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Parental coronary and peripheral artery disease and artery segments in patients and partners – The first and second generation in the Norwegian Stroke in the Young Study

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Keywords
Heredity; atherosclerosis; parental history of cardiovascular disease (CVD); young stroke; carotid intima-media thickness (cIMT) and femoral intima-media thickness (fIMT)

ABSTRACT

Introduction: Age, sex and family history of cardiovascular disease (CVD) are non-modifiable risk factors of CVD in offspring. Our aim was to relate parental CVD (pCVD) to artery vessel-wall measurements in offspring.
Patients and methods: Offspring consisted of acute ischaemic stroke patients (15-60 years) and their partners. Young offspring was defined as ≤45 years old. Arterial wall changes were assessed as intima-media thickness of carotid and femoral arteries (cIMT/fIMT), abdominal aortic plaques (AAP), and ankle-arm index (AAI). Any offspring reported parental coronary artery disease (pCAD) and parental peripheral artery disease (pPAD). In addition, pCAD and pPAD were also verified by standardized questionnaires for living parents, or by medical records for deceased parents.
Results: Reported vs. verified pCVD was present for around 90% vs. 50% of parents. Reported pCAD/pPAD was positive for 227/67 offspring and verified pCAD/pPAD was positive for 148/36 offspring, respectively.
Reported and verified pCAD and pPAD were related to higher cIMT and fIMT. Reported and verified pCAD was also related to AAP and reported pPAD to AAI. The effect attenuated after adjusting for age, hypertension, dyslipidemia, diabetes mellitus and smoking. Among young offspring, reported pCAD was associated with higher cIMT and fIMT, even though the total number of young offspring was 4-fold lower compared to middle-aged offspring.
Conclusions: Parental CVD is related to artery wall changes in offspring, particularly in young offspring. Regarding CVD risk assessment, extensive parental verification of CVD might not be necessary as many young patients and partners seem to be well-orientated about their parental CVD. Primary prevention from young age should get more attention.

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Introduction

Most diseases are now recognized as results of genetic aspects and environmental and lifestyle risk factors. Atherosclerosis is a generalized disease and a major risk factor for cardiovascular events (CVE), such as ischaemic stroke, coronary artery disease (CAD), and peripheral artery disease (PAD). Several studies demonstrated increased early mortality in young stroke patients, mainly as result from coronary death due to atherosclerosis [1-3].

Challenges in performing family studies of CVE include accuracy in documenting the different types of strokes. In addition, previous studies have also combined negative parental CVE with uncertain

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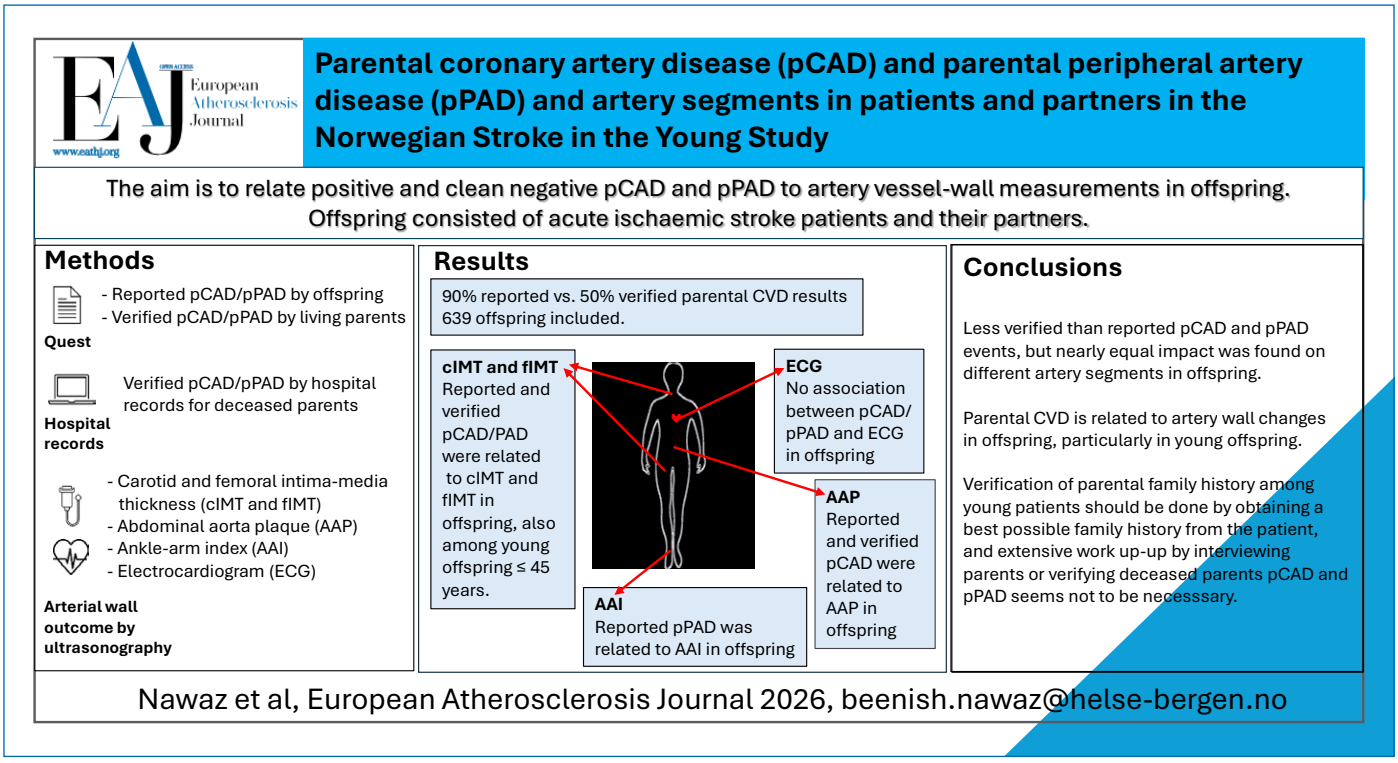


Graphical Abstract

parental CVE, grouping them altogether as negative to avoid exaggeration of the results [4, 5]. However, uncertainty may have led to blurred results, and premature parental CAD (pCAD) is widely accepted as a marker of increased CVE risk in offspring [6].

The aim of this study was to present data as accurate as possible by restricting parental CVD (pCVD) to CAD and PAD, both mainly caused by atherosclerosis. Comparing parental CAD (pCAD) and parental PAD (pPAD) information from offspring with verified information from living parents and verified information by medical records for deceased parents contributed to the accuracy of pCVD. Only either positive or pure negative pCVD data were then related to standardized artery segment measurements by a standardized ultrasound protocol in offspring, consisting of acute ischaemic stroke patients and their partners.

Patients and methods

First and second generation

Inclusion was conducted between 1st September 2010 to 31st December 2015. The first generation consisted of parents of young stroke patients and their partners. pCAD and pPAD were obtained either as reported by their offspring (r-pCAD and r-pPAD), who were

Abbreviations

AAI	Ankle arm index
AAP	Abdominal aorta plaque
CAD	Coronary artery disease
CVD	Cardiovascular disease
CVE	Cardiovascular events
CI	Confidence interval
cIMT	Carotid intima-media thickness
ECG	Electrocardiogram
fIMT	Femoral intima-media thickness
OR	Odds ratio
PAD	Peripheral artery disease
pCAD	Parental coronary artery disease
pCVD	Parental cardiovascular disease
pPAD	Parental peripheral artery disease

r-pCAD	Reported parental coronary artery disease
r-pCADneg	Negative reported parental coronary artery disease
r-pCADpos	Positive reported parental coronary artery disease
r-pCVD	Reported parental cardiovascular disease
r-pPAD	Reported parental peripheral artery disease
r-pPADneg	Negative reported parental peripheral artery disease
r-pPADpos	Positive reported parental peripheral artery disease
v-pCAD	Verified parental coronary artery disease
v-pCADneg	Negative verified parental coronary artery disease
v-pCADpos	Positive verified parental coronary artery disease
v-pCVD	Verified parental cardiovascular disease
v-pPAD	Verified parental peripheral artery disease
v-pPADneg	Negative verified parental peripheral artery disease
v-pPADpos	Positive verified parental peripheral artery disease

regarded as the second generation [7] or verified directly by participating parents by standardized questionnaires or by medical records for deceased parents (v-pCAD and v-pPAD) [8, 9].

Parental history was defined as positive if at least one parent had a positive history of CAD or PAD ($pCAD^{pos}$ and $pPAD^{pos}$). Parental history was defined as negative if none of the parents had a history of CAD or PAD ($pCAD^{neg}$ and $pPAD^{neg}$). Missing or uncertain parental history was excluded from analysis.

The second generation included ischaemic stroke patients at age 15-60 years and their partners or ex-partners, if the patients consented to invite them for inclusion. Partners were at least 18 years old. Inclusion criteria were young and middle-aged acute stroke patients at age 15-60 years, who were admitted to the Department of Neurology at Haukeland University Hospital. Young study participants were defined as 15-45 years old, and middle aged were defined as >45 years old. The diagnosis of ischaemic stroke was verified radiologically. Patients with post-traumatic stroke, stroke caused by sinus venous thrombosis, septicaemia, intracerebral haemorrhage, procedure-related cerebral infarction, serious co-morbidity (advanced cancer or multiple sclerosis) or otherwise limited co-operation (non-native language speakers or patients with severe psychiatric illness) were excluded from the study. Patients consented to contact their partners/ex-partners and parents, and partners/ex-partners consented to contact their parents. Living parents were invited to participate actively by returning a standardized questionnaire [10].

Outcome variables of artery wall measurements and vascular risk factors in the second generation

Patients and partners performed a standardized ultrasound protocol for staging of atherosclerosis by a) carotid and femoral intima-media thickness (cIMT and fIMT). Mean IMT measurements were obtained at 1 cm predefined segments of the common carotid artery, carotid bifurcation, internal carotid artery, common femoral artery and superficial femoral artery. We used the maximum of 12 mean cIMT segment values and 4 fIMT segment values for further analysis, and plaques were included into the IMT measurements at pre-defined standardized sites [11]; b) presence of abdominal aortic plaques (AAP); c) pathological ankle-arm index (AAI) ≤0.9 and d) presence of ischaemic electrocardiogram (ECG), evaluated by a cardiologist (SS). Detailed description of methods was published previously, including the ultrasound protocol, by which any including doctor was internationally certified [10].

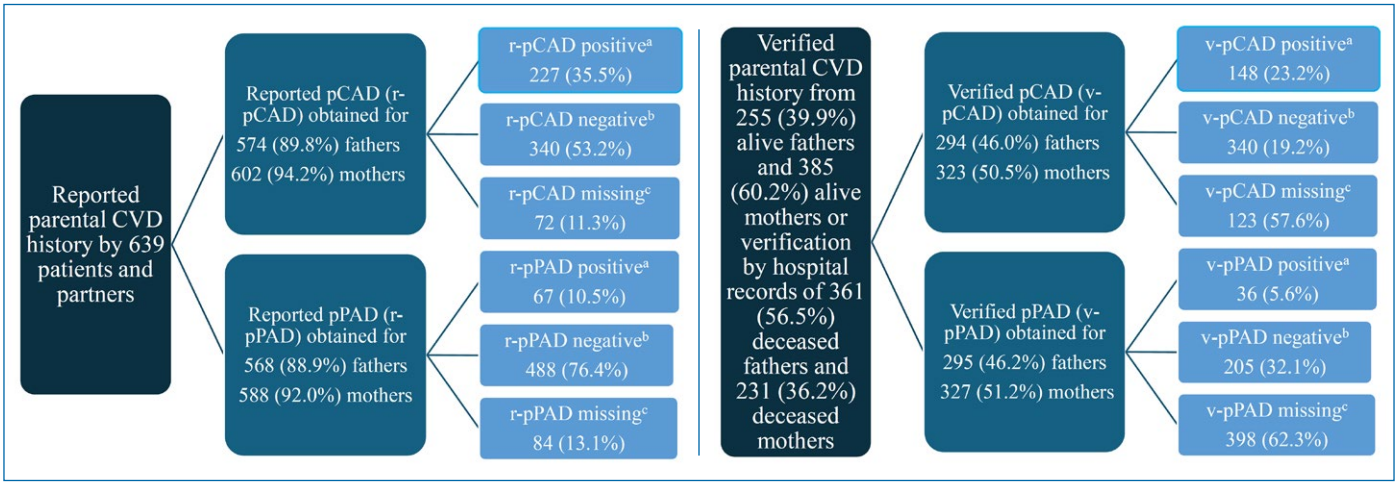
Hypertension and dyslipidaemia were defined as known when treated by lifestyle changes and/or by medications. Hypertension was newly diagnosed if blood pressure was >140/90 mmHg in two separate measurements in both arms after 15-30 minutes rest in supine position after performed ultrasound. Diabetes mellitus and dyslipidaemia was diagnosed by blood samples by HbA1c ≥ 6.5%, a total cholesterol >5.0 mmol/L, low-density lipoprotein >3.0 mmol/L, high density lipoprotein <1.0 mmol/L, and/or fasting triglycerides >2.5 mmol/L in stroke patients only. The history of smoking was considered present if an active study participant was a current (smoked within the past year before inclusion) or former smoker.

Ethical considerations

The study complies with the Declaration of Helsinki and is approved by the Regional Ethics Committee (REK-Vest 2010/74) and registered in ClinicalTrials.gov: NCT01597453. Written consent is present for all active study participants. Parents of patients and partners/ex-partners were invited to the study after patients' and partners' consent, respectively. Verification of pCAD and pPAD in hospital records of deceased parents was done after patients' or partners' consent.

Statistics

Descriptive statistics are presented as frequencies or mean values and 95% confidence intervals (CI). Comparisons between positive and negative pCAD and pPAD, and outcome variables of atherosclerosis in their offspring were done by performing t-test and linear regression for continuous variables (cIMT and fIMT), and chi-square test and logistic regression for dichotomous variables (ECG, AAP, AAI). The results for linear and logistic regression were given as coefficients and odds ratios (OR) with 95% CI, respectively. Multivariable linear and



Flowchart 1 | Participation rates of parents and results of parental coronary heart disease (pCAD) and peripheral artery disease (pPAD) in Norwegian Stroke in the Young Study.
Abbreviations: CVD = cardiovascular disease.
[a]At least one parental positive result.
[b]Both parents were negative.
[c]One or both parents with uncertain results.

logistic regression analyses were also adjusted for age, sex and vascular risk factors including hypertension, diabetes mellitus, dyslipidaemia and smoking. Data analyses were performed using Stata SE 18.0. A P-value <0.05 was considered significant.

Results

Participation rates of parents in the first generation

Reported pCVD history was obtained for around 90% of parents (**Flowchart 1**). For the purpose of verification of the pCVD, patients and partners consented to contact 255 (39.9%) living fathers and 385 (60.2%) living mothers, whereas hospital records were checked for 361 (56.5%) deceased fathers and 231 (36.2%) deceased mothers. In total, verified pCVD history was obtained for around 50% of parents (**Flowchart 1**).

Participation rates of offspring in the second generation

After exclusion of 6 adopted study participants, 381 ischaemic stroke patients (59.6%) and 258 partners (40.4%) were included. Of 639 study participants, 168 (26.3%) were at young age ≤45 years, and 340 (53.2%) were men. Patients were at age 15-60 years, and partners were at age 21-69 years. The mean age of offspring was 49.8 (SD ±9.3) years.

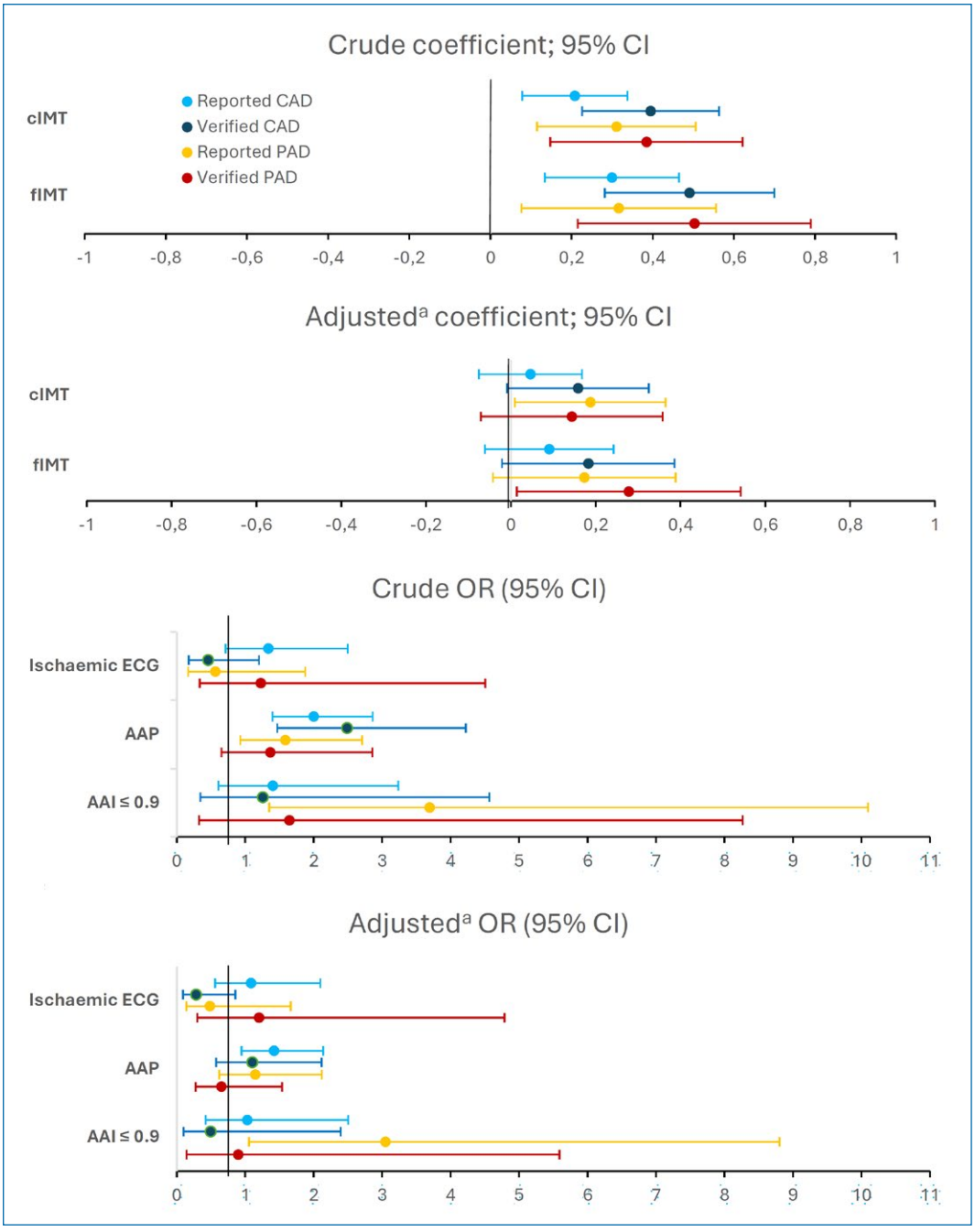


Figure 1A
Forest plot showing association between reported and verified parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) to arterial outcome measurements among 639 offspring, consisting of acute ischaemic stroke patients and their partners in the Norwegian Stroke in the Young Study.

Parental cardiovascular events

There were more r-pCVD results than v-pCVD results (around 90% vs 50%, Flowchart 1). The missing data was much lower for the r-pCVD group than for the v-pCVD group (around 12% vs 60%, **Figure 1**).

After exclusion of missing data, the prevalence of r-pCAD vs. v-pCAD was 40.0% vs. 54.6%; r-pPAD vs. v-pPAD was 12.1% vs. 14.9%, respectively. Among young participants ≤45 years, the prevalence of r-pCAD vs. v-pCAD was 23.0% vs. 30.0%, and r-pPAD vs. v-pPAD was 7.1% vs. 6.8%, respectively.

Prevalent atherosclerosis among the second generation

Mean cIMT and fIMT among all study participants were 1.23 mm and 1.24 mm, respectively (**Table 1**). AAP had the highest prevalence with 42.1%.

Mean cIMT and fIMT among young study participants were 0.79 mm and 0.75 mm, respectively. Young study participants had significantly lower cIMT, fIMT, AAP and AAI compared to middle-aged participants (**Table 1**).

Association of parental CAD and PAD to artery segments in offspring in the second generation

r-pCAD and v-pCAD were associated with higher cIMT, fIMT and AAP. r-pPAD and v-pPAD were associated with higher cIMT and fIMT, and r-pPAD was also associated with AAI (**Table 2**, **Figure 1a** and **Supplementary Table 1a**). The effect was not affected by sex of study participants.

r-pCAD was associated with higher fIMT after adjustment for vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia and smoking), and with AAP after adjustment for age. v-pCAD was associated with higher cIMT and fIMT after adjustment for age and vascular risk factors separately, and there was a trend towards higher cIMT and fIMT after adjustments for both age and vascular risk factors (p = 0.063 and p = 0.078, respectively). v-pCAD was inversely related to ischaemic ECG. (**Figure 1b** and **Supplementary table 1a**).

Table 1 | Prevalent atherosclerosis among offspring in the second generation, consisting of young and middle-aged ischaemic stroke patients and their partners in the Norwegian Stroke in the Young Study.

	Offspring, n = 639	NA	≤45 years, n = 168 (26.3%)	>45 years, n = 471 (73.7%)	P-value
Mean cIMT, mm (95% CI)	1.23 (1.17, 1.29)	3	0.79 (0.74, 0.83)	1.39 (1.31, 1.46)	**<0.001**[a]
Mean fIMT, mm (95% CI)	1.24 (1.16, 1.32)	8	0.75 (0.67, 0.83)	1.41 (1.32, 1.51)	**<0.001**[a]
Ischaemic ECG, n (%)	47 (7.4)	4	9 (5.3)	38 (8.1)	0.238[b]
AAP, n (%)	247 (42.1)	52	24 (15.4)	223 (51.7)	**<0.001**[b]
AAI ≤0.9, n (%)	24 (3.9)	28	1 (0.6)	23 (5.1)	**0.011**[b]

Abbreviations: n = number of offspring; NA = missing; cIMT = carotid intima-media thickness; mm = millimeter; CI = confidence interval; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle arm index.
[a] P-value is estimated by t-test.
[b] P-value is estimated by chi-square test.

Table 2 | Association between reported and verified parental coronary artery disease (CAD) and peripheral artery disease (PAD) and arterial outcome variables among offspring, consisting of acute ischaemic stroke patients and partners in the Norwegian Stroke in the Young Study.

	Reported parental CAD			Verified parental CAD		
Arterial outcome variables in offspring	**n**	**Value (95% CI)**	**P-value**	**n**	**Value (95% CI)**	**P-value**
Mean cIMT[a]	564	1.20 (1.14, 1.27)	**0.002**	270	1.15 (1.06, 1.24)	<0.001
Mean fIMT[a]	561	1.21 (1.14, 1.30)	**<0.001**	270	1.12 (1.01, 1.23)	<0.001
Ischaemic ECG[b]	563	1.34 (0.72, 2.49)	0.362	269	0.46 (0.17, 1.20)	0.106
AAP[b]	520	2.00 (1.40, 2.86)	**<0.001**	250	2.49 (1.47, 4.22)	0.001
AAI ≤0.9[b]	544	1.40 (0.61, 3.24)	0.631	260	1.26 (0.35, 4.56)	0.727
	Reported parental PAD			**Verified parental PAD**		
Mean cIMT[a]	552	1.21 (1.14, 1.27)	**0.018**	240	1.12 (1.04, 1.21)	0.045
Mean fIMT[a]	547	1.19 (1.11, 1.27)	**0.016**	240	1.06 (0.95, 1.16)	0.005
Ischaemic ECG[b]	553	0.56 (0.17, 1.88)	0.343	239	1.23 (0.33, 4.50)	0.757
AAP[b]	512	1.58 (0.93, 2.71)	0.090	225	1.36 (0.65, 2.86)	0.408
AAI ≤0.9[b]	532	3.69 (1.35, 10.09)	**0.007**	232	1.65 (0.33, 8.27)	0.542

Abbreviations: CAD = coronary artery disease; *n* = number of offspring; CI = confidence interval; cIMT = carotid intima-media thickness; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaque; AAI = ankle-arm index; PAD = peripheral artery disease.
[a] Mean difference (95% CI), p-value estimated by t-test
[b] Odds ratio (95% CI), p-value estimated by chi-square test.

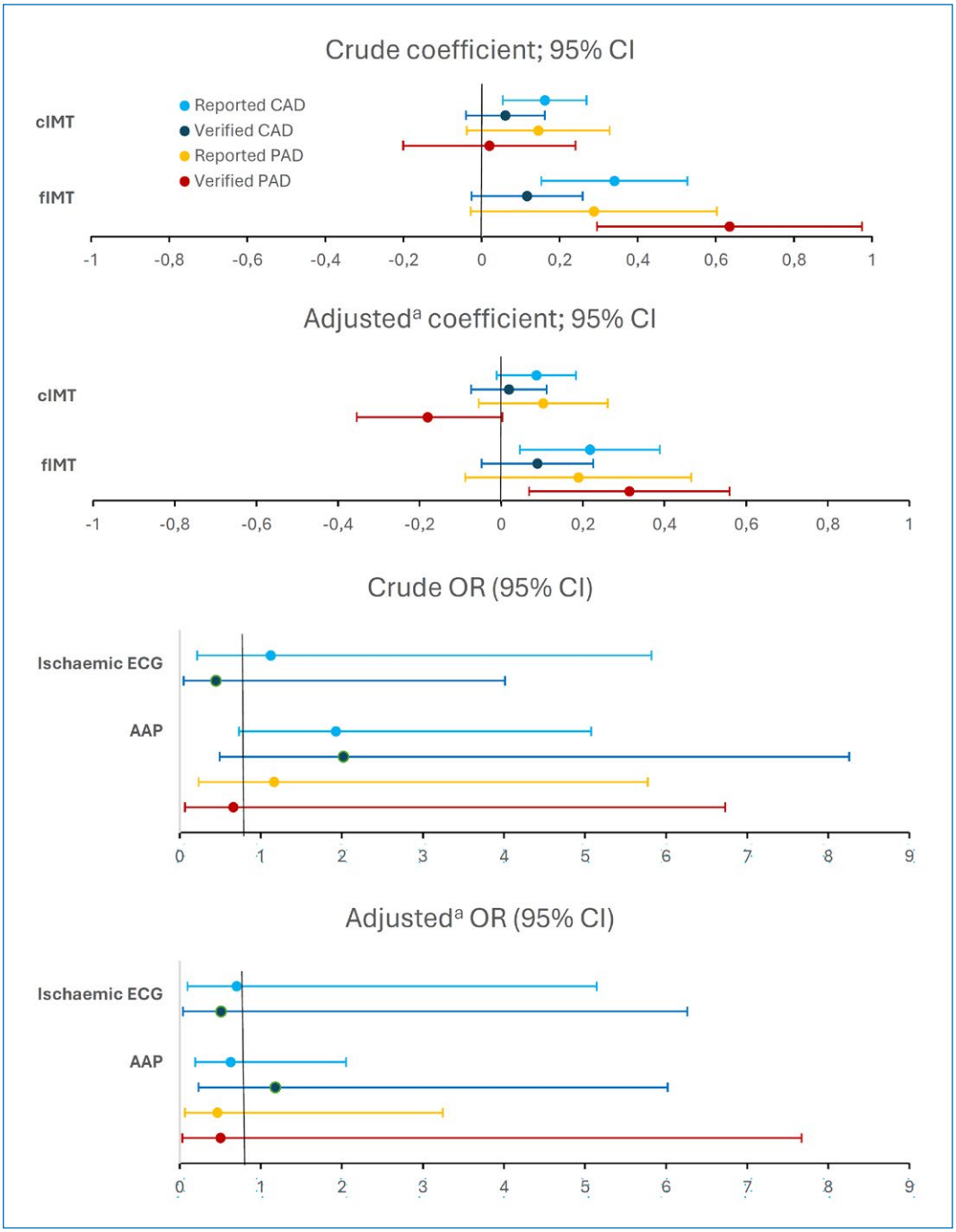


Figure 1B
Forest plot showing association between reported and verified parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) to arterial outcome measurements among 168 offspring, consisting of acute ischaemic stroke patients and their partners aged ≤45 years in the Norwegian Stroke in the Young Study. Abbreviations: CI = confidence interval, cIMT = carotid intima-media thickness; fIMT = femoral intima-media thickness; OR = odds ratio; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle-arm index; a Adjusted for age and vascular risk factors (hypertension, diabetes mellitus, dyslipidaemia and smoking).

r-pPAD was related to higher cIMT and AAI after adjustments for age and risk factors. v-pPAD was related to higher cIMT after adjustment for risk factors, and to fIMT after adjustments for age and risk factors. (**Figure 1b** and **supplementary Table 1a**).

A sub-analysis for young study participants showed that r-pCAD was related to higher cIMT and fIMT (**Table 3b**, **Figure 1b** and **Supplementary Table 1b**). v-pPAD was related to higher fIMT. Sex had no impact on the results. After adjusting for age and vascular risk factors, r-pCAD and v-pPAD were related to higher fIMT. (**Supplementary Table 1b**).

Comparison of reported positive and negative parental family history to arterial wall changes in the second generation

Crude results of reported vs. verified pCVD were almost similar, however, there were more missing results in the verified group. Therefore, comparisons of positive and negative pCAD and pPAD to arterial wall changes among offspring were only performed for the reported group. Mean cIMT and fIMT were higher and AAP was more frequent among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg} (**Table 3A**). Mean cIMT and fIMT were higher and AAI more frequent

among study participants with r-pPAD^{pos} compared with those with r-pPAD^{neg}.

For young study participants ≤45 years, mean cIMT and fIMT were higher among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg} (**Table 3B**). For middle-aged study participants, AAP was more frequent among study participants with r-pCAD^{pos} compared with those with r-pCAD^{neg}, and AAI was more frequent among study participants with r-pPAD^{pos} compared to those with r-pPAD^{neg} (**Table 3C**).

Discussion

Positive pCAD and pPAD is along with age and sex a well-known non-modifiable marker of atherosclerosis, and is regarded as a

Table 3 | Arterial outcome variables among offspring, consisting of ischaemic stroke patients and their partners for reported positive and negative parental coronary artery disease (CAD) and peripheral artery disease (PAD) in the Norwegian Stroke of the Young Study.

Arterial outcome variables among all offspring	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 226	1.33 (1.22, 1.44)	*n* = 338	1.12 (1.04, 1.20)	0.002[a]
Mean fIMT, mm (95% CI)	*n* = 226	1.39 (1.26, 1.53)	*n* = 335	1.10 (0.99, 1.20)	<0.001[a]
Ischaemic ECG, n (%)	*n* = 225	20 (8.9)	*n* = 338	23 (6.80)	0.362[b]
AAP, *n* (%)	*n* = 209	107 (51.2)	*n* = 311	107 (34.4)	<0.001[b]
AAI ≤0.9, *n* (%)	*n* = 217	11 (5.1)	*n* = 327	12 (3.7)	0.631[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 67	1.48 (1.23, 1.73)	*n* = 485	1.17 (1.11, 1.24)	0.018[a]
Mean fIMT, mm (95% CI)	*n* = 66	1.47 (1.22, 1.71)	*n* = 481	1.15 (1.07, 1.23)	0.016[a]
Ischaemic ECG, *n* (%)	*n* = 66	3 (4.5)	*n* = 487	38 (7.8)	0.343[b]
AAP, *n* (%)	*n* = 61	31 (50.8)	*n* = 451	178 (39.47)	0.090[b]
AAI ≤0.9, *n* (%)	*n* = 63	6 (9.5)	*n* = 469	13 (2.8)	0.007[b]
Arterial outcome variables among offspring ≤45 years	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 35	0.90 (0.76, 1.03)	*n* = 115	0.73 (0.69, 0.78)	0.024[a]
Mean fIMT, mm (95% CI)	*n* = 35	0.99 (0.74, 1.23)	*n* = 114	0.64 (0.57, 0.71)	0.010[a]
Ischaemic ECG, n (%)	n = 35	2 (5.7)	*n* = 117	6 (5.1)	0.892[b]
AAP, *n* (%)	n = 35	8 (22.9)	*n* = 105	14 (13.3)	0.180[b]
AAI ≤0.9, *n* (%)	n = 35	0 (0.0)	*n* = 113	1 (0.9)	0.577[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 11	0.91 (0.69, 1.14)	*n* = 141	0.77 (0.72, 0.82)	0.192[a]
Mean fIMT, mm (95% CI)	*n* = 11	0.99 (0.55, 1.44)	*n* = 140	0.71 (0.62, 0.79)	0.189[a]
Ischaemic ECG, *n* (%)	*n* = 11	0 (0.0)	*n* = 143	8 (5.6)	0.649[b]
AAP, *n* (%)	*n* = 11	2 (18.2)	*n* = 131	21 (16.0)	0.852[b]
AAI ≤0.9, *n* (%)	*n* = 11	0 (0.0)	*n* = 140	1 (0.70)	0.779[b]
Arterial outcome variables among offspring >45 years	**Positive reported parental CAD**		**Negative reported parental CAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 191	1.41 (1.29, 1.53)	*n* = 223	1.32 (1.22, 1.43)	0.291[a]
Mean fIMT, mm (95% CI)	*n* = 191	1.47 (1.32, 1.62)	*n* = 221	1.33 (1.19, 1.47)	0.174[a]
Ischaemic ECG, *n* (%)	*n* = 190	18 (9.5)	*n* = 221	17 (7.7)	0.519[b]
AAP, *n* (%)	*n* = 174	99 (56.9)	*n* = 206	93 (45.1)	0.022[b]
AAI ≤0.9, *n* (%)	*n* = 182	11 (6.0)	*n* = 214	11 (5.1)	0.696[b]
	Positive reported parental PAD		**Negative reported parental PAD**		**P-value**
Mean cIMT, mm (95% CI)	*n* = 56	1.59 (1.31, 1.88)	*n* = 344	1.34 (1.25, 1.42)	0.089[a]
Mean fIMT, mm (95% CI)	*n* = 55	1.56 (1.28, 1.84)	*n* = 341	1.33 (1.23, 1.44)	0.126[a]
Ischaemic ECG, n (%)	*n* = 55	3 (5.5)	*n* = 344	30 (8.7)	0.414[b]
AAP, n (%)	*n* = 50	29 (58.0)	*n* = 320	157 (49.1)	0.240[b]
AAI ≤0.9, n (%)	*n* = 52	6 (11.5)	*n* = 329	12 (3.6)	0.013[b]

Abbreviations: cIMT = carotid intima-media thickness; mm = millimeter; CI = confidence interval; n = number of offspring; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle arm index; PAD = peripheral artery disease.
[a] P-value is estimated by t-test.
[b] P-value is estimated by chi-square test.

surrogate marker for genetic predisposition [12]. Few studies have analyzed the sharing of familial susceptibility to atherosclerotic disease at several vascular areas. In a Swedish nationwide register study, risk of CAD, ischaemic stroke, PAD and aortic disease was increased among siblings and offspring [13]. To our knowledge, our study is unique as this is a prospective study where patients/partners as the second generation were thoroughly examined at standardized artery segments at different vascular areas by an extensive ultrasonographic protocol. Previous studies of pathology have shown that atherosclerosis is not equally distributed in the body [14]. A study of 212 patients without known CVD showed high presence of subclinical atherosclerosis in carotid, femoral and coronary areas, but only a weak concordance between different vascular territories, and suggested that all three vascular areas should be investigated [15].

Interestingly, most of our crude (unadjusted) results were not affected by the methods chosen to obtain the pCVD history. Our previous study showed that reported pCVD history by patients was in good concordance with parental reports [8]. Our results show that comprehensive verification work of parental history may give us slightly higher prevalence of CAD and PAD in the verified group, however, due to the large number of missing data among the verified group, it is not easy to draw a conclusion.

We found a positive association between pCAD and higher cIMT, fIMT and AAP, suggesting that parental CAD increases the risk of generalized atherosclerosis in the next generation, mainly in carotid and femoral arteries and aorta. A positive association of pCAD to cIMT in offspring has been well-documented in other studies, also in the younger population [16-21] However, data is scarce for the association of pCAD with fIMT and AAP. A study has shown that parental occurrence of premature CVD may predict abdominal aortic calcification in the second and third generation [22].

Our study showed a weak inverse relation of v-pCAD to ischaemic ECG changes in the offspring. This may be attributed to selection bias among partners who participated, and a low sample size with low prevalence of ischaemic ECG (7.4%). Another possible explanation could have been a trend towards a healthier lifestyle for young adults with known pCAD history. However, a cross sectional study from three large epidemiological studies reported positive association of pCAD with ECG changes in offspring after adjustment for age, smoking, BMI and sex, [23] so there may be a type 1 error in our study.

Overall, pPAD is less studied than pCAD. We found a positive association of pPAD to cIMT and pathological AAI, suggesting that pPAD increases the risk of generalized atherosclerosis. There is scarce literature on the association of pPAD to cIMT, which makes our study quite unique. The San Diego Population study of 2404 participants from an ethnically diverse population aged between 29-91 years, found that there was a strong association between pPAD to PAD prevalence (OR 1.83) and PAD-severity (OR 2.42) in the offspring. PAD was defined as AAI ≤0.90.(24) In another study, young individuals with occult PAD ≤49 years were three times more likely to have a family history of PAD (OR 2.76) [25]. In another study, pPAD and pCAD were independently associated with the presence of PAD, and the association was age-dependent, being stronger in younger individuals (<68 y vs ≥68 y) [26].

Another important observation in our study is that r-pCAD was strongly associated with higher cIMT and fIMT among the young study participants, even though the total number of participants in the young group was 4-fold lower (26.3%) compared to the middle-aged group, which may potentially have limited the statistical power. This demonstrates that positive history of r-pCVD shows the risk of arterial wall changes already early in life in the offspring. In the middle-aged group, positive history of r-pCAD was related to AAP and positive history of r-pPAD to AAI. However, there were a lot more participants in the middle-aged group (73.7%), and the prevalence of peripheral artery disease and abdominal aorta plaques increases with age [27-28].

Strengths of our study include a thorough investigation of pCAD and pPAD. We increased the accuracy of our study by excluding uncertain family history information and including only pure positive and negative pCAD and pPAD. The comparisons of reported and verified pCVD represents also a methodological strength and provides meaningful insight into the reliability of routine clinical assessment. The assessment of artery wall changes was done by objective and extensive ultrasound protocol to enhance the robustness of the findings.

There were also limitations. The offspring in this study consisted of ischaemic stroke patients and their partners rather than a general population sample due to the three-generation design of the Norwegian Stroke in the Young Study, which may restrict generalizability, and could lead to a possible selection bias. Another limitation was that only patients performed blood tests for blood-lipids and glucose, while partners provided information on dyslipidaemia and diabetes mellitus only by self-reported questionnaires, probably underestimating dyslipidaemia and diabetes mellitus among partners. Among the v-pCVD group, there was a substantial amount of missing information attributed due to either non-consent from study participants to contact their parents, or due to serious comorbidity among living parents. However, most of the crude results of reported and verified pCVD still were similar. Furthermore, as our study participants were young and middle-aged, it would be of great interest to know whether their pCVD was premature, but this information was not obtained as we did not ask about age at the time of the parental event.

This study explores the relationship between pCVD to presence of subclinical and clinical atherosclerosis in the offspring, and particularly among the young offspring. Our study highlights the value of using a clear parental history in CVD risk assessment. As the study showed almost similar crude results for reported and verified pCVD history, there might not be a need for an extensive verification of the parental history of young patients. It would also be time saving both in research and in clinical practice. Early arterial wall changes are associated with positive pCVD, particularly in young adults ≤45 years. This would be of great practical value in clinical practice with higher focus on screening and primary prevention of modifiable risk factors for cardiovascular disease.

Conflict of interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article

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Author contribution

UWA – conceived the study and was involved in protocol development and gaining ethical approval. Data collection was done by BN, HØ, AF and UWA. Data interpretation of parental family history was done by HØ, SB and BN. Data interpretation of electrocardiograms were done by SS. BN did the literature search and wrote the first draft of the manuscript. Statistical analysis was done by BN and JA. All authors reviewed and edited the manuscript and approved the final version.

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Supplementary material

Parental coronary and peripheral artery disease and artery segments in patients and partners – The first and second generation in the Norwegian Stroke in the Young Study

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Table 1a | Association between positive parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) and arterial outcome measurements among 639 study participants, adjusted for age, sex and vascular risk factors.

	Reported parental CAD			Verified parental CAD			Reported parental PAD			Verified parental PAD		
Continuous variables	**n**	**Coefficient (95% CI)**	**P value**	**n**	**Coefficient (95% CI)**	**P value**	**n**	**Coefficient (95% CI)**	**P-value**	**n**	**Coefficient (95% CI)**	**P value**
Mean cIMT[a] Crude	564	0.21 (0.08, 0.34)	0.002	270	0.39 (0.23, 0.56)	<0.001	552	0.31 (0.11, 0.51)	0.002	240	0.38 (0.15, 0.62)	0.002
Adjusted for sex	564	0.21 (0.09, 0.34)	**0.001**	270	0.38 (0.21, 0.54)	<0.001	552	0.31 (0.12, 0.50)	0.002	240	0.37 (0.14, 0.61)	0.002
Adjusted for age	564	0.08 (-0.04, 0.21)	0.197	270	0.20 (0.03, 0.37)	0.023	552	0.22 (0.03, 0.40)	0.020	240	0.20 (-0.02, 0.42)	0.079
Adjusted for RF[b]	563	0.12 (-0.01, 0.24)	0.062	268	0.26 (0.10, 0.42)	0.002	552	0.23 (0.05, 0.42)	0.012	239	0.25 (0.03, 0.47)	0.026
Adjusted for age, RF[b]	563	0.05 (-0.08, 0.17)	0.456	268	0.16 (-0.01, 0.33)	0.063	552	0.19 (0.01, 0.37)	0.039	239	0.14 (-0.07, 0.36)	0.188
Mean fIMT[a] Crude	561	0.30 (0.13, 0.46)	<0.001	270	0.49 (0.28, 0.70)	<0.001	547	0.32 (0.08, 0.56)	0.010	240	0.50 (0.22, 0.79)	0.001
Adjusted for sex	561	0.31 (0.15, 0.47)	<0.001	270	0.45 (0.25, 0.65)	<0.001	547	0.32 (0.09, 0.55)	0.007	240	0.46 (0.18, 0.75)	0.001
Adjusted for age	561	0.15 (-0.01, 0.32)	0.063	270	0.26 (0.04, 0.47)	0.019	547	0.22 (-0.01, 0.45)	0.061	240	0.32 (0.04, 0.60)	0.025
Adjusted for RF[b]	560	0.16 (0.01, 0.31)	0.040	268	0.28 (0.08, 0.48)	0.005	547	0.21 (-0.00, 0.43)	0.054	239	0.36 (0.10, 0.63)	0.007
Adjusted for age, RF[b]	560	0.09 (-0.06, 0.24)	0.242	268	0.18 (-0.02, 0.39)	0.078	547	0.17 (-0.04, 0.39)	0.114	239	0.28 (0.01, 0.54)	0.039
Dichotomous variables	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**
Ischaemic ECG[c] Crude	563	1.34 (0.72, 2.50)	0.363	269	0.46 (0.17, 1.20)	0.113	553	0.56 (0.17, 1.88)	0.349	239	1.23 (0.33, 4.50)	0.758
Adjusted for sex	563	1.35 (0.72, 2.52)	0.352	269	0.46 (0.18, 1.23)	0.122	553	0.56 (0.17, 1.87)	0.344	239	1.26 (0.34, 4.65)	0.729
Adjusted for age	563	1.22 (0.65, 2.32)	0.534	269	0.38 (0.14, 1.05)	0.061	553	0.53 (0.16, 1.76)	0.298	239	1.08 (0.28, 4.14)	0.906
Adjusted for RF[b]	563	1.10 (0.57, 2.11)	0.769	268	0.29 (0.10, 0.85)	0.025	553	0.48 (0.14, 1.67)	0.254	239	1.20 (0.31, 4.67)	0.783
Adjusted for age, RF[b]	563	1.08 (0.56, 2.09)	0.811	268	0.28 (0.09, 0.85)	0.025	553	0.48 (0.14, 1.66)	0.249	239	1.20 (0.30, 4.78)	0.794
AAP[c] Crude	520	2.00 (1.40, 2.86)	<0.001	250	2.49 (1.47, 4.22)	0.001	512	1.58 (0.93, 2.71)	0.092	225	1.36 (0.65, 2.86)	0.409
Adjusted for sex	520	2.04 (1.42, 2.93)	<0.001	250	2.40 (1.40, 4.09)	0.001	512	1.57 (0.92, 2.71)	0.101	225	1.30 (0.61, 2.74)	0.498
Adjusted for age	520	1.55 (1.06, 2.26)	0.025	250	1.38 (0.76, 2.51)	0.286	512	1.35 (0.77, 2.38)	0.294	225	0.76 (0.34, 1.70)	0.505
Adjusted for RF[b]	519	1.68 (1.13, 2.49)	0.010	249	1.65 (0.91, 3.02)	0.102	512	1.23 (0.67, 2.25)	0.487	224	0.95 (0.41, 2.19)	0.910
Adjusted for age, RF[b]	519	1.42 (0.95, 2.14)	0.090	249	1.10 (0.57, 2.11)	0.769	512	1.14 (0.62, 2.11)	0.664	224	0.65 (0.27, 1.54)	0.329
AAI ≤ 0.9[c] Crude	544	1.40 (0.61, 3.24)	0.429	260	1.26 (0.35, 4.56)	0.728	532	3.69 (1.35, 10.09)	**0.011**	232	1.65 (0.33, 8.27)	0.546
Adjusted for sex	544	1.42 (0.61, 3.28)	0.415	260	1.33 (0.36, 4.85)	0.669	532	3.68 (1.35, 10.07)	0.011	232	1.73 (0.34, 8.76)	0.511
Adjusted for age	544	1.13 (0.49, 2.63)	0.775	260	0.70 (0.19, 2.64)	0.601	532	3.24 (1.17, 8.96)	0.023	232	0.85 (0.16, 4.63)	0.854
Adjusted for RF[b]	543	1.11 (0.46, 2.71)	0.804	170	0.76 (0.16, 3.46)	0.728	532	3.13 (1.09, 8.92)	0.033	149	1.34 (0.23, 7.53)	0.739
Adjusted for age, RF[b]	543	1.02 (0.42, 2.50)	0.949	170	0.49 (0.10, 2.39)	0.381	532	3.04 (1.05, 8.80)	0.039	149	0.89 (0.14, 5.58)	0.906

Abbreviations: *n* = number of observations; CI = confidence interval; cIMT = carotid intima-media thickness; RF = risk factors; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle-arm index.
[a]Coefficient using linear regression; [b]RF are hypertension, diabetes mellitus, dyslipidaemia, smoking; [c]Odds ratio using multiple regression.

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Table 1b | Association between positive parental coronary artery disease (CAD) and parental peripheral artery disease (PAD) and arterial outcome measurements among 168 study participants aged ≤45 years, adjusted for age, sex and vascular risk factors.

	Reported parental CAD			Verified parental CAD			Reported parental PAD			Verified parental PAD		
Continuous variables	**n**	**Coefficient (95% CI)**	**P value**	**n**	**Coefficient (95% CI)**	**P value**	**n**	**Coefficient (95% CI)**	**P-value**	**n**	**Coefficient (95% CI)**	**P value**
Mean cIMT[a] Crude	150	0.16 (0.05, 0.27)	0.003	89	0.06 (-0.04, 0.16)	0.232	152	0.15 (-0.04, 0.33)	0.119	87	0.02 (-0.20, 0.24)	0.857
Adjusted for sex	150	0.17 (0.06, 0.27)	**0.002**	89	0.07 (-0.03, 0.17)	0.145	152	0.15 (-0.03, 0.34)	0.094	87	0.03 (-0.19, 0.25)	0.759
Adjusted for age	150	0.09 (-0.02, 0.19)	0.101	89	0.01 (-0.09, 0.10)	0.898	152	0.09 (-0.08, 0.26)	0.294	87	-0.10 (-0.29, 0.10)	0.340
Adjusted for RF[b]	150	0.13 (0.04, 0.23)	0.008	89	0.07 (-0.03, 0.17)	0.165	152	0.14 (-0.03, 0.30)	0.105	87	-0.11 (-0.32, 0.08)	0.251
Adjusted for age, RF[b]	155	0.07 (-0.02, 0.16)	0.112	89	0.02 (-0.07, 0.11)	0.687	152	0.10 (-0.05, 0.26)	0.199	87	-0.18 (-0.36, 0.00)	0.053
Mean fIMT[a] Crude	149	0.34 (0.15, 0.53)	<0.001	89	0.17 (-0.03, 0.26)	0.107	151	0.29 (-0.03, 0.60)	0.074	87	0.63 (0.30, 0.97)	<0.001
Adjusted for sex	149	0.35 (0.17, 0.54)	<0.001	89	0.13 (-0.00, 0.28)	0.057	151	0.31 (-0.00, 0.61)	0.051	87	0.67 (0.33, 0.99)	<0.001
Adjusted for age	149	0.25 (0.06, 0.44)	0.010	89	0.07 (-0.07, 0.21)	0.338	151	0.22 (-0.09, 0.52)	0.162	87	0.53 (0.20, 0.87)	0.002
Adjusted for RF[b]	149	0.26 (0.09, 0.43)	0.002	89	0.13 (-0.01, 0.26)	0.063	151	0.27 (-0.01, 0.56)	0.062	87	0.36 (0.11, 0.61)	0.005
Adjusted for age, RF[b]	154	0.17 (0.02, 0.32)	0.031	89	0.09 (-0.05, 0.23)	0.201	151	0.23 (-0.05, 0.52)	0.108	87	0.31 (0.07, 0.56)	0.013
Dichotomous variables	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**	**n**	**OR (95% CI)**	**P value**
Ischaemic ECG[c] Crude	152	1.12 (0.22, 5.82)	0.892	90	0.45 (0.50, 4.01)	0.471	143	-	-	82	-	-
Adjusted for sex	152	1.18 (0.23, 6.20)	0.843	90	0.41 (0.05, 3.78)	0.435	143	-	-	82	-	-
Adjusted for age	152	0.79 (0.14, 4.36)	0.782	90	0.34 (0.04, 3.24)	0.348	143	-	-	82	-	-
Adjusted for RF[b]	147	1.43 (0.23, 8.99)	0.702	90	0.78 (0.07, 8.87)	0.849	54	-	-	41	-	-
Adjusted for age, RF[b]	147	0.70 (0.10, 5.14)	0.727	90	0.51 (0.04, 6.26)	0.598	54	-	-	41	-	-
AAP[c] Crude	140	1.93 (0.73, 5.08)	0.185	83	2.02(0.49, 8.26)	0.328	142	1.16 (0.23, 5.78)	0.853	82	1.49 (0.16, 14.22)	0.730
Adjusted for sex	140	2.01 (0.76, 5.34)	0.162	83	2.13 (0.51, 8.87)	0.299	142	1.20 (0.24, 6.01)	0.821	82	1.63 (0.17, 15.92)	0.676
Adjusted for age	140	0.87 (0.30, 2.53)	0.795	83	1.08 (0.23, 5.00)	0.919	142	0.67 (0.13, 3.61)	0.645	82	0.66 (0.06, 6.73)	0.726
Adjusted for RF[b]	140	1.38 (0.48, 3.98)	0.554	83	2.17 (0.47, 10.01)	0.319	142	0.87 (0.14, 5.45)	0.880	82	0.91 (0.06, 13.72)	0.947
Adjusted for age, RF[b]	140	0.63 (0.19, 2.05)	0.440	83	1.18 (0.23, 6.02)	0.843	142	0.46 (0.07, 3.25)	0.438	82	0.50 (0.03, 7.67)	0.622
AAI ≤ 0.9[c] Crude	113	-	-	-	-	-	140	-	-	-	-	-
Adjusted for sex	52	-	-	-	-	-	62	-	-	-	-	-
Adjusted for age	113	-	-	-	-	-	140	-	-	-	-	-
Adjusted for RF[b]	10	-	-	-	-	-	12	-	-	-	-	-
Adjusted for age, RF[b]	-	-	-	-	-	-	-	-	-	-	-	-

Abbreviations: *n* = number of observations; CI = confidence interval; cIMT = carotid intima-media thickness; RF = risk factors; fIMT = femoral intima-media thickness; ECG = electrocardiogram; AAP = abdominal aorta plaques; AAI = ankle-arm index.
[a] Coefficient using linear regression; [b] RF are hypertension, diabetes mellitus, dyslipidaemia, smoking; [c] Odds ratio using multiple regression.