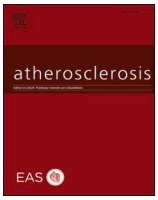
Atherosclerosis 408 (2025) 120426

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis



Prevalence of carotid atherosclerosis in 3-92-year-old Finns. The 3-generational cardiovascular risk in young Finns study

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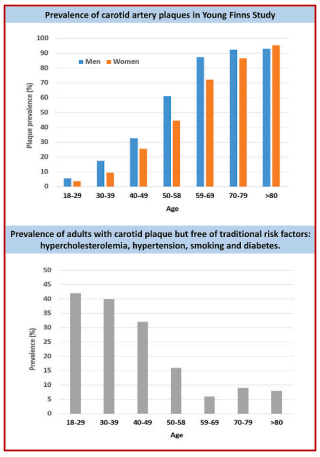
https://doi.org/10.1016/j.atherosclerosis.2025.120426

Available online 12 July 2025

HIGHLIGHTS

- Carotid artery plaques are prevalent among Finnish adults but not observed in children of the general population.
- High LDL-cholesterol concentration and hypertension are strongly associated with plaques, especially among young adults.
- Nevertheless, a large proportion of individuals with plaques are identified by the assessment of conventional risk factors.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Vascular ultrasound
Carotid plaques
Pre-clinical atherosclerosis
Cohort studies
Epidemiology
Risk factors

ABSTRACT

Background and aims: Population based data are limited on the prevalence of carotid atherosclerosis across broad age-ranges from early childhood to old age. We aimed to determine the prevalence and determinants of carotid artery plaques in a Finnish population.

Methods: We examined carotid arteries using ultrasound in 6692 participants from the 3-generational Young Finns Study (age 3–92 years; 56.6 % female).

Results: Carotid plaques were detected beginning from the age of 18 years. In adults aged 18–92 years, the overall prevalence was 48.2 % (men 51.7 %, women 45.7 %). The prevalence increased by age groups, being ~5 % under age of 30, ~30 % between ages 30 and 50, ~60 % between ages 50 and 70, and ~90 % above age 70. Plaques were predominantly found in the carotid bifurcation and in the internal carotid artery. High LDL-cholesterol (≥3.4 mmol/L or ≥130 mg/dL) and hypertension were strong risk factors for plaques especially among young adults under the age of 40. Despite this, about 40 % of young adults who had a plaque were not identified by these conventional risk factor assessments. The prevalence of clinical cardiovascular disease was 2.2 % among individuals without plaque vs. 18.9 % among those with plaque (age and sex adjusted risk ratio 2.2 95 %CI 1.7–2.9).

Conclusions: Carotid artery plaques are very prevalent finding among Finnish adults but not observed in children of the general population. High LDL-cholesterol concentration and hypertension are strongly associated with plaques, especially among young adults. On the other hand, these data demonstrate that a substantially large proportion of young and middle-aged adults with plaques cannot be identified by the assessment of conventional risk factors.

1. Introduction

Clinical cardiovascular diseases, including coronary artery disease and stroke, are the leading causes of morbidity and mortality worldwide [1]. These are most often caused by atherosclerosis, which is characterized by slowly occurring build-up of lipids and inflammatory cells in the walls of medium-sized and large-sized arteries leading to the formation of atherosclerotic plaques [2]. The initiation of atherosclerosis often begins early in life and the progression into clinical cardiovascular diseases occurs silently over several decades [3]. Apart from atherogenic lipoproteins, several other risk factors have been identified that have important roles in the development of atherosclerosis. Therefore, the major strategies to prevent atherosclerosis involve interventions that target causal risk factors [4].

Although effective population strategies can reduce cardiovascular morbidity and mortality substantially [5], the challenges of global pandemic of atherosclerotic cardiovascular diseases remain. In addition to the population strategy, the current paradigm for the prevention emphasizes the identification of high-risk individuals based on risk factor algorithms. Unfortunately, such assessments are often inaccurate [6]. While the algorithms provide average risk estimates based on population data, the individual responses to risk factors and disease progression can vary widely. Fox example, a study from Denmark indicated that risk factor algorithms would have identified very few patients hospitalized with a first acute myocardial infarction if they had completed the health check the day before the event [6]. Furthermore, many times high-risk strategies at individual level have turned out to be disappointing as the prediction from risk factors followed by individual lifestyle counselling has not been successful in reducing morbidity or mortality [7,8].

An alternative approach for predicting the risk of cardiovascular diseases is based on identifying subclinical atherosclerosis in presumably healthy people. The assumption is that the risk is very low in the absence of atherosclerosis in major arteries, and high when it is present [9]. In line with this idea, several studies have documented that the presence of a carotid plaque provides incremental prognostic information to the existing risk prediction algorithm for incident cardiovascular disease [10–15]. Atherosclerotic plaques in the carotid artery are markers of generalized atherosclerosis and sources of thromboemboli [16]. Previous studies have reported that uncomplicated carotid plaques

are associated about 2-times increased risk of coronary artery disease and stroke [17–19], and over 10-times increased risk estimates for lacunar strokes have been reported for complicated plaques [16].

Therefore, to inform the strategies to prevent cardiovascular diseases, it is important to define the prevalence of atherosclerosis in the general population. Especially, there is a consensus that more research is needed to define the prevalence of silent atherosclerosis in children and young adults [20]. This knowledge is fundamental in changing the focus from treating the late stages of cardiovascular outcomes to identifying and managing subclinical atherosclerosis early on, potentially leading to a reduction in overall cardiovascular events.

Here, we examined the prevalence of carotid artery plaques in the multigenerational Young Finns Study (YFS) including participants between ages 3 and 92 years. Our study provides rare insights into general population of children and young adults covering the age range dismissed in previous studies.

2. Methods

The YFS is a prospective multicenter study from Finland. The first large baseline examination was conducted in 1980 (baseline age, 3–18 years, N = 3596) [21]. The latest follow-up in 2018–2020 was extended to cover the original participants as well as their parents and offspring aged 3 years and older. This extension was done as part of the Multiepigen project that aims to examine epigenetic inheritance in humans [22]. After excluding those who had deceased, decided to withdraw from the study or for whom we did not have contact information, we invited 3217 original participants (Generation 1; G1, aged 40–58 y). Additionally, we invited 5696 offspring (Generation 2; G2, 3–38 y), and 3940 parents (Generation 0; G0, 59–92 y) of the original participants, including parents and adult offspring of those original participants who had deceased. This report uses cross-sectional information of 6692 participants with data on carotid artery ultrasound assessments, risk factors, and prevalent cardiovascular diseases. The details of the study design and methods are given in Supplemental Material, and have been previously published [22].

2.1. Clinical examination and questionnaires

Height and weight were measured at the clinic visit, and body mass index (BMI; kg/m^2) was calculated. Blood pressure was measured three times in a sitting position from the right arm brachial artery by an automatic Omron HBP-1300 blood pressure measurement device (Omron Corporation, Kyoto, Japan). Data on medical conditions diagnosed by a physician, medications, smoking habits (smoking was defined as daily smoking in the present report) and alcohol consumption were collected by self-report questionnaires.

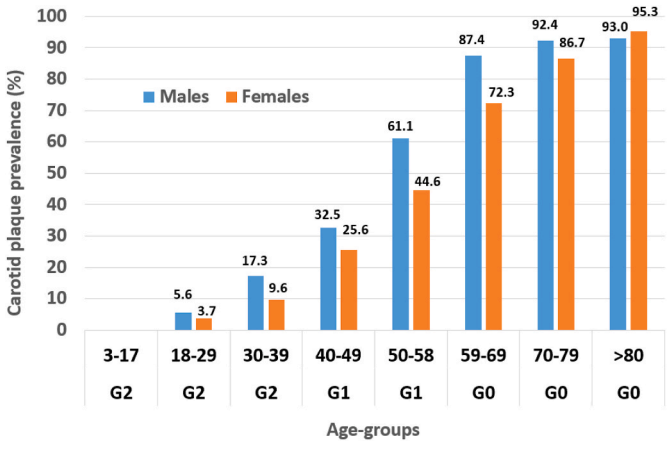


Fig. 1. Prevalence of carotid artery plaques in the 3-generational Young Finns study population (G1 = original cohort members; G2 = offspring of G1; G0 = parents of G1).

2.2. Biochemical measurements

Venous blood samples for biomarker analyses were taken after a minimum 4 h fast and stored at −70 °C until analysis. Serum lipids were measured with standard methods (details in Supplemental Material).

2.3. Definition of type 2 diabetes and hypertension

Participants were determined to have type 2 diabetes if at least one of the following criteria was fulfilled 1) fasting glucose ≥7.0 mmol/l, 2) HbA1c ≥ 6.5 % (47.55 mmol/mol), 3) self-reported type 2 diabetes diagnosis, 4) self-reported use of peroral diabetes medication, 5) diabetes medication for type 2 diabetes based on the register data of the Social Insurance Institution of Finland. Participants were determined to have hypertension if at least one of the following criteria was fulfilled 1) systolic blood pressure ≥140 mmHg, 2) diastolic blood pressure ≥90, 3) self-reported diagnoses for hypertension, 4) self-reported medication for hypertension.

2.4. Definition of clinical cardiovascular diseases

In the original cohort members (G1), the diagnoses of clinical cardiovascular diseases were based on registry data, including the Care Register for Health Care and the National Death Index [23]. For generations G0 and G2, the diagnoses were based on self-reports (details in Supplemental Material).

2.5. Carotid ultrasonography

Carotid ultrasound studies were performed using General Electric (GE) Logiq S8 (GE Vingmed Ultrasound A/S, Horten, Norway) ultrasound mainframes according to standardized protocols to assess intima-media thickness (IMT) of the left common carotid artery, carotid bifurcation, and internal carotid artery, and left and right carotid artery plaques. Plaques were defined as a focal structure protruding into the arterial lumen of at least 0.5 mm or 50 % of the surrounding IMT value or demonstrating a thickness greater than 1.5 mm as measured from the media-adventitia interface to the intima-lumen interface, as well as stenosis 50 % or more, including occlusion [24]. The number of carotid plaques for each carotid segment were derived from the longitudinal view. Plaque area was measured for each plaque from the highest quality longitudinal frame. Manual tracing of plaque lumen-intima and media-adventitia boundaries was performed around the perimeter, and the area within these boundaries was automatically measured. If more than one plaque was detected, then the plaque areas were summed. The maximum thickness for each plaque was measured manually from the same frame, representing the thickest distance from the media-adventitia interface to the lumen-intima interface. If multiple plaques were present, their thicknesses were also summed (details in Supplemental Material).

2.6. Statistical methods

Standard statistical analyses were performed using Statistical Analysis System (SAS, version 9.4). We compared characteristics between individuals with and without carotid plaques using linear (continuous) or logistic regression (categorical). Relative risks and 95 % confidence intervals were calculated using Modified Poisson regression to determine the multivariable associations between binary risk factors and carotid plaque, as well as the associations between the number of plaques and clinical cardiovascular diseases. We calculated the number of plaques, as sum of all plaques in all sites, right and left. This variable was highly skewed with range 0–22. For statistical analyses, it was

Table 1
Number of carotid artery plaques, plaque area and over 50 % stenosis by sex and age group.

Age group	Sex	N	Number of plaques (%)					Mean plaque area (mm2)	Prevalence of over 50 % stenosis (%)
			0	1	2–3	4–5	>5		
Females									
3–17		526	100	0.0	0.0	0.0	0.0	0.0	0
18–29		737	96.3	3.3	0.4	0.0	0.0	4.5	0
30–39		125	90.4	4.8	4.8	0.0	0.0	8.3	0
40–49		593	74.4	16.4	8.8	0.3	0.2	11.2	0.2
50–58		539	55.6	18.8	20.5	4.1	1.1	19.3	0.4
59–69		394	27.8	18.6	33.0	14.7	6.0	21.6	0.8
70–79		756	13.3	20.0	29.9	24.1	12.7	26.5	3.0
>80		150	4.7	8.1	26.4	35.1	25.7	37.1	9.5
Males									
3–17		525	100	0.0	0.0	0.0	0.0	0.0	0
18–29		539	94.4	4.7	0.9	0.0	0.0	5.0	0
30–39		75	82.7	12.0	5.3	0.0	0.0	7.1	0
40–49		501	67.5	16.4	14.0	2.2	0.0	16.4	0
50–58		431	38.8	22.1	28.4	7.9	2.8	24.6	0.2
59–69		211	12.6	12.1	30.6	22.3	22.3	33.3	4.9
70–79		519	7.6	8.6	25.9	23.8	34.1	42.4	5.3
>80		116	7.0	5.2	21.7	21.7	44.4	48.8	9.5

Table 2
The distribution of 9101 carotid artery plaques identified in 2720 participants (out of 6692) by arterial segment.

Population	Carotid segment	No. plaques	Prevalence (%)
All individuals with one or more plaques (N = 2720)	Common carotid	875	9.6
	Bifurcation	5937	65.2
	Internal carotid	2289	25.2
Women with one or more plaques (N = 1490)	Common carotid	354	8.0
	Bifurcation	3060	68.7
	Internal carotid	1040	23.3
Men with one or more plaques (N = 1230)	Common carotid	521	11.2
	Bifurcation	2877	61.9
	Internal carotid	1249	26.9
Under 60-year-olds with one or more plaques (N = 901)	Common carotid	42	2.4
	Bifurcation	1147	66.5
	Internal carotid	536	31.1
60 years and older with one or more plaques (N = 1819)	Common carotid	833	11.3
	Bifurcation	4790	64.9
	Internal carotid	1753	23.8

categorized into five classes: No plaques, N = 3972; one plaque, N = 745; 2–3 plaques, N = 980; 4–5 plaques N = 549; and ≥6 plaques, N = 446. The categorized variable correlated strongly with the original plaque number variable (Spearman's r = 0.998, p < 0.0001). Spearman's correlations coefficients were calculated to examine the associations between plaques and carotid artery IMT.

3. Results

3.1. Prevalence of carotid plaques by age and sex

Carotid artery plaques were present from the age 18 years onwards (no plaques were detected in children between ages 3 and 17). The overall prevalence between ages 18–92 years was 48.2 % - higher in males than in females (51.7 % vs. 45.7 %, p < 0.0001). The prevalence of carotid artery plaques across age groups is shown in Fig. 1 and graphical abstract. The prevalence increased by age, being about 5 % in those aged 18–29 years and >90 % in those aged 80 years or older. Men had higher prevalence than females until the age of 70. Sex differences were not observed among those aged 70 years and older. Similarly, the number of plaques and plaque area increased by age (Table 1) in both sexes. The prevalence of plaques with >50 % narrowing was rare and increased by age in both sexes (Table 1).

3.2. Distribution of plaques between carotid artery segments

One or more carotid plaques were present in 2720 individuals. In total, 9101 plaques were recorded. The distribution of the plaques within the carotid regions (common carotid, carotid bifurcation and internal) are shown in Table 2. Plaques were most commonly detected in the carotid bifurcation (65 % of all plaques detected), followed by internal carotid (25 %). About 10 % of the plaques were located in the common carotid artery. Men had larger prevalence of multiple plaques than women (Table 1), and the distribution of plaques between arterial regions differed slightly between the sexes. For example, in men the occurrence of common carotid plaques (11.2 % of all plaques) was slightly more common than in women (8.0 %).

The distribution of plaques between carotid regions also differed by age. In participants under 60 years, most plaques were located in the carotid bifurcation and internal carotid artery, only 2.4 % in common carotid. In individuals 60 or older, 88.7 % of plaques were located in carotid bifurcation and internal carotid, and 11.3 % in the common carotid.

3.3. Characteristics of participants with and without plaque

The comparisons between participants with and without detected carotid artery plaque are shown in Table 3. The three generations are presented separately. In each generation, individuals with plaque tended to be older and more often males than individuals without plaque. In generations G1 and G2 (ages 18–58 years), individuals with plaque were characterized by higher concentrations total cholesterol, LDL-cholesterol, non-HDL-cholesterol, and triglycerides. In the oldest generation G0 (ages 59–92 years), the lipid profile did not seem to differ between individuals with or without plaque, except for triglycerides and HDL-cholesterol (Table 3). This is presumably due to more frequent use

Table 3
Characteristics study participants stratified by plaque status and generation.

	Age group 18–39 (G2)		Age group 40–58 (G1)		Age group 59–92 (G0)		*P*-value[d]
	Plaque +	Plaque -	Plaque +	Plaque -	Plaque +	Plaque -	
No	82	1391	817	1245	1821	285	
Age	28.1 (4.5)	24.9 (4.2)	50.5 (4.7)	48.0 (4.9)	73.9 (5.6)	70.7 (5.4)	
Males (%)	52	41	52	41	42	26	
BMI (kg/m2)	25.8 (4.3)	25.2 (5.1)	27.9 (5.2)	27.7 (5.4)	28.1 (4.8)	27.7 (4.7)[c]	0.82
Total-C (mmol/L)	5.07 (1.04)	4.41 (0.85)[a]	5.31 (1.04)	5.13 (0.97)[b]	4.92 (1.19)	5.27 (1.04)	<0.0001
LDL-C (mmol/L)	3.21 (0.97)	2.59 (0.71)[a]	3.34 (0.95)	3.18 (0.83)[b]	2.91 (1.05)	3.20 (0.95)	<0.0001
HDL-C (mmol/L)	1.31 (0.39)	1.32 (0.34)	1.27 (0.39)	1.33 (0.38)[b]	1.36 (0.39)	1.45 (0.40)[c]	0.08
non-HDL-C (mmol/L)	3.76 (1.14)	3.09 (0.84)[a]	4.04 (1.07)	3.80 (0.99)[b]	3.56 (1.11)	3.83 (1.04)	<0.0001
Triglycerides (mmol/L)	1.22 (0.64)	1.11 (0.65)	1.61 (1.21)	1.42 (1.53)[b]	1.46 (0.74)	1.38 (0.62)[c]	<0.0001
Systolic BP (mmHg)	124.1 (12.9)	120.52 (12.2)	132.4 (16.2)	127.9 (15.4)[b]	143.7 (21.8)	140.0 (19.6)[c]	<0.0001
Diastolic BP (mmHg)	76.4 (10.3)	73.1 (8.1)[a]	84.0 (10.4)	81.9 (9.5)	78.9 (10.5)	80.7 (9.1)	<0.01
Hypertension (%)	23.2	8.5[a]	50.1	34.7[b]	82.3	67.4[c]	<0.0001
Daily smoking (%)	12.3	15.9	16.0	10.4[b]	6.6	3.7[c]	<0.0001
Alcohol drinks per day	0.5 (0.5)	0.5 (0.6)	0.8 (1.2)	0.7 (1.0)	0.6 (1.0)	0.4 (0.4)	0.18
Statin use (%)	0	0	12	5[b]	44	27[c]	<0.0001
BP medication (%)	4	1	24	14[b]	61	42[c]	<0.0001
Type 2 diabetes (%)	0	0.6	10.3	5.6[b]	24.6	12.0[c]	<0.001
Any cardiovascular disease (%)	1.2	0.5	5.6	2.4[b]	25.6	9.5[c]	<0.0001
Coronary artery disease (%)	0	0.2	3.2	0.8[b]	15.8	3.6[c]	<0.001
Cerebrovascular disease (%)	0	0.3	1.7	1.3	10.2	6.9	0.98

The values are mean (SD) or prevalences (%).
[a] Age and sex adjusted *P*-value <0.05 in intra-group comparison within age group 18–39 years.
[b] Age and sex adjusted *P*-value <0.05 in intra-group comparison within age group 40–58 years.
[c] Age and sex adjusted *P*-value <0.05 in intra-group comparison within age group 59–92 years.
[d] P-values are from linear (continuous variables) or logistic (binary variables) regression models in the complete study population adjusted for sex, age, statin use, and blood pressure medication use. G1 = generation one (the original YFS participants); G2 = generation two (offspring of the original YFS participants); G0 = generation zero (the parents of the original YFS participants).

Table 4
Associations between plaque features and clinical cardiovascular diseases.

	Any cardiovascular disease (10.2 %)[a]	Coronary artery disease (6.0 %)[a]	Cerebrovascular disease (4.3 %)[a]
Number of plaques	*Risk Ratio (95 % C)*[b]	*Risk Ratio (95 % CI)*	*Risk Ratio (95 % CI)*
No plaque	ref.	ref.	ref.
1	1.72 (1.21–2.43)	2.11 (1.18–3.77)	1.18 (0.73–1.91)
2–3	2.25 (1.64–3.01)	3.50 (2.09–5.87)	1.23 (0.78–1.93)
4–5	2.62 (1.88–3.65)	3.89 (2.26–6.70)	1.49 (0.93–2.39)
>5	3.44 (2.47–4.81)	5.67 (3.28–9.78)	1.58 (0.97–2.57)
Plaque area			
No plaque	ref.	ref.	ref.
Q1	1.83 (1.30–2.59)	2.33 (1.32–4.13)	1.33 (0.83–2.12)
Q2	2.05 (1.48–2.84)	2.91 (1.71–4.93)	1.29 (0.81–2.04)
Q3	2.38 (1.73–3.29)	3.84 (2.27–6.47)	1.24 (0.78–1.96)
Q4	3.00 (2.19–4.12)	4.72 (2.81–7.94)	1.40 (0.88–2.22)
Plaque thickness			
No plaque	ref.	ref.	ref.
Q1	1.89 (1.35–2.65)	2.46 (1.41–4.30)	1.36 (0.85–2.16)
Q2	2.12 (1.54–2.91)	2.97 (1.76–5.02)	1.22 (0.76–1.94)
Q3	2.32 (1.68–3.19)	3.68 (2.18–6.23)	1.30 (0.82–2.06)
Q4	2.86 (2.09–3.92)	4.60 (2.74–7.70)	1.37 (0.89–2.17)

[a] Overall prevalence in the adult population (ages 18–92 years).
[b] Age and sex adjusted risk ratios and 95 % confidence intervals compared to the reference group without plaque.

of statins among the individuals with plaque in the oldest age group. Systolic blood pressure was higher and the diagnoses of hypertension more prevalent in individuals with plaque across all generations. Daily smoking was more frequent among individuals with plaque in generations G1 and G0. The diagnoses of type 2 diabetes and cardiovascular diseases were more prevalent in individuals with plaque in generations G1 and G0 (40–92 years of age). These diagnoses were too rare in the youngest generation to allow meaningful comparisons. The characteristics of 3–17-year-old individuals are shown in a supplementary Table.

3.4. Relations between carotid artery plaques and clinical cardiovascular diseases

The overall prevalence of clinical cardiovascular diseases in adults aged 18–92 years was 10.2 % (18.9 % in individuals with plaque and 2.2 % in individuals without plaque, age and sex-adjusted risk ratio 2.2, 95 %CI 1.7–2.9). The association between plaque and clinical cardiovascular disease was of nearly similar magnitude in each generation (age and sex adjusted risk ratios 1.9, 1.7 and 2.3 in generations G2, G1 and G0, respectively). Coronary heart disease was the most prevalent clinical diagnoses present in 11.6 % of individuals with plaque and in 0.8 % of individuals without plaque (age and sex adjusted risk ratio 3.3 95 %CI 2.1–5.3). The prevalence of peripheral artery disease was 2.3 % in individuals with plaque and 0.1 % in individuals without plaque (age and sex adjusted risk ratio 6.0, 95 %CI 1.9–18.8). Cerebrovascular disease was present in 7.5 % in those with plaque and 1.4 % in those without plaque (age and sex adjusted risk ratio 1.3, 95 %CI 0.9–1.9).

The associations between clinical cardiovascular diseases and the severity of carotid atherosclerosis in adults defined by the number of plaques, plaque area and plaque thickness are shown in Table 4. Compared to the reference group without plaques, individuals with more than 5 plaques had about 3-fold increased risk for any cardiovascular disease, about 5-fold increased risk for coronary artery disease, and about 1.6-fold risk for cerebrovascular disease. Similar but slightly weaker associations were observed when atherosclerosis severity was defined by plaque area or plaque thickness. The number of individuals with peripheral artery disease who did not have plaque was too small (N = 3) to allow calculations of meaningful risk ratio estimates.

3.5. Relations between carotid artery plaques and IMT

The comparisons of carotid IMT values between participants with and without detected carotid artery plaque are shown in Table 5. In each generation, individuals with plaque had on average 8–20 % higher IMT values than those without plaques. The age and sex adjusted Spearman's rank order correlation coefficient was r = 0.16 between plaque and

Table 5
Average carotid IMT values in individuals with and without plaque in each generation.

Arterial site	Age group 3–17 (G2)	Age group 18–39 (G2)		% diff in IMT	Age group 40–58 (G1)		% diff in IMT	Age group 59–92 (G0)		% diff in IMT
		Plaque +	Plaque -		Plaque +	Plaque -		Plaque +	Plaque -	
No.	1051	82	1391		817	1245		1821	285	
Common carotid (mm)	0.43	0.502	0.450	12	0.670	0.604	11	0.849	0.755	12
Bifurcation (mm)	0.51	0.675	0.593	14	0.852	0.771	11	0.915	0.830	10
Internal carotid (mm)	0.33	0.458	0.383	20	0.552	0.506	9	0.617	0.570	8

G2 = Generation 2 (offspring of the original cohort members); G1 = Generation 1 (original cohort); G0 = Generation 0 (parents of the original cohort members). None of the 3-17-year-olds had carotid plaques. All age and sex adjusted comparisons $p < 0.0001$, except for internal carotid IMT in G0 $p = 0.009$.

Table 6
Multivariable determinants of carotid plaques in three generations.

Generation	Risk Ratio	95 % CI	p-value
G2, Age 18–39 yrs			
High LDL-c	2.96	1.91–4.59	<0.0001
Hypertension	2.00	1.25–3.19	0.004
Smoking	0.74	0.39–1.41	0.36
Type 2 diabetes	n/a		
G1, Age 40–58 yrs			
High LDL-c	1.22	1.09–1.38	0.0008
Hypertension	1.19	1.06–1.34	0.004
Smoking	1.27	1.10–1.46	0.001
Type 2 diabetes	1.12	0.92–1.36	0.25
G0, Age 59–92 yrs			
High LDL-c	1.00	0.95–1.06	0.97
Hypertension	1.12	1.05–1.19	0.001
Smoking	1.15	1.07–1.23	0.0001
Type 2 diabetes	1.06	1.00–1.11	0.024

G1 = generation one (the original YFS participants); G2 = generation two (offspring of the original YFS participants); G0 = generation zero (the parents of the original YFS participants). The multivariable models are adjusted for age and sex, and additionally for statin use in G1 and G2. Risk factors are defined as elevated LDL-cholesterol >3.4 mmol/L (or >130 mg/dL), daily smoking, hypertension (blood pressure >140/90 or medication or self-reported hypertension), and type 2 diabetes. n/a = not applicable (Type 2 diabetes prevalence in G2 <1 %).

Table 7
Proportion of individuals who are free of clinical cardiovascular disease but have carotid plaque categorized by the number of conventional risk factors[a].

Age group	N	Zero risk factors (%)	One risk factor (%)	Two or more risk factors (%)
18–29 yrs	53	42	40	18
30–39 yrs	25	40	44	16
40–49 yrs	270	32	41	27
50–58 yrs	413	16	43	41
59–69 yrs	334	6	42	52
70–79 yrs	721	9	45	49
over 80 yrs	135	8	47	45

[a] Risk factors are defined as elevated LDL-cholesterol >3.4 mmol/L (or >130 mg/dL), daily smoking, hypertension (blood pressure >140/90 or medication or self-reported hypertension), and type 2 diabetes.

common carotid IMT, $r = 0.05$ between plaque and internal carotid IMT, and $r = 0.11$ between plaque and bifurcation IMT (all $p < 0.0001$).

3.6. Multivariable determinants of carotid plaques

The multivariable associations between carotid plaques and the key conventional risk factors (high LDL-cholesterol, hypertension, smoking and type 2 diabetes) are shown in Table 6. These analyses were restricted to individuals free of clinical cardiovascular diseases. In the youngest generation (age 18–38 years), the strongest independent risk factor was LDL-cholesterol. High LDL-cholesterol (using cut-off 3.4 mmol/L or 130 mg/dL) was associated with about 3-fold increased risk of carotid plaque. Hypertension was also a strong independent risk factor in this age group and associated with 2-fold risk of plaque. Smoking was not associated with plaque in the youngest age group, and the association between type 2 diabetes and plaque could not be estimated due to low number participants with type 2 diabetes in this age group. In generation G1 (age group 40–58 years), both high LDL-cholesterol and hypertension were independently associated with plaque, however the effect estimates were smaller than in the youngest age group. Both high LDL-cholesterol and hypertension were associated about 20 % increased risk of plaque. In this age group, smoking was also associated with 27 % increased risk of plaque. Type 2 diabetes was associated with 12 % increased risk of plaque, but this association failed to reach conventional statistical significance. In the oldest generation (G0, 59–92 years), the independent correlates of plaque were hypertension (12 % increased risk), smoking (27 % increased risk) and type 2 diabetes (6 % increased risk), whereas high LDL-cholesterol showed no association with plaque.

3.7. Distribution of conventional risk factors in individuals with plaque

Table 7 shows the number of conventional risk factors in individuals who have plaque but who have not been diagnosed with a clinical cardiovascular disease. These data show that a substantially large proportion of individuals aged less than 50 years with subclinical carotid atherosclerosis are not identified by conventional risk factor assessments (see also graphical abstract). The proportion of individuals who had plaque but were free of conventional risk factors was the highest (42 %) in the youngest age group (18-29-year-olds). Similarly, in 30–39-year-olds, 40 % of the participants had no conventional risk factors.

For individuals ≥40-years, we also calculated the Systematic COronary Risk Evaluation score (SCORE2) that indicates the 10-year risk of fatal and non-fatal cardiovascular events. In the age group 40–49 years, 51 % of individuals with plaque were classified as having very low-risk (<2.5 % 10-year incidence), 44 % as having moderate risk (2.5 %–7.5 % 10-year incidence), and only 5 % as having high risk (>7.5 %). In the age-group 50–58 years, 19 % were classified as having low risk, 65 % as moderate risk, and 16 % as high risk.

4. Discussion

According to the 2021 European Guidelines on cardiovascular disease prevention [4], a documented carotid artery plaque in ultrasound examination is considered as established atherosclerotic cardiovascular disease that should be treated by using appropriate goals for LDL-cholesterol and systolic blood pressure. This recommendation is based on the premise that carotid plaque is a clear phenotypic sign of the ongoing atherosclerotic process that is associated with substantially increased risk of symptomatic cardiovascular disease outcomes. However, as carotid artery imaging is not routinely used as part of risk factor surveillance, most individuals with asymptomatic carotid atherosclerosis are unaware of their condition and not treated accordingly.

We found that the overall prevalence of carotid plaque was 48.2 % in

adults between ages 18–92 years. The prevalence increased sharply by age. A systematic review based on 59 studies published in 2020 estimated that the global prevalence of carotid plaque in the age group 30–79 years was 21.1 %, which is equivalent to 815.76 million people worldwide [25]. The global estimates are somewhat lower than in our study. The estimates from other studies are more in line with our observations. For example, the refine-Reykjavik study [26] reported plaque prevalence in 6524 participants between ages 25 and 68 years: the prevalence was about 5 % in the age group of 25–29 years and increased linearly being >80 % in the oldest age group of 65–69 years. In the PESA study (Progression of Early Subclinical Atherosclerosis), 31 % of Spanish participants aged between 40 and 54 (mean age 46 years) had carotid artery plaques [27]. In the Swedish VIPVIZA trial, carotid plaque prevalence was 28 % in the participants aged 40–47 years [20]. In the US BioImage study, carotid plaque was found in 78 % of participants aged 55–80 years (mean age 69 years) [9]. In a population-based Norwegian study, 87 % of the participants aged 63–65 years had carotid plaque [28]. Similarly, comparable prevalence estimates (about 56 % in 50–64 year-olds) of carotid artery plaques have been reported by the SCAPIS study in a Swedish population [29]. Thus, most of the recent studies have published very similar plaque prevalence estimates in adult populations. The only exception is the report by Song et al. on global estimates for carotid atherosclerosis [25] - a meta-analysis that included 59 studies from six WHO regions, including regions with estimated low (<20 %) carotid plaque prevalence, such as African region, region of the Americas, South-East Asia region and Eastern Mediterranean region. All European studies included in the meta-analyses using standard definition of plaques, including studies performed in Sweden, Denmark, Norway and Iceland, reported very similar prevalence estimates than in our study [25]. The slight differences between studies may reflect true differences between study populations, dissimilarities in the sensitivities of the used ultrasound methods to detect atherosclerosis, and slight variations in the definitions of the plaque. Overall, the studies indicate that asymptomatic carotid atherosclerosis is a very common finding in adult populations and increases by age.

Whereas carotid plaques were frequently present in adults, we did not detect them in individuals under the age of 18 years. Diffuse thickening of the intima–media complex in the carotid artery, on the other hand, is a common finding in children and adolescents with atherosclerotic risk factors, such as lipid disorders and type 1 diabetes [30,31], and such thickening may precede the development of atherosclerotic plaques [32,33]. Distinct plaques may also develop in children with a very high burden of atherosclerotic risk, as has been shown in one study including children with familial hypercholesterolemia that found about 10 % plaque prevalence in the second decade of life [34]. Atherosclerosis frequently begins early in life. In line, we have previously demonstrated that childhood dyslipidemia and smoking predict the development of carotid plaque in adulthood independent of the adult risk status [35]. Furthermore, growing evidence supports an association between early risk factor exposure and an increased risk of subsequent cardiovascular events later in life [3,36].

Carotid plaques were most commonly detected in the carotid bifurcation (65 % of the plaques), followed by internal carotid (25 %), and common carotid artery (10 %). These observations are in line with the notion that plaques occur rarely in the common carotid artery except in very advanced disease. This is related to the varying hemodynamics, with plaques developing in areas of low sheer stress [37]. Such conditions are present in the carotid bifurcation and internal carotid artery but not in the distal common carotid artery where shear stress is higher.

Apolipoprotein B-containing lipoproteins, of which LDL particles are the most abundant, are causally linked with atherosclerosis (mechanisms recently reviewed by Borén et al. [38]). We have previously shown in the Young Finns cohort that exposure to non-HDL-cholesterol levels (reflecting the concentration of apolipoprotein B lipoproteins) in childhood and adolescence contribute more than half of the lifetime effect to carotid plaque outcomes in mid-adulthood [39]. In the present study, we found that exposure to high LDL-cholesterol was associated with increased risk of carotid plaque, especially among young individuals. In individuals under the age of 40 years, high LDL-cholesterol (>3.4 mmol/L or 130 mg/dL) was associated with ~3-times greater risk of plaque (200 % increase in relative risk). In individuals aged between 40 and 58, high LDL-cholesterol was associated with about 20 % increase in plaque risk, and no association was seen in those older than 58 years. The strength of the association between hypertension and plaque also varied with age. Hypertension was associated with 2-times greater risk in individuals aged under 40 years (100 % increase in relative risk), but only 19 % risk increase was observed in the age group 40–58, and a modest 12 % increase in risk was seen in individuals older than 58 years. Together, these observations emphasize the importance of optimal LDL-cholesterol and blood pressure control starting early in life, and are reinforced by modelling studies indicating that substantial reductions in expected cardiovascular disease risk are achievable by lipid lowering in individuals in their 40s and 50s with non-optimal lipid levels [40].

Although high LDL-cholesterol and hypertension were strongly correlated with carotid plaque in young and middle-aged individuals, a large proportion of especially young adults with plaques had no conventional risk factors. For example, ~40 % of individuals with plaque between ages 18 and 39 were free of conventional risk factors, and among 40-49-year-olds, about half of those with plaque were defined as having very low cardiovascular risk according to the SCORE2 risk calculator. Thus, conventional risk factor assessments fail to identify a large proportion of young individuals who have an ongoing atherosclerotic process. Therefore, many young individuals with silent atherosclerosis do not fulfil criteria for initiating interventions. This may not be surprising, given that, for example, the atherogenicity of LDL particles is not solely determined by their concentration, but also by various other properties influencing their retention and modification in the arterial wall not captured by the LDL-cholesterol concentration measures [38]. The proportion of individuals with plaques not identified by conventional risk factors became smaller by increasing age but was still 19 % between ages 50 and 58 years. These results are in line with previous observations noting that conventional risk factor assessments do not perform optimally in identifying individuals with silent atherosclerosis [27,41] and suggest added value of imaging in cardiovascular prevention, especially in young individuals [20]. Thus, atherosclerosis is not solely a concern for older individuals or those with established conventional risk factors.

It could be argued that the performance of standard risk factors could be improved by the inclusion of other circulatory biomarkers, such as inflammatory markers and polygenic risk scores. In this report, however, our aim was not to find an optimal set of biomarkers to identify atherosclerosis, but to examine how well standard risk factors, used in everyday practice, perform in identifying individuals with plaques.

Several studies have shown that carotid plaque imaging improves risk reclassification and identifies individuals at increased risk for cardiovascular events [4,42]. Most research has focused on older populations, but evidence is emerging that asymptomatic plaques are also strong risk factors for future events in young adults [19,23]. However, it remains unclear whether screening for silent atherosclerosis reduce cardiovascular events, as direct evidence from randomized clinical trials is missing. The international research initiative “Reversal of Early Atherosclerosis through personalized Curative Treatment”, aims to provide such evidence. The study will screen for subclinical atherosclerosis through imaging and other potential risk factors [20]. The inclusion of additional phenotypic and genotypic risk markers, alongside imaging, is warranted because the prevalence of subclinical atherosclerosis is very high in middle-aged and older individuals. However, not all of these individuals will develop symptomatic cardiovascular disease as majority of plaques remain clinically silent. Therefore, an imaging-guided approach for early treatment might lead to overtreatment [20]. Clearly, more research is needed to develop tools to identify subtypes of silent atherosclerosis with a higher risk of adverse

cardiovascular events [43].

Although the evidence from randomized trials is missing demonstrating the benefits of atherosclerosis screening in the reduction of cardiovascular events, there is trial evidence indicating that screening may strengthen health promotion [44]. A recent systematic review and meta-analysis demonstrated that patient visualization of subclinical atherosclerosis is associated with improvement of conventional risk factors, including LDL-cholesterol and systolic blood pressure [45].

In our population, adults with plaque had about 2-times increased age and sex adjusted risk for any prevalent clinical cardiovascular disease, and about 3-times increased risk for prevalent coronary artery diseases. Furthermore, the prevalence of clinical cardiovascular diseases was directly related to the severity of atherosclerosis, assessed by the number of plaques, plaque area and plaque thickness. For example, individuals with more than 5 plaques had 5-times increased prevalence of coronary artery disease compared to individuals without plaque. In our population, however, the association between plaque and atherosclerotic cerebrovascular disease was weaker than previously reported. This could be attributable to lower frequency of cerebrovascular as compared to cardiac clinical diseases, or less accurate self-reports concerning cerebrovascular diseases, *i.e.* including also other etiologies than atherosclerosis.

We found that individuals with carotid plaque had on average much higher carotid IMT values in the common carotid artery, carotid bifurcation and internal carotid artery than individuals without plaque. In line, several cross-sectional studies have demonstrated associations between these two phenotypes. It has also been shown that increased IMT is a risk factor for the development of plaque suggesting that it may be useful to identify high-risk individuals at an even earlier stage of the atherosclerosis development [33]. Both carotid plaque and high IMT values predict the incidence of cardiovascular events. One meta-analysis suggested that carotid plaque had slightly higher diagnostic accuracy for the prediction of future coronary artery disease than carotid IMT [42]. Combining the information of these two phenotypes to conventional risk factors, however, may provide the best predictive model [46]. Whereas carotid plaque is distinct phenotype of atherosclerosis, carotid IMT may not be specific to atherosclerosis, and can represent hypertensive medial hypertrophy or thickening of smooth muscles in the media [47]. Nevertheless, we have previously shown in the YFS cohort that both carotid plaques and increased IMT identified in young adults predict incident cardiovascular events [23]. As increase in IMT predicts the development of plaques it may present an important risk phenotype, especially among young populations where distinct plaques occur rarely. Furthermore, Bao et al. [48] recently reported from the large Malmö Study that both carotid plaque and IMT significantly added predictive information to conventional risk factors for cardiovascular events. The use of carotid IMT as a clinical screening tool may be challenging, however, because IMT values are highly dependent on the ultrasound equipment and methods used in analyzing the images, hence making it difficult to establish uniform reference values.

4.1. Limitations

We used 2D ultrasound and manual tracing of the ultrasound images to visualize plaques using software imaging tools. While this method allows for precise delineation of plaque borders, especially in complex or irregular plaques, it is very time-consuming and requires significant operator expertise. Automated image analysis could have offered faster and potentially more objective alternative, but has other challenges, such as acoustic shadowing from calcification or vessel tortuosity that may hinder automated analysis [49]. Furthermore, using a newer 3D ultrasound technique may have offered some advantages over the 2D ultrasound, primarily due to its ability to capture comprehensive volumetric plaque data [50]. In addition, we only scanned carotid arteries, but not other potential sites accessible for ultrasound, such as femoral arteries. In the PESA study, femoral plaques were the most common type of plaque observed. The study found that 44 % of participants had plaques in their femoral arteries, surpassing the prevalence of carotid plaques [27]. This suggests that the iliofemoral territory might be particularly susceptible to atherosclerosis development. We had to rely on self-reported cardiovascular diagnoses for part of the population. These are subject to reporting biases, potentially leading to underestimation or misclassification, particularly for cerebrovascular diseases. Therefore, weaker associations noted for cerebrovascular events likely reflects ascertainment bias rather than true pathophysiological differences. We did not measure coronary calcium scores, which may be a more robust predictor of cardiovascular events than carotid ultrasound [4]. Finally, the study was conducted in Finland and the participants included were mainly of European descent. Therefore, it may not be appropriate to extrapolate our findings to other ethnicities.

In conclusion, we found that carotid artery plaques are very prevalent finding among Finnish adults but not observed in children of the general population. High LDL-cholesterol concentration and hypertension are strongly associated with plaques, especially among young adults. On the other hand, we also found that a substantially large proportion of young and middle-aged adults with plaques are not identified by the assessment of conventional risk factors.

CRediT authorship contribution statement

Olli T. Raitakari: Study design, administration, data collections, data analyses, writing the manuscript. **Juhani S. Koskinen:** ultrasound image analyses, data collections, commenting and writing the manuscript. **Katja Pahkala:** data collections, commenting and writing the manuscript. **Suvi Rovio:** data collections, commenting and writing the manuscript. **Juha Mykkänen:** data collections and commenting. **Noora Kartiosuo:** statistical consulting and commenting, . **Sini Stenbacka:** data-management, commenting. **Irina Lisinen:** data-management, commenting. **Britt-Marie Loo:** data collections, laboratory analyses, commenting. **Terho Lehtimäki:** data collections and commenting. **Mika Kähönen:** data collections and commenting. **Markus Juonala:** data collections and commenting. **Tomi P. Laitinen:** data collections and commenting. **Eero Jokinen:** data collections and commenting. **Jari Kaikkonen:** data collections and commenting. **Päivi Tossavainen:** data collections and commenting. **Jorma S.A. Viikari:** study design, Project administration, data collections, writing the manuscript.

Financial support

The Young Finns Study has been financially supported by the Academy of Finland: grants 356405, 322098, 286284, 134309 (Eye), 126925, 121584, 124282, 129378 (Salve), 117797 (Gendi), and 141071 (Skidi); the Social Insurance Institution of Finland; Competitive State Research Financing of the Expert Responsibility area of Kuopio, Tampere and Turku University Hospitals (grant X51001); Juho Vainio Foundation; Paavo Nurmi Foundation; Finnish Foundation for Cardiovascular Research; Finnish Cultural Foundation; The Sigrid Juselius Foundation; Tampere Tuberculosis Foundation; Emil Aaltonen Foundation; Yrjö Jahnsson Foundation; Signe and Ane Gyllenberg Foundation; Diabetes Research Foundation of Finnish Diabetes Association; EU Horizon 2020 (grant 755320 for TAXINOMISIS and grant 848146 for To Aition); European Research Council (grant 742927 for MULTIEPIGEN project); Tampere University Hospital Supporting Foundation; Finnish Society of Clinical Chemistry; the Cancer Foundation Finland; pBETTER4U_EU (Preventing obesity through Biologically and bEhaviorally Tailored inTERventions for you; project number: 101080117); CVDLink (EU grant no. 101137278) and the Jane and Aatos Erkko Foundation.

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.2025.120426.

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