemia. Given the low prevalence of cardiovascular disease in the sample, our study was underpowered to analyze the associations of family history of cardiovascular risk factor with a personal history of cardiovascular events in the participants. Finally, our findings may not apply to non-Caucasians.

In the present study, a positive family history of hypertension, diabetes, and hypercholesterolemia was associated with clinically relevant effect sizes on the corresponding cardiovascular risk factor. These results confirm that family history, whenever known, is a simple, specific, inexpensive, and powerful tool to assess cardiovascular risk in the general population. The importance to consider what subjects know about the health of their first-degree relatives may rapidly increase with the growing availability of detailed genotypic information, such as to guide selective genetic testing in order to target preventive measures to high-risk individuals. Our results further suggest that 'don't know' responses do in fact contain information on the level of risk factor. This aspect should be carefully considered in future research focusing on the family history of cardiovascular risk factors.

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P. Vollenweider, G. Waeber, V. Mooser and F. Paccaud designed the study. P. Vollenweider collected the data. G. Wandeler and M. Bochud conducted the statistical analyses and drafted the paper. All authors critically revised the paper and approved its final version.

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