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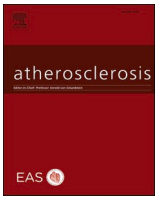

Subclinical atherosclerosis in young adults predicting cardiovascular disease: The Cardiovascular Risk in Young Finns Study

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ABSTRACT

Background and aims: Atherosclerosis is accompanied by pre-clinical vascular changes that can be detected using ultrasound imaging. We examined the value of such pre-clinical features in identifying young adults who are at risk of developing atherosclerotic cardiovascular disease (ASCVD).
Methods: A total of 2641 individuals free of ASCVD were examined at the mean age of 32 years (range 24–45 years) for carotid artery intima-media thickness (IMT) and carotid plaques, carotid artery elasticity, and brachial artery flow-mediated endothelium-dependent vasodilation (FMD). The average follow-up time to event/censoring was 16 years (range 1–17 years).
Results: Sixty-seven individuals developed ASCVD (incidence 2.5%). The lowest incidence (1.1%) was observed among those who were estimated of having low risk according to the SCORE2 risk algorithm (<2.5% 10-year risk) and who did not have plaque or high IMT (upper decile). The highest incidence (11.0%) was among those who were estimated of having a high risk (≥2.5% 10-year risk) and had positive ultrasound scan for carotid plaque and/or high IMT (upper decile). Carotid plaque and high IMT remained independently associated with higher risk in multivariate models. The distributions of carotid elasticity indices and brachial FMD did not differ between cases and non-cases.
Conclusions: Screening for carotid plaque and high IMT in young adults may help identify individuals at high risk for future ASCVD.

1. Introduction

Atherosclerotic cardiovascular diseases (ASCVDs) are the end stages of a slow process of atherosclerosis that affects the walls of medium-sized and large-sized arteries. Despite the fact that there are currently effective means to prevent the development of atherosclerosis and even induce regression of established atherosclerotic lesions, ASCVDs remain the leading causes of morbidity and mortality worldwide [1,2]. Their

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eradication has been challenging because atherosclerosis often goes undetected and preventive measures are inadequate or come too late [3,4]. Although successful public health programs have the potential to result in dramatic reductions in ASCVD-related morbidity and mortality, as it has been witnessed in Finland over the past 40 years [5], it is widely believed that additional benefits could be gained by accurate high-risk strategies. Therefore, all current guidelines on ASCVD prevention emphasize the importance of risk-based screening approaches.

Before the manifestation of symptomatic disease, the atherosclerotic process is accompanied by structural and functional changes in the vasculature that can be detected using imaging techniques. These pre-clinical phenotypes may include diffuse thickening of arterial walls, the development of focal atherosclerotic plaques, as well as changes in arterial elasticity and endothelial function [6].

The Cardiovascular Risk in Young Finns Study (YFS) is a long-standing cohort study into the determinants of cardiovascular disease. The study recruited 3596 children between ages 3 and 18 in 1980. Thereafter, this cohort has been followed up with regularly organized field studies [7]. Non-invasive imaging methods were introduced to the study when the participants had entered young adulthood. The measured vascular phenotypes included carotid artery intima-media thickness (IMT) and plaques, carotid artery elasticity, and brachial artery flow-mediated endothelium-dependent vasodilation (FMD). In theory, such vascular features may identify high-risk individuals who would benefit from targeted prevention. In our previous publications, we have shown that all of these vascular phenotypes are linked with childhood risk factor exposures, supporting the hypothesis that exposure to risk factors early in life induces changes in arteries that associate with the development of atherosclerosis [8–11].

Here, we examined the utility of pre-clinical vascular phenotypes in identifying young adults who are at risk of developing clinical ASCVD outcomes.

2. Patients and methods

Anonymized data are available on reasonable request from the YFS research group. The YFS is a prospective multicenter study from Finland initiated in the late 1970s. The first large baseline examination was conducted in 1980 (baseline age, 3–18 years, N = 3596) [7]. Children aged 3, 6, 9, 12, 15, and 18 years were chosen from the population register from the five Finnish university cities with medical schools (Helsinki, Kuopio, Oulu, Tampere, and Turku) and their surrounding rural areas. Of those invited in (N = 4320), 3596 (83%) participated in the first cross-sectional study in 1980. Several follow-ups during the past 40 years have been conducted to investigate the determinants of cardiometabolic health. The participation rates in follow-up studies have been satisfactory. This report uses data collected in clinical examinations in 2001 and 2007. In 2001, 2283 individuals aged 24–39 (63.5% of the original cohort) participated in clinical examinations. In 2007, 2202 individuals participated (61.2% of the original cohort). A detailed analysis of participants who dropped out was done after the 21-year follow-up study in 2001 [12]. We observed that the participation has been dynamic: over half of the participants lost-to follow-up early in the study have returned to the study later on. When we tested the representativeness of the participants in 2001 by comparing their baseline (year 1980) characteristics to those who had not participated in the 2001 examination, we found similar distributions in key baseline characteristics [12]. In the current report, we have examined pre-clinical vascular phenotypes that were measured with non-invasive ultrasound from participants as adults aged between 24 and 45 years using data collected in 2001 and 2007 examinations. These data have been linked with the clinical ASCVD outcome diagnoses collected from the national registries available for all study participants regardless of their participation in the field studies. The study was approved by local ethics committees, and the study was performed according to the Declaration of Helsinki. All participants provided written informed consent.

2.1. ASCVD outcomes

Linkages to national registries, including the Care Register for Health Care and the National Death Index, were used to ascertain ASCVD outcomes, including coronary artery disease, atherosclerotic cerebrovascular disease and peripheral artery disease [13,14]. The outcomes included both thrombotic events and confirmed diagnoses without a thrombotic event. Cardiovascular events included the first instance of adjudicated myocardial infarction, stroke, transient ischemic attack, ischemic heart failure, angina, peripheral artery disease, carotid intervention, abdominal aortic aneurysm, or coronary revascularization. All Finnish citizens are covered in the registry data; thus the diagnoses were available for 3579 participants (17 individuals declined the use of their registry data). Of these participants, a total of 2641 individuals free of ASCVD participated in the ultrasound examination in study years 2001 and/or 2007, and were followed up until ASCVD event or censoring, whichever occurred first. The censoring year was 2018, i.e. the end of register follow-up. By this time, 67 of them had been diagnosed with ≥1 ASCVD events (incidence 2.5%). Supplementary Table S1 shows the age and sex of each patient, the duration of follow-up since the carotid study and their specific ASCVD diagnosis.

2.2. Ultrasound studies

Vascular ultrasound measurements were made in follow-ups performed in 2001 and 2007 using Siemens Sequoia 512 ultrasound mainframes (Acuson, Mountain View, CA) equipped with 13.0 MHz linear array transducer as previously detailed [8–10,15]. Briefly, carotid IMT was measured on the far wall of the left common carotid artery and scanned for the presence of local plaques, defined as a focal structure of the arterial wall protruding into the lumen >50% compared to the adjacent intima-media thickness [16]. All plaques were located in the carotid bifurcation. To assess carotid artery elasticity indices, the best-quality cardiac cycle was selected from the 5-s image clips. The common carotid diameter 10 mm from carotid bifurcation was measured from the B-mode images with ultrasonic calipers at least twice in end diastole and end systole, respectively. The means of the measurements were used as the end-diastolic and end-systolic diameters. Ultrasound and concomitant brachial blood pressure measurements were used to calculate the three indices of arterial elasticity: 1) carotid distensibility ([Ds-Dd]/Dd)/(Ps-Pd); 2) Young's elastic modulus ([Ps-Pd]xDd)/([Ds-Dd]/IMT; and 3) stiffness index ln (Ps/Pd)/([Ds-Dd]/Dd). Dd is the diastolic diameter, Ds is the systolic diameter, Ps is systolic blood pressure, Pd is diastolic blood pressure, and IMT is common carotid artery intima-media thickness [9].

To assess FMD, the left brachial artery diameter was measured both at rest and during reactive hyperemia. Increased flow was induced by inflation of a pneumatic tourniquet placed around the forearm to a pressure of 250 mm Hg for 4.5 min, followed by release [10]. Three measurements of arterial diameter were performed at end-diastole at a fixed distance from an anatomic marker at rest and at 40, 60, and 80 s after cuff release. The vessel diameter in scans after reactive hyperemia was expressed as the percentage relative to the resting scan. The average of 3 measurements at each time point was used to derive the maximum FMD (the greatest value between 40 and 80 s).

2.3. Risk factors

Venous blood samples were drawn after an overnight fast during the physical examination. Total cholesterol levels were measured by the enzymatic cholesterol esterase–cholesterol oxidase method (Cholesterol reagent, Beckman Coulter Biomedical). The same reagent was used for estimating HDL-cholesterol levels after precipitation of very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein particles with dextran sulphate-MgCl2. Non-HDL-cholesterol was calculated as total cholesterol - HDL-cholesterol. Triglycerides

concentration was determined using the enzymatic glycerol kinase–glycerol phosphate oxidase method (Triglyceride reagent, Beckman Coulter Biomedical, Ireland). All the above assays were performed on an AU400 instrument (Olympus, Japan). LDL-cholesterol was estimated using Friedewald's equation from measured values of total cholesterol, HDL-cholesterol and triglycerides.

Height and weight were measured. Body mass index was calculated using the formula: weight [kg]/(height [m])^2. Obesity was defined as body mass index ≥30 kg/m^2. Blood pressure was measured using a random zero sphygmomanometer. The average of three measurements was used in the analysis. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or antihypertensive medication for the condition. Smoking habits and family history of coronary heart disease were inquired with the use of questionnaires [17]. An updated Systematic COronary Risk Evaluation (SCORE2) algorithm was used to estimate the 10-year fatal and non-fatal ASCVD disease risk [18]. It estimates the 10-year risk of first-onset ASCVD based on age, sex, smoking status, systolic blood pressure, and non-HDL-cholesterol. All European countries were classified into four risk regions (low, moderate, high, or very high) according to their overall ASCVD mortality, and the SCORE2 calculation was conducted separately for different European regions.

We used the SCORE2 risk chart for moderate risk countries (such as Finland) to estimate the risk for each participant. For participants aged <50 years, SCORE2 values < 2.5% indicate low-to-moderate risk; values 2.5–7.5% indicate high risk; and values ≥ 7.5% indicate very high risk [18]. The components of the risk score were measured at the year of the ultrasound examination.

2.4. Statistical methods

Standard statistical analyses were performed using Statistical Analysis System (SAS, version 9.4). We compared baseline characteristics between cases and non-cases using linear (continuous) or logistic regression (categorical), adjusting for age and sex. We used Cox proportional hazards regression to assess Hazard ratios (HR) and their 95% confidence intervals representing the associations between pre-clinical vascular phenotypes and ASCVD outcomes. Deaths due to non-cardiovascular causes were considered as competing events. Fine-Gray subdistribution hazard model was used to account for competing risks [19]. The possible effect modification of sex on the examined associations was tested by introducing sex-specific interaction terms in the Cox proportional hazard models. Primarily, the year 2001 values were used in the analyses (year 2001 values were available for 59 cases and 2196 non-cases). In case the year 2001 measurement was missing, the year 2007 value was used – this increased the number of cases by 8–67 and non-cases by 351 to 2547.

We calculated receiver operator statistics to identify an optimal IMT cutoff for predicting future ASCVD occurrences. We tested logistic models using different cut-points of 75th, 80th, 85th, 90th and 95th percentiles for high IMT. The age and sex adjusted c-statistics values varied between 0.689 (being lowest for the 75th percentile) and 0.699 (being highest for the 90th percentile).

3. Results

The average follow-up time from ultrasound examination to event/censoring was 15.9 ± 2.5 years (range 1–17 years). By year 2018, 67 individuals had been diagnosed with ≥1 ASCVD events (incidence 2.5%). Forty-one participants had an competing event during the follow-up time. The median age at ASCVD diagnosis was 48 years (range 32–56 years), and the median follow-up time from ultrasound examination to ASCVD diagnosis was 16 years. Most diagnoses were coronary artery disease (n = 37, 55%). The non-coronary diagnoses (n = 30, 45%) included ischemic stroke, peripheral artery disease, transient ischemic attack or temporary stroke, blocked carotid artery, and abdominal aneurysm (Supplementary Table S1).

Table 1
Vascular phenotypes and risk factors in young adults free of ASCVD at the time of ultrasound assessment (in year 2001 or 2007) stratified by ASCVD status assessed in year 2018 (average follow-up time 16 years, range 1–17 years).

	Non-cases	Cases	*p*-value[a]
N	2574	67	
Age (years, range)	32 (24–45)	35 (24–45)	
Males (%)	45	67	
BMI (kg/m^2)	25.2 (4.5)	26.8 (4.8)	0.053
Obese (BMI ≥30 kg/m^2, %)	12.6	25.4	0.017
LDL-cholesterol (mmol/L)	3.23 (0.82)	3.87 (1.08)	<0.0001
Non-HDL-cholesterol (mmol/L)	3.83 (0.96)	4.59 (1.20)	<0.0001
Systolic blood pressure (mmHg)	117 [13]	125 [15]	0.0002
Diastolic blood pressure (mmHg)	71 [11]	78 [12]	0.002
Hypertension (%)	10.1	31.3	0.0002
Daily smoking (%)	22.6	46.3	<0.0001
Family risk (%)	11.5	23.9	0.0027
Average SCORE2 (10-year risk of CVD, %)	2.0 (1.3)	3.4 (2.1)	<0.0001
Low-to-moderate risk (<2.5%)	74.7	40.3	
High risk (2.5–7.5%)	24.9	52.2	
Very high risk (≥7.5%)	0.4	7.5	
Vascular ultrasound measurements			
Common carotid IMT (mm)	0.587 (0.092)	0.631 (0.127)	0.025
High IMT (>90th percentile, %)	9.8	24.0	0.039
Carotid plaque (N/%)	80 (3.1)	8 (11.9)	0.0069
Carotid plaque and/or high IMT (N/%)	298 (11.6)	22 (32.8)	0.0009
Carotid distensibility (%/10 mmHg)	2.14 (0.74)	1.94 (0.67)	0.73
Young's elastic modulus (mmHg*mm)	318 (167)	371 (160)	0.48
Stiffness Index (unitless)	5.56 (2.36)	5.74 (1.94)	0.59
Low distensibility (<10th percentile, %)	9.8	13.4	0.85
Brachial FMD (%)	8.27 (4.49)	7.12 (3.71)	0.12
Low FMD response (<10th percentile, %)	9.8	13.4	0.49

Values are mean (standard deviation) unless indicated otherwise. ASCVD = atherosclerotic cardiovascular disease; BMI = body mass index; FMD = flow-mediated dilatation; HDL = high-density lipoprotein; IMT = intima-media thickness; LDL = low-density lipoprotein; SCORE2 = Systematic COronary Risk Evaluation 2.
[a] Age and sex adjusted.

3.1. Baseline risk factors in cases and non-cases

The characteristics of individuals who developed (cases) or remained free (non-cases) of ASCVD are shown in Table 1. At the time of the ultrasound examination, the cases were older than the non-cases (35 vs. 32 years), and more often males (67 vs. 45%). In age and sex adjusted comparisons, the cases had more adverse risk factor profile than the non-cases, including higher rates of obesity, hypertension, smoking, positive family history of coronary heart disease, as well as higher levels of LDL-cholesterol, non-HDL-cholesterol, triglycerides, and blood pressure. The average estimated 10-year risk using the SCORE2 algorithm was 2.0% in non-cases and 3.4% in cases. Most of the non-cases (74.7%) were estimated to have a low-to-moderate ASCVD risk (<2.5%) [18], whereas most of the cases (59.7%) were estimated to have a high (2.5–7.5%) or very-high (≥7.5%) ASCVD risk.

3.2. Vascular ultrasound measurements in cases and non-cases

In age and sex adjusted comparisons, mean common carotid IMT values were higher in cases than non-cases (Table 1). The average difference in IMT between the groups was 0.045 mm, which equals about a half of a standard deviation of our sample's distribution. In addition, the proportion of individuals with high IMT (defined as IMT over the 90th percentile) was over 2-times greater among cases than non-cases. Distinct carotid plaques were present about 4-times more often in cases (11.9%) than in non-cases (3.1%). The prevalence of high IMT and/or plaque was 32.8% in cases and 11.6% in non-cases. The mean values for carotid elasticity indices and brachial FMD in cases and non-cases were in the anticipated direction (decreased elasticity and lower FMD values in cases) but failed to reach conventional statistical significance.

3.3. Risk factors for ASCVD outcomes

The age and sex adjusted hazard ratios and their 95% confidence intervals for ASCVD outcomes are shown in Table 2, ranked according to the magnitude of the observed association. The highest hazard ratio was observed when comparing SCORE2 groups: individuals estimated as having a high or very high ASCVD risk (≥2.5%) had about 4-times greater risk of developing ASCVD than individuals estimated having low ASCVD risk (<2.5%). Hypertension and daily smoking were associated with about 3-times greater risk of ASCVD. Carotid plaque alone or carotid plaque and/or high IMT were associated with about 2.5-greater risk of ASCVD. High non-HDL-cholesterol and high IMT were associated with about 2-times greater risk of ASCVD.

In multivariable models (Table 3), carotid plaque and high IMT were associated with about 2-times greater risk of incident ASCVD when mutually adjusted with the SCORE2 grouping though the p-values were marginal with the confidence intervals including 1. The combination variable, carotid plaque and/or high IMT, had the highest hazard ratio (Table 3). These associations were similar in men and women, as indicated by non-significant sex * carotid plaque/IMT interaction terms (p always greater than 0.2).

As a sensitivity analyses, we repeated statistical analyses by using only year 2001 examination values, including 59 cases and 2196 non-cases. The salient results remained essentially similar in this subpopulation: no differences were found between cases and non-cases in brachial FMD and carotid elasticity indices, whereas the differences in carotid IMT and plaques were similar as in the whole study population using primarily 2001 values supplemented with 2007 values (Supplementary Tables S2 and S3).

The incidence of ASCVD in four groups categorized by the SCORE2 and carotid plaque/IMT status are shown in Fig. 1. The lowest incidence (1.1%) was observed in those who had low ASCVD risk according to the SCORE2 (<2.5%) and who did not have plaque and/or high IMT in the ultrasound examination. The highest incidence (11.0%) was observed in individuals, who were estimated of having high or very high ASCVD risk (≥2.5) and had positive ultrasound scan for carotid plaque and/or high IMT.

The age and sex adjusted hazard ratios and the p-values for group comparisons are also shown in Fig. 1. Compared to the reference group (low ASCVD risk according to the SCORE2 (<2.5%) and no evidence of plaque and/or high IMT), the highest risk (HR 7.8) was seen in those estimated to have high or very high ASCVD risk (≥2.5) and a positive ultrasound scan for carotid plaque and/or high IMT. These associations were similar in men and women, as indicated by non-significant sex*group interaction term (p=0.8).

Table 2
Age and sex adjusted hazard ratios for incident ASCVD associated with vascular phenotypes and risk factors.

	Hazard ratio	95% CI	*p*-value
SCORE2 (low *vs.* high/very high risk)	3.83	1.90–7.71	<0.001
High non-HDL-cholesterol (>3.4 mmol/L)	3.27	1.48–7.23	0.003
Hypertension	3.05	1.76–5.27	<0.001
Daily smoking	2.70	1.66–4.38	<0.001
Carotid plaque and/or high IMT	2.53	1.44–4.46	0.001
Carotid plaque	2.41	1.10–5.28	0.028
High IMT	2.02	1.10–3.68	0.022

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; HDL = high-density lipoprotein; IMT = intima-media thickness; SCORE2 = Systemic Coronary Risk Estimation.
SCORE2 low risk group includes individuals with <2.5% 10-year ASCVD risk.
SCORE2 high/very high risk group includes individuals with high (2.5–7.5%) or very high risk (≥7.5%) 10-year ASCVD risk [18].

Table 3
Multivariable Cox-regression models for incident ASCVD.

	Hazard ratio	95% CI	*p*-value
Model 1:			
Carotid plaque	2.08	0.97–4.48	0.062
SCORE2 (low vs. high/very high risk)	3.66	1.85–7.25	0.0002
Model 2:			
High IMT	1.81	0.98–3.22	0.056
SCORE2 (low vs. high/very high risk)	3.65	1.82–7.32	0.0003
Model 3:			
Carotid plaque and/or high IMT	2.25	1.28–3.97	0.005
SCORE2 (low *vs.* high/very high risk)	3.50	1.77–6.93	0.0003

ASCVD = atherosclerotic cardiovascular disease; CI = confidence interval; IMT = intima-media thickness; SCORE2 = Systematic COronary Risk Evaluation 2.
SCORE2 low risk group includes individuals with <2.5% 10-year ASCVD risk.
SCORE2 high/very high risk group includes individuals with high (2.5–7.5%) or very high risk (≥7.5%) 10-year ASCVD risk [18].
All models were additionally adjusted for age and sex.

4. Discussion

Atherosclerosis often develops silently for decades before clinical ASCVD outcomes appear [3,14]. Therefore, it would be useful to have means to identify high-risk features that predict early-onset ASCVD(4). Meta-analyses has demonstrated that carotid plaques and high IMT predict incident ASCVD in middle-aged and older adults [20,21], however, the clinical value of identifying these pre-clinical signs of atherosclerosis in young adults has been unclear. Here, we demonstrate that the presence of asymptomatic carotid atherosclerosis in young adults is associated with the subsequent development of ASCVD events. Individuals with a carotid artery plaque or a high IMT (defined as values exceeding 90th percentile) had about 2 times greater risk of developing ASCVD during an average follow-up of 16 years, compared with individuals without these characteristics. Similar findings have been

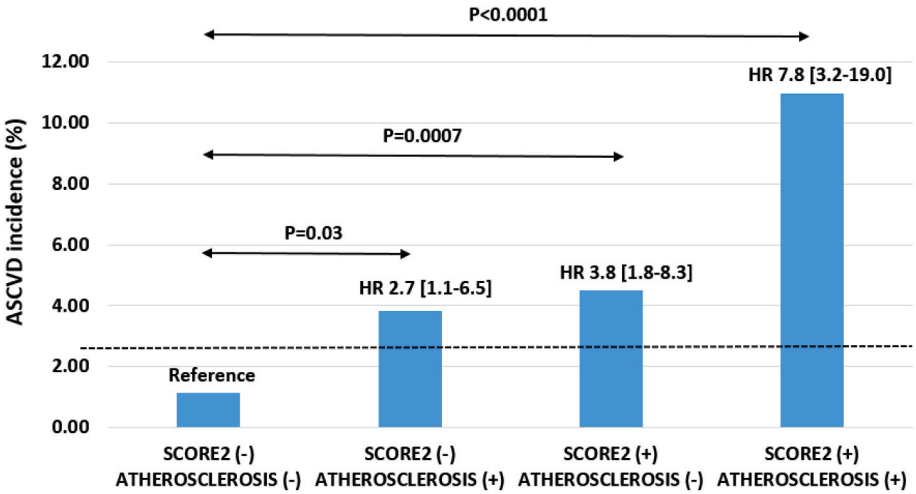

Fig. 1. ASCVD incidence (%) in 4 groups of young adults defined by SCORE2 grouping and carotid atherosclerosis status. SCORE2 (−) = Less than 2.5% 10-year risk of CVD in apparently healthy individuals. SCORE2 (+) = Over 2.5% 10-year risk of CVD in apparently healthy individuals. Atherosclerosis (−) = No evidence of plaque or high IMT in carotid ultrasound. Atherosclerosis (+) = Evidence of plaque and/or high IMT in carotid ultrasound. HR = Hazard ratio (age and sex-adjusted); ASCVD = Atherosclerotic cardiovascular disease; SCORE2 = Systematic COronary Risk Evaluation 2. The dashed line represents the average ASCVD incidence in the study population.

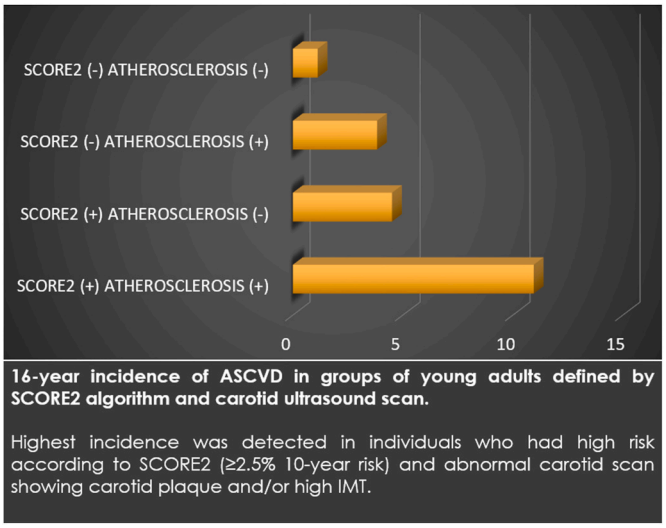

Fig. 2. Graphical abstract.

previously reported among young adults in the Strong Heart Study Family Study [22].

Identifying persons who will benefit most from ASCVD risk factor treatment is central to prevention efforts. For example, in Europe, the current ESC guidelines recommend using the updated SCORE2 algorithm to calculate the 10-year ASCVD risk. Adults under the age of 50 years can be categorized into three groups based on their estimates: <2.5% low-to-moderate risk (treatment generally not recommended); 2.5–7.5% high risk (treatment should be considered); and ≥7.5% very high risk (treatment generally recommended) [18]. Thus, these risk categories do not automatically translate into recommendations for starting drug treatment, and risk modifiers, such as the result of an imaging study, can potentially be used to guide treatment decisions. Our data support this notion: the presence of carotid plaque and/or high IMT was associated with incident ASCVD independent of traditional risk factors, and individuals with high ASCVD risk based on the SCORE2 algorithm and evidence of subclinical atherosclerosis (positive for high IMT and/or plaque) had about 8 times higher risk of ASCVD compared to individuals without these features (Figs. 1 and 2).

At present, there is no consensus on the best strategy to identify young adults at high risk for future ASCVD who would benefit from preventive measures. These data suggest that a prevention program combining information on adult risk factors accompanied by carotid artery ultrasound examination would help in identifying asymptomatic individuals with very high risk of developing premature clinical ASCVD. The current ACC/AHA and ESC guidelines acknowledge two imaging methods to detect subclinical atherosclerosis as useful risk modifiers: coronary artery calcium scoring and plaque diagnostics [18,23]. Coronary artery calcium is a highly specific feature of coronary atherosclerosis [24], and has substantive evidence to support its usefulness as a risk modifier [18]. Although the evidence is less extensive than it is for coronary calcium [25,26], carotid artery plaque may also be considered as a risk modifier [18]. The use of carotid IMT to improve risk assessment is currently not recommended due to the absence of added value of IMT in predicting future ASCVD events [18,27]. However, Bao et al. [28] recently reported data from the large Malmö Study that both carotid plaque and IMT significantly added predictive information to conventional risk factors for ASCVD events in individuals aged 46–68 years followed up to 10 years. Besides the utility of identifying high-risk individuals, imaging of subclinical atherosclerosis has the potential to improve clinician-patient risk communication. A recent systematic review and meta-analyses demonstrated that patient visualization of subclinical atherosclerosis is associated with overall ASCVD risk reduction and improvement of individual risk factors, including LDL-cholesterol and systolic blood pressure [29].

Brachial artery FMD test measures the release of nitric oxide by the endothelium due to a transient flow stimulus [30]. Arterial endothelial dysfunction is thought to be a key early event in atherosclerosis. Impaired brachial FMD response correlates with coronary atherosclerosis, and has been shown to predict ASCVD events in older adults [31]. In the Multi-Ethnic Study of Atherosclerosis, the brachial FMD test improved the classification of subjects as low, intermediate, and high ASCVD risk compared with the Framingham score [32]. In our data, however, the FMD test did not meaningfully discriminate the ASCVD cases and non-cases. Similarly, we did not find evidence that the indices of carotid artery elasticity would be useful as risk modifiers, although decreased arterial elasticity has been implicated as predictor of cardiovascular events in other studies [33,34]. As we noted in the results, however, the associations of these vascular features were in the expected direction and our case numbers were relatively low.

4.1. Limitations

The ultrasound protocol used included only the left common carotid artery and carotid bifurcation and did not involve imaging of the internal carotid artery or the right carotid. Therefore, the observed plaque prevalence (3.3%) is an underestimation. In our most recent follow-up study where we used imaging protocol including both sides and all three segments, including common carotid, bifurcation and internal carotid, we found that the prevalence of carotid plaques was about 8% in the age group of 20–30 years and about 20% in the age group of 30–40 years (unpublished data). These estimates are in line with the prevalence values previously reported in the middle-aged PESA cohort [35]. In addition, due to the young age of our population, the incidence of ASCVD is still relatively low. Because of the small number of participants with ASCVD events and carotid plaques, some of the confidence intervals were wide due to limited power. In addition, because of lack of power, we were not confident to apply formal statistical tests to examine whether adding the information of carotid imaging on top of the risk factor status improves prediction. The incremental value for predicting ASCVD events of adding carotid plaque or IMT to SCORE2 was recently evaluated using formal performance statistics in the large Malmö Study among 4588 older adults [28]. They found that both carotid plaque and IMT added predictive performance to SCORE2 for assessment of ASCVD risk. Bias attributed to differential loss to follow-up is possible in prospective cohort studies. However, the YFS has a high retention of participants relative to similar cohort studies. The Finnish national registries are considered a reliable source of data that are based on hospital records, therefore all identified ASCVD diagnoses are likely true positives, however, we acknowledge that the possibility of missing or incomplete data still exist. Furthermore, since our population is ethnically homogenous it may be difficult to generalize our results to other populations that vary in race and ethnicity from ours. Finally, the purpose of this study was to examine the role of vascular phenotypes in predicting ASCVD outcomes not their causal role in the etiology of ASCVD events. Therefore, statistical adjustments were restricted to age and sex.

In conclusion, our data suggest that assessment of subclinical atherosclerosis by carotid imaging, in addition to traditional risk factor assessment, may be helpful in identifying young adults who are at high risk of developing symptomatic early-onset ASCVD. Thus, these results support the suggested new approach to identify individuals with subclinical atherosclerosis, before plaque progression leads to ASCVD, through having a personalized atherosclerotic phenotyping [36].

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CRediT authorship contribution statement

Olli T. Raitakari: All individuals listed as authors meet all of the following conditions, All have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, All have drafted the work or reviewed it critically for important intellectual content, All have given final approval of the version to be published, All have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved, In addition to these, other individual contributions are listed below. **Costan G. Magnussen:** Conceptualization, Project administration, Study design, data collections, writing the manuscript. **Markus Juonala:** commenting and writing the manuscript. **Noora Kartiosuo:** data collections, commenting and writing the manuscript. **Katja Pahkala:** statistical consulting, writing. **Suvi Rovio:** data collections, commenting and writing the manuscript. **Juhani S. Koskinen:** data collections, commenting and writing the manuscript. **Juha Mykkänen:** analyzing image data, writing, commenting. **Tomi P. Laitinen:** data collections, commenting and writing the manuscript. **Mika Kähönen:** data collections, commenting and writing the manuscript. **Joel Nuotio:** data collections, commenting and writing the manuscript. **Jorma S.A. Viikari:** commenting, writing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2024.117515.

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