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Life-time risk factors and progression of carotid atherosclerosis in young adults: the Cardiovascular Risk in Young Finns study

Markus Juonala[1,4]*, Jorma S.A. Viikari[1], Mika Kähönen[5], Leena Taittonen[8], Tomi Laitinen[9], Nina Hutri-Kähönen[7], Terho Lehtimäki[6], Antti Jula[10], Matti Pietikäinen[11], Eero Jokinen[12], Risto Telama[14], Leena Räsänen[13], Vera Mikkilä[13], Hans Helenius[3], Mika Kivimäki[15], and Olli T. Raitakari[2,4]

[1]Department of Medicine; [2]Department of Clinical Physiology; [3]Department of Biostatistics and; [4]Research Centre of Applied and Preventive Cardiovascular Medicine, University of Turku and Turku University Central Hospital, PO Box 52, 20500 Turku, Finland; [5]Department of Clinical Physiology; [6]Department of Clinical Chemistry and; [7]Department of Pediatrics, University of Tampere and Tampere University Hospital, Tampere, Finland; [8]Department of Pediatrics, University of Oulu, Oulu, Finland; [9]Department of Clinical Physiology, University of Kuopio, Kuopio, Finland; [10]National Institute for Welfare and Health, Turku, Finland; [11]Center of Social and Health Services, City of Kuopio, Finland; [12]Hospital for Children and Adolescents and; [13]Department of Applied Chemistry and Microbiology, Division of Nutrition, University of Helsinki, Helsinki, Finland; [14]Department of Sport Sciences, University of Jyväskylä, Jyväskylä, Finland; and [15]Department of Epidemiology, University College London, London, UK

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Aims The aim of this study is to evaluate whether childhood risk factors are associated with a 6-year change in carotid intima-media thickness (IMT) in young adulthood independent of the current risk factors.

Methods and results The Cardiovascular Risk in Young Finns cohort consisted of 1809 subjects who were followed-up for 27 years since baseline (1980, age 3–18 years) and having carotid IMT measured both in 2001 and 2007. Cardiovascular risk factors were assessed repeatedly since childhood. A genotype risk score was calculated using 17 newly identified genetic variants associating with cardiovascular morbidity. The number of childhood risk factors (high LDL-cholesterol, low HDL-cholesterol, high blood pressure, obesity, diabetes, smoking, low physical activity, infrequent fruit consumption) was associated with a 6-year change in adulthood IMT. In subjects with 0, 1, 2, and $\geq$3 childhood risk factors, IMT [mean (95% CI)) increased by 35 (28–42), 46 (40–52), 49 (41–57), and 61 (49–73) μm ($P = 0.0001$). This association remained significant when adjusted for adulthood risk score and genotype score ($P = 0.007$). Of the individual childhood variables, infrequent fruit consumption ((β (95% CI) for 1-SD change $-5(-9$ to $-1)$, $P = 0.03$) and low physical activity ($-6(-10$ to $-2)$, $P = 0.01$) were associated with accelerated IMT progression after taking into account these variables assessed in adulthood.

Conclusion These findings indicate that children with risk factors have increased atherosclerosis progression rate in adulthood, and support the idea that the prevention of atherosclerosis by means of life style could be effective when initiated in childhood.

Keywords Cardiovascular • Childhood • Risk factors

Introduction

Atherosclerosis begins in childhood and may eventually lead to myocardial infarction or stroke. Carotid artery intima-media thickness (IMT) is a marker of preclinical atherosclerosis.[1] We[2,3] and others[4,5] have demonstrated that exposure to cardiovascular risk factors during childhood predicts increased IMT two decades later. However, the contribution of childhood risk factors to the progression of atherosclerosis during adulthood remains unknown. From a public health policy perspective, it would be important to establish whether adult risk factors reverse the effect of childhood risk factors or whether childhood risk factors

* Corresponding author. Tel: +358 407 507 969, Fax: +358 2 3337270, Email: mataju@utu.fi

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continue to predict the progression of atherosclerosis, independently of adulthood influences. Furthermore, the extent to which genetic predisposition affects these long-term associations is not known but has important implications on prevention.

To gain novel information on the effects of cardiovascular risk factors on preclinical atherosclerosis beyond prior reports,[2–6] the main aim of the analyses based on the Cardiovascular Risk in Young Finns study was to examine whether childhood risk factors are associated with IMT progression independent of current, adulthood risk factors. We also studied whether effects of coronary disease-related genetic variants, identified in genome-wide association studies,[7–18] contribute to these associations.

Methods

Subjects

The first cross-sectional survey was conducted in 1980, when 3596 subjects aged 3–18 years participated. They were randomly chosen from the national register. In childhood, follow-up studies were conducted in 1983 and 1986, with 2991 and 2779 participants, respectively. In adulthood, follow-up studies have been conducted in 2001 and 2007 with 2283 and 2204 participants, respectively. In these adulthood follow-ups, vascular ultrasound measurements of carotid IMT were performed. A total of 1809 subjects had IMT data both in 2001 and 2007, thus comprising the study cohort for this analysis (*Figure 1*). During the follow-up, 76 subjects have died, two of them due to atherosclerotic diseases. Subjects gave written informed consent and the study was approved by local ethics committees.

Risk variables

Height and weight were measured using a similar protocol in all study years. Body mass index (BMI) was calculated as weight, kg/(height, m)^2. Blood pressure was measured with a standard mercury sphygmomanometer in 1980 and 1983. In 1980, among 3-year-olds an ultrasound device was used. In 1986, 2001, and 2007, a random zero sphygmomanometer was used. The average of three measurements was always used in statistical analyses.

Venous blood samples were drawn after an overnight fast. Standard enzymatic methods were used for serum total cholesterol, triglycerides, and HDL-cholesterol. LDL-cholesterol concentration was calculated using Friedewald equation. Glucose concentrations were measured in study years 1986, 2001, and 2007. Details of methods have been described previously.[19]

Questionnaires using self-reports were performed to collect data on smoking, diabetes, dietary habits, physical activity, and parental history of coronary heart disease (CHD).[19,20] In childhood, smoking was assessed in subjects aged ≥12 years. Smoking data were collected in connection with the medical examination in a solitary room, where the participants could respond confidentially. Both in childhood and in adulthood, subjects smoking daily were considered smokers. The subjects who reported having a diabetes diagnosis by a physician were considered diabetics. In adulthood, also subjects with fasting glucose ≥7 mmol/l were classified as diabetics. Information on dietary habits was obtained with a non-quantitative food frequency questionnaire (FFQ). In 3–9-year-old subjects, data were requested from their parents. At the age of 12–18 years, study subjects answered the questions themselves, with the help of parents if needed. To examine the frequency of vegetables and fruit consumption, the subjects were asked to fill in a questionnaire on habitual dietary choices with six response categories: 1 = daily, 2 = almost every day, 3 = a couple of times per week, 4 = about once a week, 5 = a couple of times per month, 6 = more seldom. The response categories were converted into times of consumption per week (1, >9.5; 2, >6.3; 3, >3; 4, >1.2; 5, >0.3; 6, >0.1). In 2007, a more detailed FFQ providing an estimate of food consumption in grams per day was used. Subjects were also asked whether they use butter-based spreads on bread. The dietary variables chosen for this analysis are indicators of two major dietary patterns, health conscious, and traditional.[21] These patterns are stable over time[21] and associate with cardiovascular risk factors.[22] Physical activity index (range 5–15) was calculated by assessing the duration, intensity, and frequency of physical activity.[23] In childhood, these data were gathered at the age of 9–18 years, so that study

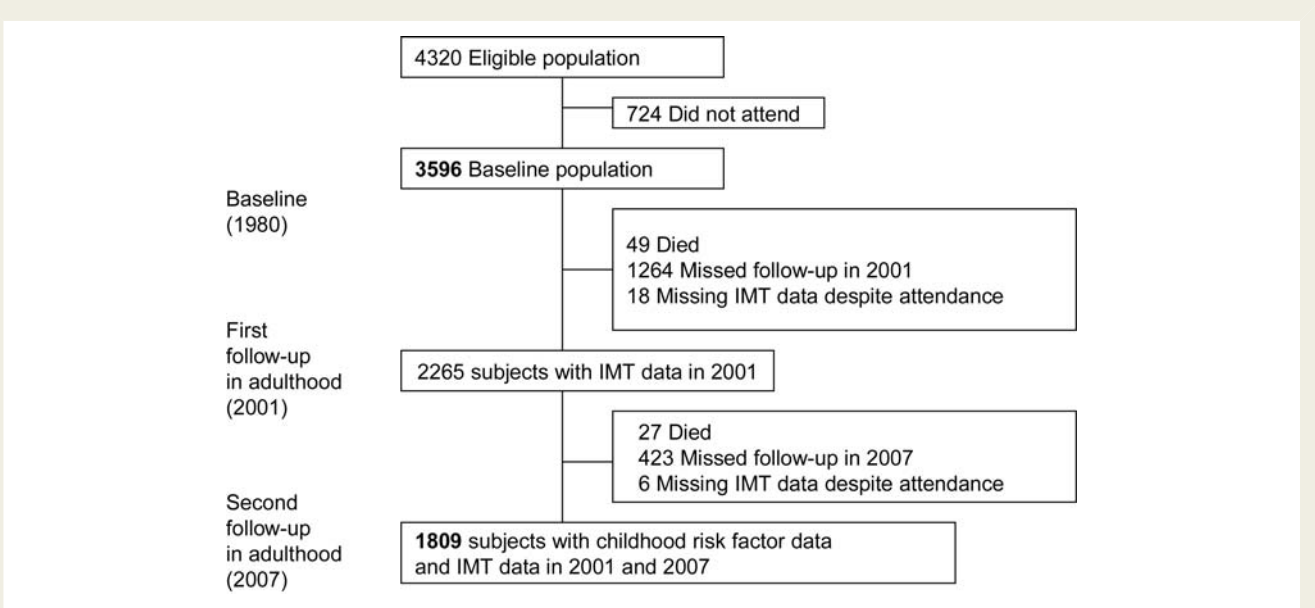

Figure 1 Study flow chart.

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subjects answered the questions themselves, but if needed parents helped them. Data on parental history of cardiovascular diseases were gathered in 2001 and 2007.[20]

Genotyping

Genomic DNA was extracted from peripheral blood leucocytes with a commercially available kit (Qiagen Inc., Valencia, CA, USA). DNA samples were genotyped as described previously.[19] In the present study, we have analysed 17 single nucleotide polymorphism (SNPs) that have been among the strongest signals in genome-wide association studies assessing genetic variants for CHD outcomes and serum lipids. The available SNPs with $P < 0.5 \times 10^{-6}$ for the association between SNP and the risk of CHD and/or $P < 0.5 \times 10^{-7}$ for the association between SNP and LDL- or HDL-cholesterol were analysed.[7–18] These SNPs included data on following genes/chromosomes: Proprotein convertase subtilisin/kexin type 9 (rs11591147), lipoprotein(a) (rs3798220), chromosome 9p21 (rs2383206, rs1333049, rs10757278, rs10757274), chromosome 16 (rs2549513), chromosome 2 (rs754523), lipoprotein lipase (rs328), proline/serine-rich coiled-coil 1 (rs599839), 3-hydroxy-3-methylglutaryl-coenzyme A reductase (rs12654264), apolipoprotein B (rs693), TBC1D7 (rs499818), ATP-binding cassette subfamily A member 1 (rs3890182), chromosome 2q36.3 (rs2943634), low-density lipoprotein receptor (rs6511720), hepatic lipase (rs1800588).

Carotid artery studies

Ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, CA, USA) with 13.0 MHz linear array transducers.[2] A similar scanning protocol was used in 2001 and 2007. Carotid IMT was measured on the posterior (far) wall of the left carotid artery. Atleast four measurements were taken ≈10 mm proximal to the bifurcation to derive mean carotid IMT. At this region, none of the subjects had plaques. The digitally stored scans were manually analysed by the same reader in 2001 and 2007 blinded to subjects' details. The between-visit coefficient of variation (CV) of IMT measurements was 6.4% and intra-observer CV was 3.4%.[2]

Statistical methods

To study the effects of risk variables on IMT, we calculated age- and sex-specific *z*-scores for each risk variable in each study year. The *z*-score values were used to take into account the possible biases caused by age, sex, secular trends in risk factors, and the few changes in risk factor assessment methodology during study years. Childhood risk variable load was assessed by calculating the average of *z*-scores from years 1980 to 1986. In these analyses, only measurements conducted at ages 3–18 years were used. Adulthood risk load was assessed by calculating the average of measurements in 2001 and 2007.

To examine whether sex modifies the associations between risk variables and IMT progression, we included sex risk variable interaction terms in regression models. These analyses were performed separately for each risk variable. The associations between risk variables and IMT progression were of similar magnitude in both sexes. Therefore, the results are shown with sexes combined. The univariate relations between study variables and IMT progression were examined using regression analysis. To study the independent effects of risk variables on IMT progression, backward stepwise multivariable models were constructed. To study whether the effects of childhood risk factors are independent of current risk factors, we fitted a multivariable model including also adulthood data on those risk factors with significant effects in the childhood multivariable model.

To examine the effect of multiple risk variables on IMT, we calculated risk scores according to the number of childhood and adulthood risk factors. Statistical analyses testing the associations between risk scores and linear trend in IMT progression were performed using linear regression analysis. To examine the effect of genetic factors on the associations between conventional risk factors and IMT progression, we additionally included genetic risk score in the model as a covariate. This score was constructed on the basis of the number of unfavourable alleles carried by each subject for the 17 SNPs that have been associated with cardiovascular morbidity in prior studies[7–18] (range of alleles 0–28).

We also studied whether changes in HDL/LDL cholesterol ratio and obesity status between childhood and adulthood were associated with IMT progression. In these analyses, a cut-point of 50th percentile was used in determining unfavourable HDL/LDL cholesterol ratio and BMI. We used *t*-tests to assess whether subjects with (i) unfavourable risk factor status in childhood and favourable in adulthood; (ii) favourable status in childhood and unfavourable in adulthood; and (iii) favourable status in childhood and in adulthood differed from those having unfavourable risk factor status in childhood and in adulthood.

The statistical tests were performed using SAS version 9.2. Values for triglycerides, fruit consumption, and vegetable consumption were $\log_{10}$-transformed prior to analyses owing to skewed distributions. Statistical significance was inferred at a two-tailed *P*-value <0.05.

Results

The baseline characteristics of study subjects are shown in *Table 1*. The representativeness of the present cohort was studied by comparing the characteristics at the original baseline study (1980) between the participants of the present study and non-participants. Non-participants were younger than participants (males 9.9 vs. 10.9 years, females 10.1 vs. 10.9 years, *P* for both <0.001). BMI was higher in female non-participants than in participants (17.8 vs. 17.5 kg/m^2, $P = 0.005$). No statistically significant differences were seen in other risk factors in age-adjusted analyses.

As shown in *Figure 2*, IMT increased with age ($P < 0.001$). IMT progression was faster in men than women during the 6-year follow-up [54 (9) vs. 40 (8) μm, mean (SD), $P = 0.009$).

Childhood risk factors and IMT progression in adulthood

Childhood HDL cholesterol, fruit intake, and physical activity were inversely, and BMI directly associated with adulthood IMT progression (*Table 2*, Models A and B). Childhood HDL/LDL cholesterol ratio was also associated with IMT progression in the childhood multivariable model (−5 (−9 to −1) μm, $P = 0.01$). When taking into account the effects of adulthood risk variables, the associations between childhood fruit consumption and physical activity with IMT progression remained significant (*Table 2*, Model C). A composite childhood risk factor score was also associated with IMT progression, and this effect remained significant when adjusted for adulthood risk score (*Figure 3*).

The associations of the changes in risk factors between childhood and adulthood with IMT progression

As observed in *Table 2* (Model C), the effects of dyslipidaemia and obesity in childhood on IMT progression became non-significant

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Table 1 Childhood characteristics of study subjects at baseline in 1980

Variable	Males	Females	*P*-value
n	794	1015	
Age	10.9 (5.1)	10.8 (5.1)	0.81
LDL cholesterol (mmol/L)	3.37 (0.79)	3.50 (0.82)	<0.0001
HDL cholesterol (mmol/L)	1.55 (0.31)	1.56 (0.30)	0.3
Triglycerides (mmol/L)	0.56 (0.43–0.67)	0.61 (0.47–0.80)	<0.0001
Systolic blood pressure (mmHg)	114 (13)	112 (11)	0.004
BMI (kg/m^2)	17.9 (3.1)	17.8 (3.0)	0.32
Glucose (mmol/L)[a]	4.78 (0.61)	4.59 (0.91)	<0.0001
Diabetics (%)	0.4	0.2	0.36
Smokers (%)[b]	15.4	11	0.0001
Vegetables, consumption frequency per week	6.3 (3.0–9.5)	6.3 (3.0–9.5)	0.09
Fruit, consumption frequency per week	6.3 (6.3–9.5)	6.3 (6.3–9.5)	0.08
Users of butter-based spreads (%)	66.2	65.2	0.58
Physical activity index[b]	9.5 (2.0)	8.6 (1.6)	<0.0001

Values are mean (SD) for variables with normal distribution or median (interquartile range) for variables with skewed distributions. *P*-values are from *t*-tests for continuous variables with normal distribution, Wilcoxon non-parametric testing for variables with skewed distribution, and χ^2-tests for categorical variables.
[a]Glucose levels are from study year 1986.
[b]Smoking data were gathered from subjects aged 12–18 years and physical activity among 9–18-year olds.

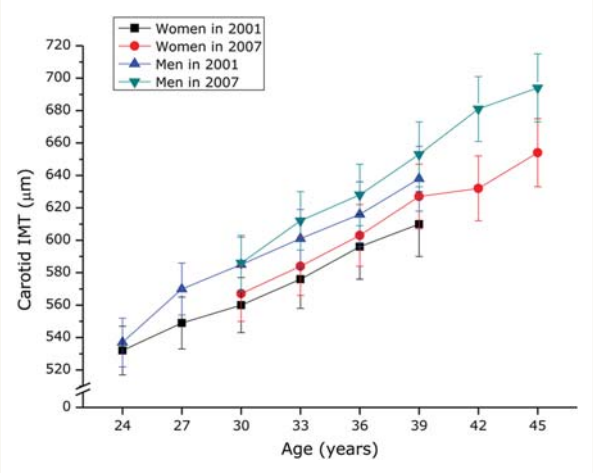

Figure 2 Carotid IMT values (mean (95% CI)) in 2001 and 2007.

when taking into account the effects of current risk factors. To gain more insight on this issue, we studied the effects of risk factor changes on IMT progression (*Figure 4*). Subjects with an unfavourable HDL/LDL cholesterol ratio in childhood, but a favourable ratio in adulthood had slower IMT progression compared to those with permanently unfavourable ratio (*Figure 4A*). Similarly, a favourable change in obesity status between childhood and adulthood was associated with slower IMT progression (*Figure 4B*). In a correlation analysis, a decrease in BMI *z*-score from childhood to adulthood was strongly associated with an increase in HDL/LDL ratio *z*-score($r = -0.29$, $P < 0.001$).

Contribution of genotype score to the associations between risk factors and IMT progression

Genotype score was associated with IMT progression, so that each additional unfavourable allele was related to a 1.3 μm increase in IMT progression (β (95% CI) 1.3 (0.3–2.3), $P = 0.02$). When the genotype score was included in a model examining the effects of childhood and adulthood risk scores on IMT progression, it was significantly associated with IMT progression (1.3 (0.1–2.5), $P = 0.02$). Inclusion of the genotype score did not dilute the significant associations between childhood and adulthood risk factor scores with IMT progression.

Discussion

Our findings from a population-based cohort show that exposure to cardiovascular risk factors in childhood is associated with increased progression of atherosclerosis, as assessed by a 6-year change in carotid IMT, over 20 years later in adulthood.

To our knowledge, this is the first prospective study of the association between childhood risk factors and IMT progression in adulthood. Previous studies have shown associations between childhood risk factors and carotid IMT measured at one point of time in adulthood.[2–5] We[2] have previously reported in this cohort that risk factors in childhood are associated with IMT in adulthood after 21 years. In the current extended follow-up with repeated IMT measurements, we observed that exposure to risk factors in childhood was associated with increased IMT progression rate in adulthood. The childhood risk score, reflecting the composite load of youth risk exposure, was associated with IMT progression even after taking into account the current risk score. When the effects of individual risk variables were assessed

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Table 2 Relations between childhood (ages 3–18 years, between 1980 and 1986) risk factor load and 6-year change (ages 24–39 years, between 2001 and 2007) in carotid IMT. (A) Univariate associations between childhood risk factors and IMT progression. (B) Multivariable model for associations between childhood risk factors and IMT progression. (C) Multivariable model including those risk factors with independent effect on IMT progression in childhood multivariable model and taking also into account the effects of respective adulthood risk factors. Beta-values are regression coefficients (expressed in micrometres) for a 1-SD change in continuous variables. *P*-values are from linear regression models

Risk variable	β (95% CI)	*P*-value
(A) Univariate models–childhood ($n = 1809$)		
LDL cholesterol	3 (−1 to 7)	0.24
HDL cholesterol	−7 (−11 to −3)	0.002
Triglycerides	3 (−1 to 3)	0.19
Systolic blood pressure	5 (1–9)	0.04
BMI	5 (1–9)	0.02
Smoking ($n = 1150$)[a]	−3 (−15 to 9)	0.5
Glucose ($n = 1248$)[b]	0.2 (−4 to 4)	0.86
Diabetes	−1 (−7 to 5)	0.64
Physical activity ($n = 1744$)[b]	−6 (−10 to −2)	0.004
Fruit consumption	−6 (−10 to −2)	0.009
Vegetable consumption	−3 (−7 to 1)	0.05
Butter use	0.4 (−8 to 8)	0.93
(B) Multivariable model-childhood ($n = 1744$)		
HDL cholesterol	−6 (−10 to −2)	0.005
BMI	5 (1–9)	0.047
Physical activity	−5 (−9 to −1)	0.01
Fruit consumption	−5 (−9 to −1)	0.03
(C) Multivariable model-childhood and adulthood ($n = 1728$)		
Childhood HDL cholesterol	−3 (−8 to 2)	0.24
Adulthood HDL cholesterol	−5 (−11 to 1)	0.12
Childhood BMI	0.6 (−5 to 5)	0.82
Adulthood BMI	8 (3–13)	0.004
Childhood physical activity	−6 (−10 to −2)	0.01
Adulthood physical activity	2 (−2 to 6)	0.48
Childhood fruit consumption	−5 (−9 to −1)	0.03
Adulthood fruit consumption	−0.1 (−7 to 5)	0.98

[a]Glucose levels are from study year 1986.
[b]Smoking data were gathered on subjects aged 12–18 years and physical activity among 9–18-year olds.

in multivariable models, frequent fruit consumption and high physical activity in childhood remained associated with lower adult IMT progression. These observations indicate that children with risk factors have increased atherosclerosis progression rate in adulthood and support the idea that atherosclerosis prevention by means of life style could be effective when initiated in childhood.[24]

In contrast to childhood life-style variables, the associations of childhood lipid values and BMI with IMT progression became non-significant when adjusted for the current risk factor levels. Thus, although a composite childhood risk burden was independently associated with IMT progression, the effects of these specific risk factors lost their significance after the adjustment for adult values. The greater relative importance of adult lipid levels and obesity when compared with those in childhood is also supported by the observation that favourable changes in lipid profile and obesity status from childhood to adulthood were associated with slower atherosclerosis progression. For example, in subjects with low HDL/LDL cholesterol ratio in childhood, only those with low ratio also in adulthood had increased IMT progression in adulthood. Similarly, obese youths who became lean adults had slower IMT progression than persistently obese subjects. These findings suggest that it is not too late to start interventions targeting lipids and obesity during transition from youth to adulthood to reduce progression of atherosclerosis.

Genetic susceptibility to atherosclerosis is a potential explanation for long-term associations between risk factors and IMT progression. We found that a panel of SNPs associated with cardiovascular morbidity in prior genome-wide association studies was

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associated with IMT change in young adults. However, the associations between conventional risk factors and atherosclerosis progression were independent of genetic risk score. Our genetic data contained only 17 SNPs and some of these polymorphisms have been shown to associate with CHD only in few studies. Therefore, more studies are needed to evaluate the effects of genetic factors on atherosclerosis progression.

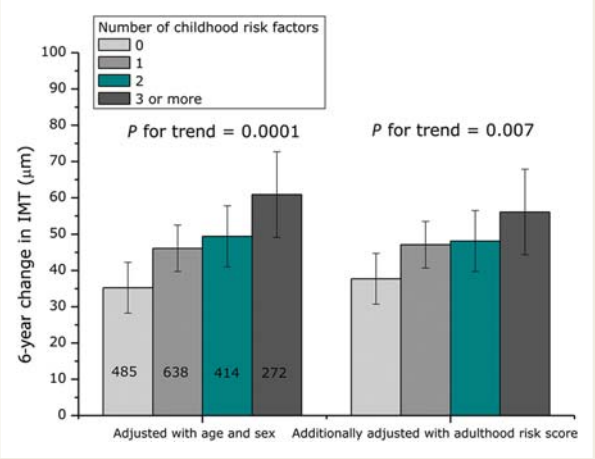

Figure 3 Associations between the number of childhood risk factors (load variable 1980–1986) including LDL cholesterol, HDL cholesterol, blood pressure, BMI, fruit consumption, physical activity (extreme quintile was considered a risk factor), smoking and diabetes with 6-year change (2001–2007) in carotid IMT (mean (95% CI)) in adulthood. Results in the left panel are adjusted with age and sex, and results in the right panel are additionally adjusted with similar adulthood risk score (load variables 2001–2007), also including data on parental history of CHD. The *P*-values for trend are from linear regression analyses.

Limitations

Interpretation of our results requires consideration of several aspects of the study design and methodology. Firstly, observational studies cannot establish causality. However, it would be extremely difficult to perform a life-long trial to study the effects of diet and physical activity on atherosclerosis progression. Well-characterized cohorts with repeated measurements offer the only feasible option to collect information on the effects of life-style changes across the life course on atherosclerosis. Secondly, in the present study, 6-year change in carotid IMT was used as a surrogate marker of cardiovascular health. As there is paucity of information concerning the association between IMT progression rate and subsequent cardiovascular events, the results should be interpreted with some caution. However, increased IMT progression is an indicator of the atherosclerotic process predisposing to cardiovascular events.[25] Thirdly, although we used a standardized protocol for the measurement of IMT both at baseline and at follow-up, a part of the computed change in IMT over the years may be distorted by measurement error, which is likely to be random and thus lead to underestimation rather than overestimation of associations. Measurements of IMT in the common carotid artery are more reliable and less difficult to obtain than IMT measurements in the carotid bifurcation or in the internal carotid artery, but also less sensitive to local atherosclerotic changes.[26] Therefore, it is possible that the IMT data from only one site may underestimate the relationships between childhood risk factors and IMT progression when compared with using data from all three segments. Finally, because our study cohort was racially homogenous, the generalizability of our results is limited to white European subjects. A further potential limitation is loss-to-follow-up. However, baseline risk factors (in 1980) were mainly similar among participants and non-participants. Thus, the present study cohort seems to be representative of the original population.

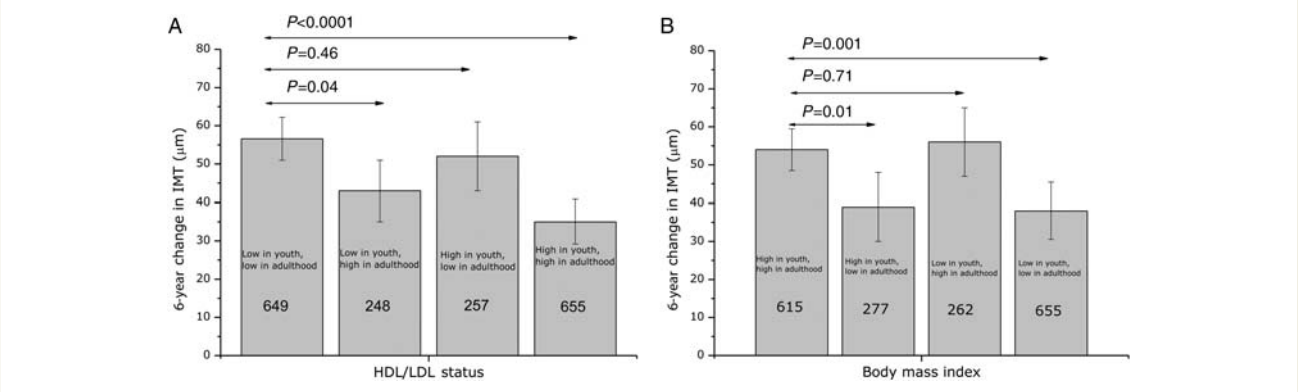

Figure 4 (*A*) Relations between HDL/LDL cholesterol in childhood (age 3–18 years) and adulthood (age 24–45 years) with IMT progression in adulthood (mean (95% CI)). A cut-point of 50th percentile was used in classifying HDL/LDL cholesterol ratio as low or high. (*B*) Relations between BMI in childhood and adulthood with IMT progression in adulthood. A cut-point of 50th percentile was used in classifying BMI as high or low. *P*-values from *t*-tests.

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Conclusions

Our findings suggest that cardiovascular risk factors in childhood predict accelerated atherosclerosis later in life independent of current risk factors. These results provide support for intervention programmes targeting risk factors in childhood.

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Conflict of interest: none declared.

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