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Cumulative dyslipidemia with arterial stiffness and carotid IMT progression in asymptomatic adolescents: A simulated intervention longitudinal study using temporal inverse allocation model

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ABSTRACT

Background and aims: We aimed to examine the longitudinal associations of total cholesterol (TC), non–high-density lipoprotein cholesterol (non–HDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and low-density lipoprotein cholesterol (LDL-C) with carotid-femoral pulse wave velocity (cfPWV) and carotid intima-media thickness (cIMT) progression.

Methods: We studied 1779, 15-year-old participants from the Avon Longitudinal Study of Parents and Children, UK birth cohort, followed up for 9 years. Fasting TC, non–HDL-C, HDL-C, triglyceride, and LDL-C were measured at 15, 17, and 24 years and age-categorized as normal, elevated, and dyslipidemia based on National Heart, Lung, and Blood Institute lipid guidelines. cfPWV and cIMT were measured at 17 and 24 years. Associations were examined using linear mixed-effect models. To simulate the treatment of dyslipidemia we conducted temporal inverse allocation model analyses.

Results: Among 1779 [49.9% female] participants, mean lipid levels and proportions at elevated or dyslipidemia categories increased from ages 15 through 24 years. Persistently elevated TC: effect estimate 0.026 mm; [95% CI 0.004 to 0.049; $p = 0.024$], elevated non–HDL-C, and elevated LDL-C were cumulatively associated with cIMT progression. Persistent borderline-low HDL-C: −0.027 mm; [-0.050 to −0.005; $p = 0.019$] and very-low HDL-C −0.035 mm; [-0.057 to −0.013; $p = 0.002$] levels were associated with cIMT progression. A temporal inverse allocation of elevated and dyslipidemic levels with normal lipid levels at age 17 years attenuated the associations of cumulative elevated TC, non–HDL-C, LDL-C, and low HDL-C with cIMT progression. Cumulative elevated lipids or dyslipidemia were not associated with cfPWV progression.

Conclusions: Late adolescence is key to preventing, halting, and reversing dyslipidemic-related preclinical atherosclerosis progression, warranting universal lipid screening in the general pediatric population.

1. Introduction

Cumulative dyslipidemia measured during childhood or adolescence through mid-adulthood has been associated with markers of preclinical atherosclerosis measured at a single time-point in mid-adulthood [1–8]. Conversely, we have shown that higher adolescent arterial stiffness, a marker of arteriosclerosis, and carotid intima-media thickness (cIMT) a marker of atherosclerosis may temporally precede cardiometabolic diseases in young adulthood [9–11]. It is unclear whether cumulative dyslipidemia from mid-adolescence through young adulthood differently influences arteriosclerotic and atherosclerotic progression measured at two-time points during adolescence and young adulthood [7,12,13].

Age 12 years has been reported as the cut point for significant cIMT

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deviation in a pediatric population with familial hypercholesterolemia [14]. In a 20-year follow-up study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed cIMT progression and reduced the risk of cardiovascular disease in adulthood [15]. However, there remains a gap in knowledge on the role of cumulative dyslipidemia on cfPWV and cIMT progression among asymptomatic adolescents and young adults without familial diseases and whether a population-based lipid intervention may be warranted [13]. Performing a temporal inverse allocation modelling to simulate the effects of treatment for dyslipidemia at specific life stages, may inform an effective timing of treatment [13]. The temporal inverse allocation model is similar to the principle of isotemporal substitution of continuous variables [16], however, rather than eliminating variables of interest, participants' categories are reversed, i.e participants with dyslipidemia at a specific time point are assigned normal lipid levels and *vice versa*, while predicting variables at other time points and vascular outcomes are unchanged. Therefore, we examined the longitudinal associations and temporal inverse allocation of total cholesterol, high-density lipoprotein cholesterol (HDL-C), non–HDL-C, triglyceride, low-density lipoprotein cholesterol (LDL-C), and triglyceride/HDL-C ratio levels at ages 15, 17, and 24 years with cfPWV and cIMT progression from ages 17 through 24 years using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort, England, United Kingdom.

2. Patients and methods

2.1. Study cohort

Data were from the ALSPAC birth cohort, which investigates factors that influence childhood development and growth. Altogether, pregnant women resident in Avon, southwestern England, United Kingdom, with expected dates of delivery 1st April 1991 to 31st December 1992, were invited to take part in the study. The initial number of pregnancies enrolled was 14,541, of which there was a total of 14,676 foetuses. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample size with eligible cases who had failed to join the study originally resulting in 14,901 children alive at 1 year of age. Regular clinic visits of the children commenced at 7 years of age and are still ongoing into adulthood. Study data at 24 years of age were collected and managed using REDCap electronic data capture tools [17]. In this study, 1779 participants who had complete clinic measurements for fasting lipid at 15 and 17 years and vascular measures at 17 years during follow-up clinic visits were eligible for analyses (Supplemental Fig. 1). The excluded participants who had only fasting blood samples without vascular measures at 17 years of age were similar to those included in the study (Supplemental Table 1). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. Informed consent for the use of data collected via questionnaires and clinics was obtained from participants following the recommendations of the ALSPAC Ethics and Law Committee at the time [18–20]. Consent for biological samples has been collected in accordance with the Human Tissue Act (2004). Please note that the study website contains details of all the data that is available through a fully searchable data dictionary and variable search tool (http://www.bristol.ac.uk/alspac/researchers/our-data/).

2.2. Anthropometry and body composition

Anthropometry (height and weight) of participants at ages 15, 17, and 24 years was assessed in line with standard protocols and body mass index (BMI) was computed as weight in kilograms per height in meters squared [9,21]. Body composition (total fat mass and lean mass) was assessed using a dual-energy Xray absorptiometry scanner at 15, 17, and 24 years as previously described [9,10,21]. Time (years) to age at peak height velocity, an objective measure of pubertal or maturation status without having to rely on physical examination or self-report, was derived using Superimposition by Translation And Rotation mixed-effects growth curve analysis [22]. The participant's mother's socioeconomic status was grouped according to the 1991 British Office of Population and Census Statistics classification [23].

2.3. Vascular phenotype

At ages 17 and 24 years, cfPWV was computed from pressure waveforms obtained using the Vicorder device (Skidmore Medical, Bristol, UK) observing standard protocols as detailed earlier [9,10,21]. All measurements were taken independently by one of two trained vascular technicians (inter-observer mean difference 0·2 m/s, SD 0·1) [10,21]. cIMT from the right and left common carotid arteries at 17 years was assessed by ultrasound using a linear 12-MHz transducer (Vivid7, GE Medical, Chicago, Illinois), and cIMT from the right and left common carotid arteries at 24 years was measured using an ultrasound machine (CardioHealth Panasonic and a 13.5 MHz linear array broadband transducer (probe; centre frequency 9.0 MHz) [9,21]. All vascular measures at 17 and 24 years were extensive and rigorous as earlier described, interobserver variability for cIMT was assessed in a separate sample of 25 young adults (coefficient of variation: 4.4 ± 2.2%) [9,10,21]. Participants were placed in a supine position with the head rotated by 45° from the midpoint. An automated guide line was placed at the bulb (a longitudinal scan that included the common carotid artery and the carotid bifurcation) with the region-of-interest box and IMT trace lines automatically positioned 1 cm away from the guide line. The scanner automatically saved an image when the region-of-interest box turned green, indicating good image quality. An automated cIMT measurement, recorded from the posterior wall of the artery, was saved after three consecutive cardiac cycles. When interrogating the common carotid, the CardioHealth system calculated and displayed the cIMT that is updated at each detected R-wave of the cardiac cycle. Once the measurement achieved a predefined quality threshold, scanning automatically stopped and a report was generated. Raw data were checked for outliers and cIMT value > 1.0 mm was reviewed by a trained research scientist to assess validity. Abnormal values due to measurement error were removed. Participants had between 1 and 3 cIMT measures for each of the right and left carotid arteries. For our analysis, we computed the mean of the average measurement of the right and left common carotid arteries as cIMT.

2.4. Cardiometabolic and lifestyle factors

Heart rate and systolic and diastolic blood pressure were measured with Omron monitor at ages 15, 17, and 24 years as previously detailed [9,21]. Using standard protocols, fasting blood samples at ages 15, 17, and 24 years were collected, spun, and frozen at −80 °C, and a detailed assessment of fasting glucose, insulin, high-sensitivity C-reactive protein, total cholesterol, estimated LDL-C, HDL-C, and triglycerides, has been reported (coefficient of variation was <5%) [9,10,21,24]. Non-HDL-C was computed by subtracting HDL-C from total cholesterol. Triglyceride/HDL-C ratio was estimated as triglyceride divided by HDL-C. Plasma lipids were performed according to the standard Lipid Research Clinics Protocol using enzymatic reagents for lipid determination. All lipid phenotypes were categorized according to the 2011 National Heart, Lung, and Blood Institute expert panel recommendation for lipid classification in youth [25]. In adolescence (15 and 17 years), non–HDL-C status was defined as normal if < 3.10 mmol/L, elevated if 3.10 to <3.73 mmol/L, and dyslipidemia if ≥ 3.73 mmol/L, total cholesterol status was defined as normal if < 4.40 mmol/L, elevated if 4.40 to <5.16 mmol/L, and dyslipidemia if ≥ 5.16 mmol/L, triglyceride status was defined as normal if < 1.02 mmol/L, elevated if 1.02 to <1.46 mmol/L, and dyslipidemia if ≥ 1.46 mmol/L, LDL-C status was defined as normal if < 2.85 mmol/L, elevated if 2.85 to <3.34 mmol/L, and dyslipidemia if ≥ 3.34 mmol/L and HDL-C status was defined as low

or dyslipidemia if < 1.04 mmol/L, borderline-low if 1.04 to <1.17 mmol/L, and normal if ≥ 1.17 mmol/L [25].

In young adulthood (24 years), non–HDL-C status was defined as normal if < 3.89 mmol/L, elevated if 3.89 to <4.90 mmol/L, and dyslipidemia if ≥ 4.90 mmol/L, total cholesterol status was defined as normal if < 4.92 mmol/L, elevated if 4.92 to <5.80 mmol/L, and dyslipidemia if ≥ 5.80 mmol/L, triglyceride status was defined as normal if < 1.30 mmol/L, elevated if 1.30 to <1.68 mmol/L, and dyslipidemia if ≥ 1.68 mmol/L, LDL-C status was defined as normal if < 3.10 mmol/L, elevated if 3.10 to <4.12 mmol/L, and dyslipidemia if ≥ 4.12 mmol/L and HDL-C status was defined as low or dyslipidemia if < 1.04 mmol/L, borderline-low if 1.04 to <1.14 mmol/L, and normal if ≥ 1.14 mmol/L. To convert to mg/dL, multiply each lipid phenotype except triglyceride by 38.6 and triglyceride by 88.6. To standardize triglyceride/HDL-C ratio, we divided mmol/L derived ratios by 0.4357. In adolescence (age 15 and 17 years), triglyceride/HDL-C ratio was defined as normal if < 2.00, elevated if 2.00 to <3.22, and dyslipidemia if ≥ 3.22. In young adulthood (age 24 years), triglyceride-HDL-C ratio was defined as normal if < 2.62, elevated if 2.62 to <3.71, and dyslipidemia if ≥ 3.71 [25].

Questionnaires to assess smoking behavior were administered at the 15, 17, and 24-year clinic visits [9]. At the 17-year clinic visit, participants were briefly asked about their personal and family (mother, father, and siblings) medical history of hypertension, diabetes, high cholesterol, and vascular disease [9]. Sedentary time, light physical activity, and moderate to vigorous physical activity at age 15 years were assessed with ActiGraphTM accelerometer worn for 7 days. At 24 years, sedentary time, light physical activity, and moderate to vigorous physical activity were assessed using ActiGraph GT3X + accelerometer device worn for four consecutive days, ideally starting the day after the clinic visit [9].

2.5. Statistical analysis

The descriptive characteristics of our cohort were summarized as means and standard deviation, medians and interquartile ranges, or frequencies and percentages. We explored sex differences using Independent t-tests, Mann Whitney-U tests, or Chi-square tests for normally distributed, skewed or dichotomous variables, respectively. Differences in lipid categories were analysed using one-way analysis of variance. Normality was assessed by histogram curve, quantile-quantile plot, and Kolmogorov-Smirnov tests. We conducted a logarithmic transformation of skewed variables and confirmed normality prior to further analysis.

We examined the separate associations of the 9-year lipid progression (15 through 24 years) in categories with each of cfPWV and cIMT progression measured from ages 17 through 24 years using linear mixed-effect models for repeated measures. The optimal model was one with sex and predictor as a factor and a random intercept modeled on the subject level. We selected a scaled identity covariance type and determined the effect of the predictor trajectory on progression in outcome variables. The mixed-effect model assumes that the data are missing at random and is robust for accounting for missing data at follow-up. The analysis strategy also accounted for baseline lipid predictors, vascular outcomes, and covariates. Analyses in Model 1 were adjusted for sex, family history of hypertension, diabetes, high cholesterol, and vascular disease, socio-economic status, pubertal maturation, and cumulative exposure to covariates measured at 15, 17, and 24 years, such as age, high sensitivity C-reactive protein, total fat mass, lean mass, heart rate, systolic blood pressure, diastolic blood pressure, smoking status, and 15- and 24-years cumulative measure of sedentary time, light physical activity, moderate to vigorous physical activity. Analyses were further adjusted for cumulative HDL-C, LDL-C, or triglyceride exposure depending on the predictor but total cholesterol and non-HDL-C and triglyceride-HDL-C ratio were not adjusted for lipids. Model 2 was an additional adjustment of model 1 for glucose and insulin. We presented sex and weight category-based results in the supplementary appendix. Sex-based analyses were not adjusted for sex. All analyses were adjusted for baseline values of predictors, outcomes, and covariates.

Lastly, we examined whether normalizing elevated lipids and dyslipidemia at 24 years only, 17 and 24 years, or 17 years only, altered cfPWV and cIMT progression using temporal inverse allocation in linear mixed-effect modelling. Prior to data restructure for the mixed-model analyses, lipid categories at selected time points were inversely reassigned to normal or elevated lipid/dyslipidemia levels whilst keeping other time points constant. Also, the vascular outcomes remain unchanged. The elevated and dyslipidemia-derived variables after temporal inverse allocation and data restructure were 1). elevated lipid/dyslipidemia at 15 years, elevated lipid/dyslipidemia at 17 years, and normal lipid level at 24 years; 2). elevated lipid/dyslipidemia at 15 years, normal lipid level at 17 and 24 years; 3). elevated lipid/dyslipidemia at 15 years, normal lipid level at 17 years, and elevated lipid/dyslipidemia at 24 years. The derived variables were associated with the cfPWV and cIMT progression against a reference category or derived normal lipid levels. The derived normal levels from temporal inverse allocation were 1). normal lipid levels at 15 years and 17 years, and elevated lipid/dyslipidemia at 24 years; 2). normal lipid levels at 15 years, elevated/dyslipidemia at 17 and 24 years; 3). normal lipid level at 15 years, elevated/dyslipidemia at 17 years, and normal lipid level at 24 years. We presented sex-based temporal inverse allocation results in the supplementary appendix. If there are no associations after the temporal inverse allocation, then dyslipidemia at the specific time point (for the inverse allocation) is likely to have caused the progression in vascular outcomes and is amenable to intervention. If the associations from using the correct values are maintained after the temporal inverse allocation, then dyslipidemia/elevated lipid levels are likely not the only cause of the progression in vascular outcomes and are not amenable to lipid intervention. Collinearity diagnoses were performed and accepted results with a variance inflation factor <5, considered differences and associations with a 2-sided p-value <0.05 as statistically significant, and made conclusions based on effect estimates and their confidence intervals (CI). We applied Sidak-correction for potential multiple comparisons [9,10,26]. Analyses involving 20% of a sample of 10,000 ALSPAC children at 0.8 statistical power, 0.05 alpha, and 2-sided p-value would show a minimum detectable effect size of 0.062 standard deviations if they had relevant exposure for a normally distributed quantitative variable [27]. All statistical analyses were performed using SPSS statistics software, Version 27.0 (IBM Corp, Armonk, NY, USA).

3. Results

3.1. Study population and characteristics

Of 14,901 children who were alive at 1 year of age, 5515 adolescents participated in the age 15-year clinic visit, 5217 adolescents participated in the age 17-year clinic visit and 4026 young adults participated in the age 24-year clinic visits (Supplemental Fig. 1). Only 1779 participants that had complete fasting lipid measures at 15 and 17 years and cfPWV and cIMT measures at 17 years were studied. From 15 through 24 years, females had higher lipid concentrations than males, but more males had very low HDL-C than females during the observation period (Tables 1 and 2). Approximately <5% of the studied population had dyslipidemia (Table 2). Other characteristics are described in Tables 1 and 2, and Supplemental Table 1.

3.2. Longitudinal associations of elevated lipids and dyslipidemia from 15 to 24 years with cfPWV and cIMT progression

Persistently elevated total cholesterol: effect estimate 0.026 mm; [95% CI 0.004 to 0.049; $p = 0.024$], elevated non–HDL-C, and elevated LDL-C across all life stages were cumulatively associated with cIMT progression (Table 3). Persistent borderline-low HDL-C and very-low levels across all life stages were also associated with cIMT progression

Table 1
Descriptive characteristics of cohort participants.

Variables	15 years					17 years					24 years				
	Male		Female		*p*-value	Male		Female		*p*-value	Male		Female		*p*-value
	N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)	
Anthropometry															
Age (years)	890	15.41 (0.27)	886	15.44 (0.30)	0.079	892	17.69 (0.29)	887	17.69 (0.32)	0.951	543	24.59 (0.74)	686	24.47 (0.70)	**0.004**
Height (m)	885	1.75 (0.08)	877	1.65 (0.06)	**<0.0001**	879	1.79 (0.07)	874	1.66 (0.06)	**<0.0001**	546	1.80 (0.07)	678	1.67 (0.06)	**<0.0001**
[a]Weight (kg)	884	62.3 (12.8)	874	57.9 (11.9)	**<0.0001**	881	70 (14.15)	874	60.5 (13.63)	**<0.0001**	545	78.4 (17.05)	677	65.2 (17.5)	**<0.0001**
Attained puberty (n,%)	851	829 (97.4)	836	>831 (>99.4)	**<0.0001**	851	>845 (>99.4)	836	>831 (>99.4)		NA				
Race- White (n,%)	820	785 (95.7)	811	783 (96.5)	0.441	NA					NA				
Body composition															
[a]Total fat mass (kg)	860	8.31 (6.92)	851	17.32 (8.70)	**<0.0001**	874	10.28 (9.51)	862	19.21 (9.96)	**<0.0001**	537	18.25 (10.59)	660	21.74 (11.67)	**<0.0001**
[a]Lean mass (kg)	860	50.3 (8.48)	851	36.87 (4.85)	**<0.0001**	874	55.29 (8.17)	862	38.01 (5.19)	**<0.0001**	537	56.64 (9.88)	660	41.16 (6.77)	**<0.0001**
[a]Body mass index (kg/m^2)	884	20.23 (3.29)	874	21.13 (3.86)	**<0.0001**	879	21.57 (3.87)	874	22.10 (4.50)	**0.004**	545	24.14 (4.74)	677	23.53 (5.80)	0.233
Metabolic profile															
Total cholesterol (mmol/L)	892	3.56 (0.59)	887	3.90 (0.65)	**<0.0001**	892	3.56 (0.63)	887	3.94 (0.69)	**<0.0001**	524	4.35 (0.85)	611	4.47 (0.81)	**0.015**
Non-HDL cholesterol (mmol/L)	892	2.34 (0.58)	887	2.55 (0.63)	**<0.0001**	892	2.37 (0.64)	887	2.59 (0.70)	**<0.0001**	524	2.95 (0.91)	611	2.81 (0.80)	**0.007**
High density lipoprotein (mmol/L)	892	1.22 (0.27)	887	1.35 (0.29)	**<0.0001**	892	1.19 (0.26)	887	1.35 (0.32)	**<0.0001**	524	1.41 (0.36)	611	1.66 (0.42)	**<0.0001**
Low density lipoprotein (mmol/L)	892	1.97 (0.52)	887	2.16 (0.57)	**<0.0001**	892	1.99 (0.56)	887	2.21 (0.64)	**<0.0001**	524	2.47 (0.80)	611	2.40 (0.73)	0.082
[a]Triglyceride (mmol/L)	892	0.72 (0.37)	887	0.77 (0.39)	**<0.0001**	892	0.74 (0.36)	887	0.75 (0.36)	0.182	524	0.87 (0.53)	611	0.80 (0.43)	**<0.0001**
[a]Triglyceride-HDL ratio	892	1.38 (0.95)	887	1.32 (0.87)	0.086	892	1.45 (0.96)	887	1.29 (0.85)	**<0.0001**	524	1.42 (1.23)	611	1.10 (0.76)	**<0.0001**
Glucose (mmol/L)	892	5.29 (0.39)	887	5.14 (0.38)	**<0.0001**	892	5.14 (0.42)	887	4.89 (0.35)	**<0.0001**	524	5.47 (0.62)	611	5.21 (0.51)	**<0.0001**
[a]Insulin (mU/L)	892	8.09 (4.71)	887	9.75 (5.84)	**<0.0001**	892	5.93 (3.92)	887	7.29 (4.29)	**<0.0001**	524	7.02 (4.97)	611	7.88 (5.41)	**<0.0001**
[a]High sensitivity C-reactive protein (mg/L)	892	0.36 (0.59)	887	0.37 (0.61)	0.400	892	0.47 (0.72)	887	0.66 (1.27)	**<0.0001**	466	0.63 (1.05)	575	0.96 (1.94)	**<0.0001**
Vascular measures															
Heart rate (beat/mins)	866	71 (12)	854	78 (12)	**<0.0001**	892	63 (9)	886	67 (10)	**<0.0001**	548	64 (10)	685	68 (10)	**<0.0001**
Systolic blood pressure (mm Hg)	867	126 (10)	857	120 (10)	**<0.0001**	892	120 (9)	886	110 (8)	**<0.0001**	548	123 (10)	685	112 (9)	**<0.0001**
Diastolic blood pressure (mm Hg)	867	66 (9)	857	66 (8)	**0.002**	892	63 (9)	886	64 (6)	**<0.0001**	548	67 (8)	685	66 (8)	**0.038**
[a]Carotid-femoral PWV (m/s)	NA					892	5.99 (0.84)	887	5.50 (0.71)	**<0.0001**	369	6.50 (1.23)	502	5.87 (1.03)	**<0.0001**
[a]Carotid intima-media thickness (mm)	NA					888	0.48 (0.06)	881	0.47 (0.06)	**<0.0001**	303	0.46 (0.06)†	430	0.45 (0.06)†	**0.003**
Lifestyle factors															
Smoked cigarettes in the past 30 days (n,%)	867	101 (11.6)	876	160 (18.3)	**<0.0001**	788	202 (25.6)	785	209 (26.6)	0.688	537	150 (27.9)	681	174 (25.6)	0.361
Sedentary time (mins/day)	427	462 (88)	469	481 (81)	**0.001**	NA					118	539 (80)	216	523 (85)	0.082
LPA (mins/day)	427	294 (67)	469	276 (61)	**<0.0001**	NA					118	143 (55)	216	150 (53)	0.305
MVPA (mins/day)	427	57 (30)	469	42 (23)	**<0.0001**	NA					118	54 (33)	216	50 (28)	0.076
Family history of H-D-C-V (n,%)	NA					891	248 (27.8)	887	266 (30)	0.321	NA				
Socio-economic status by maternal occupation	425		390		0.202	NA					NA				

(*continued on next page*)

Table 1 (*continued*)

Variables	15 years					17 years					24 years				
	Male		Female		*p*-value	Male		Female		*p*-value	Male		Female		*p*-value
	N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)		N	Mean (SD)	N	Mean (SD)	
I: Professional (n, %)		38 (8.9)		23 (5.9)											
II: Managerial and technical (n,%)		174 (40.9)		160 (41.0)											
IIIa: Skilled nonmanual (n, %)		132 (31.1)		123 (31.5)											
IIIb: Skilled manual (n,%)		8 (1.9)		9 (2.3)											
IV: Partly skilled (n,%)		61 (14.4)		61 (15.6)											
V: Unskilled (n,%)		12 (2.8)		14 (3.6)											

The values are means (standard deviations) and median (interquartile range) except for puberty status, race, and lifestyle factors in percentage. Differences between sexes were tested using Independent *t*-test for normally distributed continuous variables, Mann–Whitney *U* test for skewed continuous variables, and Chi-square test for dichotomous variables. A 2-sided *p*-value <0.05 is considered statistically significant. To convert non–HDL-C, LDL-C, HDL-C and total cholesterol from mmol/L to mg/dL, multiply values by 38.6. To convert triglycerides from mmol/L to mg/dL, multiply values by 88.6. To standardize Triglyceride-HDL cholesterol ratio, we divided mmol/L derived ratios by 0.4357.

H-D-C-V, hypertension/diabetes/high cholesterol/vascular disease; LPA, light physical activity; MVPA, moderate to vigorous physical activity; NA, not available/applicable; PWV, pulse wave velocity; *p*-value for sex differences. † Mean cIMT measurement at 24 y, whereas maximum cIMT measurement for males is 0.53 mm (0.09) and for females is 0.52 mm (0.08).

(Table 3). Among males, elevated LDL-C and very low HDL-C were associated with cIMT progression (Supplemental Table 3). Among females, elevated total cholesterol, non-HDL-C, and borderline low HDL-C were associated with cIMT progression (Supplemental Table 3). Among normal-weight participants elevated and dyslipidemia total cholesterol levels, elevated non-HDL-C, and borderline-low and very low HDL-C were associated with cIMT progression (Supplemental Table 2). There were no significant lipid associations with cIMT among overweight and obese participants. No lipids profiles at both elevated and dyslipidemia levels across all life stages were significantly associated with the 7-year cfPWV progression (Table 3 and Supplemental Tables 2–4).

3.3. Temporal inverse allocation of dyslipidemia with normalized lipids at ages 24, 17 and 24 or 17 years life stages on cfPWV and cIMT progression

A temporal inverse allocation of elevated and dyslipidemic levels at age 15 and 17 years with normal lipid levels at age 24 years did not alter the cumulative associations of elevated lipids and dyslipidemia with cIMT progression (Table 4). However, the temporal inverse allocation of elevated and dyslipidemic levels with normal lipid levels at age 17 years or age 17 and 24 years effectively attenuated the cumulative associations of elevated lipids and dyslipidemia with cIMT progression (Table 5 and Supplemental Table 5). Temporal inverse allocation did not alter the non-significant associations between dyslipidemia and cfPWV progression (Table 5 and Supplemental Tables 4 and 5). According to sex categories, temporal inverse allocation of elevated and dyslipidemic levels with normal lipid levels at age 24 years did not alter the cumulative associations of elevated lipids and dyslipidemia with cIMT progression in both males and females, but normalized lipid levels at 17 years attenuated the associations with cIMT progression in both males and females (Supplemental Tables 6 and 7).

4. Discussion

We present the largest prospective single birth cohort study on the role of cumulative dyslipidemia during mid-adolescence through young adulthood on arterial stiffness, assessed using cfPWV, and cIMT progression during late adolescence through young adulthood. We observed that all lipid indices except triglyceride were cumulatively associated with cIMT progression but not cfPWV progression. Our results buttress existing evidence on the importance of early-life cardiovascular risk factors and provide novel information regarding the early development of dyslipidemia-related preclinical atherosclerosis. In addition, using temporal inverse allocation models that simulated treatment or early intervention effect, we observed that simulated intervention at age 24 years would likely not reverse cIMT progression. However, simulated intervention or treatment at age 17 years suggests potential effectiveness in reversing cIMT progression. Thus, pediatric lipid screening, early detection, and management of elevated lipid levels and dyslipidemia may be crucial to achieving a decreased burden of cardiovascular morbidities and mortality in adulthood.

4.1. Dyslipidemia and arterial stiffness progression

Arterial stiffness measured with cfPWV is an established marker of cardiovascular events in adulthood [28]. However, due to the lack of repeated measures of cfPWV, the relationship between cumulative lipid indices and cfPWV progression remains unknown and was recently recommended as a research priority [29]. In the present study, we showed consistently that all forms of cumulative lipid indices lacked associations with cfPWV progression. This suggests that dyslipidemia may not contribute to early arteriosclerosis or arterial stiffening, especially in normal-weight adolescents and young adults; thus, lipid-lowering interventions targeted at treating or reducing arterial stiffness in youth may be ineffective. We have shown that dyslipidemia may not temporally precede arterial stiffness in the causal path but higher arterial stiffness in adolescence may temporally precede low HDL in young adulthood, although with borderline significance [10,11]. Nonetheless, among overweight and obese participants, cumulative elevated triglyceride level from ages 15–24 years was directly associated with cfPWV progression. Previous clinical trials have reported modest arterial stiffness reduction with statin treatment independent of lipid and blood pressure changes, suggesting that statins may have anti-inflammatory and antioxidant pleiotropic effects that could reduce arterial stiffening [30].

4.2. Dyslipidemia and carotid intima-media thickness progression

We observed that the adverse effect of most forms of dyslipidemia and/or elevated lipids on preclinical atherosclerosis is evident in the

Table 2
Lipids categories of cohort participants.

Variables	15 years					17 years					24 years				
	Male		Female		*p*-value	Male		Female		*p*-value	Male		Female		*p*-value
	N	n (%)	N	n (%)		N	n (%)	N	n (%)		N	n (%)	N	n (%)	
Total cholesterol	892		887		**<0.0001**	892		887		**<0.0001**	524		611		0.253
Normal		823 (92.3)		700 (78.9)			807 (90.5)		685 (77.2)			407 (77.7)		449 (73.5)	
Elevated		60 (6.7)		159 (17.9)			73 (8.2)		156 (17.6)			87 (16.6)		129 (21.1)	
Dyslipidemia		9 (1.0)		28 (3.2)			12 (1.3)		46 (5.2)			30 (5.7)		33 (5.4)	
Non-HDL cholesterol	892		887		**<0.0001**	892		887		**<0.0001**	524		611		**0.001**
Normal		809 (90.7)		724 (81.6)			778 (87.2)		707 (79.7)			443 (84.5)		557 (91.2)	
Elevated		68 (7.6)		124 (14.0)			84 (9.4)		115 (13.0)			67 (12.8)		46 (7.5)	
Dyslipidemia		15 (1.7)		39 (4.4)			30 (3.4)		65 (7.3)			14 (2.7)		8 (1.3)	
High-density lipoprotein cholesterol	892		887		**<0.0001**	892		887		**<0.0001**	524		611		**<0.0001**
Normal		490 (54.9)		648 (73.1)			449 (50.3)		627 (70.7)			401 (76.5)		562 (92.0)	
Borderline low		166 (18.6)		118 (13.3)			182 (20.4)		128 (14.4)			47 (9.0)		24 (3.9)	
Low HDL or Dyslipidemia		236 (26.5)		121 (13.6)			261 (29.3)		132 (14.9)			76 (14.5)		25 (4.1)	
Low-density lipoprotein cholesterol	892		887		**<0.0001**	892		887		**<0.0001**	524		611		**0.026**
Normal		849 (95.2)		784 (88.4)			818 (91.7)		749 (84.4)			415 (79.2)		513 (84.0)	
Elevated		30 (3.4)		77 (8.7)			55 (6.2)		90 (10.1)			95 (18.1)		89 (14.6)	
Dyslipidemia		13 (1.5)		26 (2.9)			19 (2.1)		48 (5.4)			14 (2.7)		9 (1.5)	
Triglyceride	892		887		**0.044**	892		887		0.911	524		611		**0.002**
Normal		718 (80.5)		683 (77.0)			714 (80.0)		700 (78.9)			418 (79.8)		522 (85.4)	
Elevated		131 (14.7)		145 (16.3)			117 (13.1)		139 (15.7)			49 (9.4)		55 (9.0)	
Dyslipidemia		43 (4.8)		59 (6.7)			61 (6.8)		48 (5.4)			57 (10.9)		34 (5.6)	
Triglyceride-HDL ratio	892		887			892		887		**0.001**	524		611		**<0.0001**
Normal		684 (76.7)		704 (79.4)	0.199		664 (74.4)		714 (80.5)			430 (82.1)		564 (92.3)	
Moderate		152 (17.0)		134 (15.1)			158 (17.7)		133 (15.0)			39 (7.4)		29 (4.7)	
High		56 (6.3)		49 (5.5)			70 (7.8)		40 (4.5)			55 (10.5)		18 (2.9)	

The values are sample size and percentage. Differences between lipid categories were tested using one-way analysis of variance. A 2-sided *p*-value <0.05 is considered statistically significant.

HDL; High-density lipoprotein cholesterol; Lipid cutpoints were defined according to the 2011 National Heart, Lung, and Blood Institute (NHLBI) expert panel age-specific recommendation. In adolescence (15 and 17 years), non–HDL cholesterol status was defined as normal if < 3.10 mmol/L, elevated if 3.10 to <3.73 mmol/L, and dyslipidemia if ≥ 3.73 mmol/L, total cholesterol status was defined as normal if < 4.40 mmol/L, elevated if 4.40 to <5.16 mmol/L, and dyslipidemia if ≥ 5.16 mmol/L, triglyceride status was defined as normal if < 1.02 mmol/L, elevated if 1.02 to <1.46 mmol/L, and dyslipidemia if ≥ 1.46 mmol/L, LDL cholesterol status was defined as normal if < 2.85 mmol/L, elevated if 2.85 to <3.34 mmol/L, and dyslipidemia if ≥ 3.34 mmol/L and HDL cholesterol status was defined as low or dyslipidemia if < 1.04 mmol/L, borderline-low if 1.04 to <1.17 mmol/L, and normal if ≥ 1.17 mmol/L. In young adulthood (24 years), non–HDL cholesterol status was defined as normal if < 3.89 mmol/L, elevated if 3.89 to <4.90 mmol/L, and dyslipidemia if ≥ 4.90 mmol/L, total cholesterol status was defined as normal if < 4.92 mmol/L, elevated if 4.92 to <5.80 mmol/L, and dyslipidemia if ≥ 5.80 mmol/L, triglyceride status was defined as normal if < 1.30 mmol/L, elevated if 1.30 to <1.68 mmol/L, and dyslipidemia if ≥ 1.68 mmol/L, LDL cholesterol status was defined as normal if < 3.10 mmol/L, elevated if 3.10 to <4.12 mmol/L, and dyslipidemia if ≥ 4.12 mmol/L and HDL cholesterol status was defined as low or dyslipidemia if < 1.04 mmol/L, borderline-low if 1.04 to <1.14 mmol/L, and normal if ≥ 1.14 mmol/L. To convert to mg/dL, multiply each lipid phenotype except triglyceride by 38.6 and triglyceride by 88.6. To standardize Triglyceride-HDL cholesterol ratio, we divided mmol/L derived ratios by 0.4357. In adolescence (15 and 17 years), triglyceride-HDL ratio was defined as normal if < 2.00, elevated if 2.00 to <3.22, and dyslipidemia if ≥ 3.22. In young adulthood (24 years), triglyceride-HDL ratio was defined as normal if < 2.62, elevated if 2.62 to <3.71, and dyslipidemia if ≥ 3.71.

carotid artery wall as early as age 17 through 24 years in a population without familial diseases rather than at age 35–55 years in mid-adulthood as previously established [1–3,5,6]. Recently, a community-based study among adolescents aged 15 years followed up for 2 years with repeated cIMT and lipid measures reported that LDL-C and non-HDL-C were significantly associated with cIMT progression, after covariate adjustments [29]. This study [29] and our results emphasize that repeated cIMT measures in the young population may be more sensitive in detecting early dyslipidemic alterations of the carotid arterial wall. Also, the relationship between dyslipidemia and cIMT appears unidirectional such that dyslipidemia precedes carotid thickness [10]. Thus, increased cIMT initiated by dyslipidemia may enable a

Table 3
Cumulative effect of dyslipidemia from age 15–24 years on carotid-femoral pulse wave velocity and carotid intima-media thickness progression from ages 17 through 24 years.

N = 1779	Carotid-femoral pulse wave velocity (m/s)				Carotid intima-media thickness (mm)			
	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value
	Model 1		Model 2		Model 1		Model 2	
Total cholesterol	Reference		Reference		Reference		Reference	
Elevated	0.002 (−0.028–0.033)	0.877	0.003 (−0.027–0.034)	0.843	0.027 (0.004–0.050)	**0.020**	0.026 (0.004–0.049)	**0.024**
Dyslipidemia	0.014 (−0.046–0.074)	0.648	0.019 (−0.041–0.079)	0.539	0.046 (0.004–0.088)	**0.033**	0.041 (−0.001–0.084)	0.053
Non-HDL cholesterol	Reference		Reference		Reference		Reference	
Elevated	0.005 (−0.027–0.036)	0.778	0.006 (−0.025–0.037)	0.694	0.035 (0.017–0.059)	**0.003**	0.033 (0.009–0.056)	**0.007**
Dyslipidemia	−0.010 (−0.068–0.049)	0.747	−0.004 (−0.063–0.055)	0.893	0.005 (−0.038–0.048)	0.814	−0.001 (−0.044–0.043)	0.979
HDL cholesterol	Reference		Reference		Reference		Reference	
Borderline low	−0.015 (−0.045–0.015)	0.320	−0.016 (−0.046–0.015)	0.311	−0.027 (−0.049–−0.004)	**0.020**	−0.027 (−0.050–−0.005)	**0.019**
Low or Dyslipidemia	0.029 (−0.001–0.059)	0.056	0.029 (−0.001–0.059)	0.055	−0.035 (−0.057–−0.013)	**0.002**	−0.035 (−0.057–−0.013)	**0.002**
LDL cholesterol	Reference		Reference		Reference		Reference	
Elevated	0.026 (−0.016–0.069)	0.220	0.028 (−0.015–0.070)	0.200	0.038 (0.005–0.070)	**0.022**	0.035 (0.003–0.067)	**0.034**
Dyslipidemia	−0.008 (−0.065–0.049)	0.785	−0.004 (−0.061–0.053)	0.889	−0.002 (−0.043–0.040)	0.945	−0.006 (−0.048–0.036)	0.781
Triglyceride	Reference		Reference		Reference		Reference	
Elevated	−0.004 (−0.033–0.025)	0.796	−0.002 (−0.031–0.027)	0.900	0.007 (−0.015–0.028)	0.551	0.005 (−0.017–0.027)	0.640
Dyslipidemia	−0.037 (−0.087–0.012)	0.140	−0.033 (−0.084–0.017)	0.192	0.023 (−0.013–0.059)	0.202	0.020 (−0.016–0.056)	0.274
Triglyceride-HDL ratio	Reference		Reference		Reference		Reference	
Moderate	−0.006 (−0.036–0.025)	0.715	−0.003 (−0.034–0.027)	0.828	−0.015 (−0.038–0.007)	0.187	−0.018 (−0.041–0.005)	0.120
High	−0.011 (−0.060–0.035)	0.663	−0.006 (−0.055–0.043)	0.805	−0.018 (−0.054–0.018)	0.333	−0.024 (−0.061–0.012)	0.196

Effect estimates and CI, confidence interval, from linear mixed-effect model repeated measure analyses. Associations with *p*-values <0.05 are considered statistically significant.
Model 1 was adjusted for sex, age, high sensitivity C-reactive protein, total fat mass, lean mass, heart rate, systolic blood pressure, diastolic blood pressure, sedentary time, light physical activity, moderate to vigorous physical activity, family history of cardiometabolic disease, socio-economic status, pubertal attainment, and smoking status, in addition to other covariates such as high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, or triglyceride depending on the predictor but total cholesterol, non-HDL cholesterol, and triglyceride-HDL ratio were not adjusted for lipids. Model 2 was additional adjustment of Model 1 for glucose and insulin. The outcomes, carotid-femoral pulse wave velocity and carotid intima-media thickness, were measured both at 17 and 24-year clinic visits. CI; confidence interval. Reference is age-specific normal lipid level according to the 2011 National Heart, Lung, and Blood Institute lipid classification for youth.

progressive increase in dyslipidemia and lipid deposits on the carotid arterial wall, creating a vicious cycle [10,13]. We observed important sex differences which have not been previously reported [1,2,12]. Among males, elevated LDL-C and low HDL-C were associated with cIMT progression but among females elevated total cholesterol, non-HDL-C and low HDL-C were associated with cIMT progression. A likely explanation is that the proportion of females with elevated and dyslipidemic total cholesterol and non-HDL-C levels at 15 and 17 years was more than 2-fold higher than in males, partly due to body composition. Although this higher proportion was also observed with LDL-C, it remains unclear why cumulative elevated LDL-C was associated with cIMT progression only in males. Nonetheless, these findings suggest that sex-based intervention may be warranted.

Screening for lipid disorders in adolescents for early identification and treatment of elevated lipids could delay the atherosclerotic process and thereby reduce the incidence of premature ischemic cardiovascular events in adults [13,31]. However, due to inconclusive evidence on the benefit of pediatric lipid screening, the US Preventive Services Task Force did not recommend universal pediatric lipid screening [31]. This present study presents important evidence that normal-weight adolescents may have abnormal lipids levels that already alter the carotid architecture by young adulthood. The novel model of temporal inverse allocation which simulated a treatment modality at a specific time point revealed that dyslipidemia treatment or intervention at 24 years could be too late to reverse or alter atherosclerotic progression. This potential failed treatment at 24 years is consistent with an observation among middle-aged adults where statin treatment that achieves low levels of LDL-C could not fully restore a primary prevention low-risk state among participants who had developed atherosclerosis [32]. Nonetheless, we observed that plausible treatment interventions at 17 years effectively attenuated the associations between dyslipidemia and atherosclerosis. Late adolescence (17 years of age) may indicate critical timing for a significant deviation in cIMT progression in a general pediatric population, just as age 12 years was the critical age of significant cIMT deviation in participants with familial hypercholesterolemia [14].

Importantly, the observed treatment effect appears retained for at least 7 years despite simulating rebound dyslipidemia at 24 years. Our findings are buttressed by a report from a clinical trial where participants who received individualized dietary counselling from age 7 months to 20 years were more likely to have ideal total cholesterol and optimal LDL-C levels 6 years later (at age 26 years) compared with controls [33]. Similarly, persistent exposure to lower LDL-C from early life has been associated with a greater reduction in the risk of coronary heart disease in contrast to later life statin-treated LDL-C reduction [34]. In a 20-year follow-up study, initiation of statin therapy during childhood in patients with familial hypercholesterolemia slowed cIMT progression and reduced the risk of cardiovascular disease in adulthood [15]. We know that lipid and lipoprotein levels track well and that lipid genes have a substantial effect on life course levels [35]. Thus, intervening or getting an individual off this track is herculean although late adolescence screening and intervention are important, a primordial prevention approach across the entire life course beginning much earlier in life may be more comprehensive [13]. Taken together, emerging evidence [8,13,29,33,36] may strongly inform a universal

Table 4
Temporal inverse allocation of cumulative effect of elevated lipid and dyslipidemia from ages 15–17 years with normal lipid level at 24 years on carotid-femoral pulse wave velocity and carotid intima-media thickness progression from ages 17 through 24 years.

N = 1779	Carotid-femoral pulse wave velocity (m/s)		Carotid intima-media thickness (mm)	
All participants	Effect estimate (95% CI)	*p-value*	Effect estimate (95% CI)	*p-value*
Total cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.010 (−0.019–0.039)	0.499	0.028 (0.007–0.049)	**0.010**
Non-HDL cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.001 (−0.028–0.029)	0.982	0.027 (0.006–0.049)	**0.013**
HDL cholesterol	Reference		Reference	
Borderline low and Dyslipidemia	0.004 (−0.019–0.028)	0.716	−0.030 (−0.048–−0.013)	**0.001**
LDL cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.023 (−0.013–0.058)	0.205	0.018 (−0.009–0.045)	0.202
Triglyceride	Reference		Reference	
Elevated and Dyslipidemia	−0.012 (−0.039–0.015)	0.377	0.010 (−0.010–0.030)	0.330

Effect estimates and CI, confidence interval, from linear mixed-effect model for repeated measures analyses. Associations with *p*-values <0.05 are considered statistically significant.
The model was adjusted for sex, age, glucose, insulin, high sensitivity C-reactive protein, total fat mass, lean mass, heart rate, systolic blood pressure, diastolic blood pressure, sedentary time, light physical activity, moderate to vigorous physical activity, family history of cardiometabolic disease, socio-economic status, pubertal attainment, and smoking status. The analyses were further adjusted for high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglyceride depending on the predictor but total cholesterol and non-HDL cholesterol were not adjusted for lipids. The outcomes, carotid-femoral pulse wave velocity and carotid intima-media thickness, were measured at 17 and 24-year clinic visits. CI; confidence interval. Reference is age-specific normal lipid level according to the 2011 National Heart, Lung, and Blood Institute (NHLBI) expert panel recommended cutpoint.

Table 5
Temporal inverse allocation of cumulative effect of elevated lipid and dyslipidemia at ages 15 and 24 years with normal lipid levels at 17 years on carotid-femoral pulse wave velocity and carotid intima-media thickness progression from ages 17 through 24 years.

N = 1779	Carotid-femoral pulse wave velocity (m/s)		Carotid intima-media thickness (mm)	
All participants	Effect estimate (95% CI)	*p*-value	Effect estimate (95% CI)	*p*-value
Total cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.011 (−0.017–0.038)	0.446	0.005 (−0.015–0.025)	0.627
Non-HDL cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.018 (−0.010–0.047)	0.212	0.013 (−0.008–0.034)	0.235
HDL cholesterol	Reference		Reference	
Borderline low and Dyslipidemia	−0.001 (−0.022–0.021)	0.956	−0.016 (−0.031–−0.0001)	**0.049**
LDL cholesterol	Reference		Reference	
Elevated and Dyslipidemia	0.019 (−0.014–0.054)	0.270	0.002 (−0.023–0.026)	0.913
Triglyceride	Reference		Reference	
Elevated and Dyslipidemia	0.005 (−0.019–0.030)	0.681	0.003 (−0.015–0.021)	0.737

Effect estimates and CI, confidence interval, from linear mixed-effect model for repeated measures analyses. Associations with *p*-values <0.05 are considered statistically significant. The model was adjusted for sex, age, glucose, insulin, high sensitivity C-reactive protein, total fat mass, lean mass, heart rate, systolic blood pressure, diastolic blood pressure, sedentary time, light physical activity, moderate to vigorous physical activity, family history of cardiometabolic disease, socio-economic status, pubertal attainment, and smoking status. The analyses were further adjusted for high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, or triglyceride depending on the predictor but total cholesterol and non-HDL cholesterol were not adjusted for lipids. The outcomes, carotid-femoral pulse wave velocity and carotid intima-media thickness, were measured at 17 and 24-year clinic visits. CI; confidence interval. Reference is age-specific normal lipid level according to the 2011 National Heart, Lung, and Blood Institute (NHLBI) expert panel recommended cutpoint.

recommendation for pediatric lipid screening as suggested in the 2011 National Heart, Lung, and Blood Institute expert panel guideline that was based on cross-sectional data [25].

An important observation in this present longitudinal study is that lipid intervention for preventing atherosclerosis progression in a general paediatric population without familial disease may focus on lowering total cholesterol, non-HDL-C, and increasing HDL-C rather than lowering LDL-C as previously established in statin trials among paediatric population with familial hypercholesterolemia and in general adult populations [15,30,32,34]. The documented benefit of early lipid intervention (statin treatment) in 214 paediatric participants with familial hypercholesterolemia was achieving normal LDL-C levels in twenty percent of the studied population over a 20-year follow-up period [15]. Besides, the cumulative incidence of cardiovascular events and of death from cardiovascular causes at 39 years of age was lower among the treated patients with familial hypercholesterolemia than among their affected parents (1% *vs.* 26% and 0% *vs.* 7%, respectively) [15]. The statin treatment in patients with familial hypercholesterolemia also achieved similar cIMT progression/year in comparison with their siblings [15]. The present simulated intervention study during late adolescence in 1779 participants with potential evidence of attenuating and reversing cIMT progression may yield greater population-based health benefits than previously reported tertiary lipid interventions [15], buttressing an urgent call for primordial and primary prevention of heart disease as emphasized by the American Heart Association [37]. The debate about whether intervention should be offered to paediatric populations with elevated lipid levels concerns cost implication, adherence to therapy, long-term medication-related complications, participants' misclassification, parental or child anxiety, and stressful and unnecessary intervention exposures [13,31]. Nonetheless, promising results from a non-pharmacological intervention trial showed that participants who received individualized dietary counselling from infancy to age 20 years had healthier lipid levels 6 years after the trial compared with participants in the control group [33].

4.3. Strengths and limitations

The availability of gold-standard and repeated measures during adolescence and young adulthood allowed for comprehensive longitudinal analysis in a large birth cohort, for instance, dual-energy Xray absorptiometry measured fat mass and lean mass, and objectively assessed pubertal maturation, and accelerometer measured sedentary time, light physical activity, and moderate to vigorous physical activity, thereby overcoming the limitations of previous studies [1,3,5,29,33]. Advanced statistical modelling, i.e temporal inverse allocation, allowed simulation of treatment effect at specific time points for clinical and public health applicability of our findings [13]. Also, the hierarchical mixed-effect model offered the option to control for cumulative covariates exposure measured at all time points, overcoming the bias of adjusting for only baseline variables as in previous studies [1–3]. A few limitations of our study include the unavailability of hard cardiovascular outcomes in relatively healthy young participants. However, cfPWV, cIMT, and cIMT progression are established surrogate markers of cardiovascular risk in adults [13,28,37]. Almost all participants are white therefore our findings may not be generalizable to other ethnicities. We lacked dietary data at the studied time points, but we controlled for participants' body composition and metabolic indices, which partly reflect participants' diet. Observational studies are limited in making causal inferences, however, emerging longitudinal and temporal studies suggest a unidirectional causal path in which dyslipidemia precedes preclinical atherosclerosis [1,7,10,29,33].

4.4. Conclusion

Cumulative elevated total cholesterol, non-HDL-C, LDL-C, and low HDL-C from ages 15 through 24 years were associated with cIMT progression from ages 17 through 24 years. In sex-stratified analyses, a significant association with cIMT progression was observed with elevated LDL-C and low HDL-C among males, whilst in females, total cholesterol, non-HDL-C, and HDL-C were associated with cIMT progression. These findings were observed primarily among normal-weight adolescents but not among overweight and obese adolescents likely due to the smaller sample size of the overweight population. There were no associations between lipid indices and cfPWV progression. Using a novel temporal inverse allocation model which simulated treatment intervention, our findings suggest that initiating lipid intervention at age 24 years may be too late in preventing or reversing cIMT progression whereas initiating intervention earlier such as, at age 17 years, might neutralize the cumulative effect of elevated lipids and dyslipidemia on cIMT progression. Total cholesterol, non-HDL-C, and HDL-C may be the main targets of lipid intervention in a general adolescent population, rather than LDL-C to prevent early atherosclerosis progression.

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CRediT authorship contribution statement

Andrew O. Agbaje: Conceptualization, Methodology, Software, Validation, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Donald M. Lloyd-Jones:** Visualization, Validation, Writing - review & editing. **Costan G. Magnussen:** Visualization, Validation, Writing - review & editing. **Tomi-Pekka Tuomainen:** Visualization, Project administration, Resources, Validation, Writing - review & editing.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.11.011.

References

[1] M. Juonala, F. Wu, A. Sinaiko, J.G. Woo, E.M. Urbina, D. Jacobs, et al., Non-HDL cholesterol levels in childhood and carotid intima-media thickness in adulthood, Pediatrics 145 (4) (2020), e20192114.

[2] C.G. Magnussen, A. Venn, R. Thomson, M. Juonala, S.R. Srinivasan, J.S.A. Viikari, et al., The association of pediatric low- and high-density lipoprotein cholesterol dyslipidemia classifications and change in dyslipidemia status with carotid intima-media thickness in adulthood. Evidence from the cardiovascular risk in young Finns study, the bog, J. Am. Coll. Cardiol. 53 (10) (2009) 860–869.

[3] M. Juonala, C.G. Magnussen, A. Venn, T. Dwyer, T.L. Burns, P.H. Davis, et al., Influence of age on associations between childhood risk factors and carotid intima-media thickness in adulthood: the cardiovascular risk in young finns study, the childhood determinants of adult health study, the bogalusa heart study, and the Muscatine St, Circulation 122 (24) (2010) 2514–2520.

[4] M.G. Frontini, S.R. Srinivasan, J. Xu, R. Tang, M.G. Bond, G.S. Berenson, Usefulness of childhood non-high density lipoprotein cholesterol levels versus other lipoprotein measures in predicting adult subclinical atherosclerosis: the bogalusa heart study, Pediatrics 121 (5) (2008) 924–929.

[5] O.T. Raitakari, M. Juonala, M. Kähönen, L. Taittonen, T. Laitinen, N. Mäki-Torkko, et al., Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the cardiovascular risk in young Finns study, J. Am. Med. Assoc. 290 (17) (2003) 2277–2283.

[6] N.B. Allen, A.E. Krefman, D. Labarthe, P. Greenland, M. Juonala, M. Kähönen, et al., Cardiovascular health trajectories from childhood through middle age and their association with subclinical atherosclerosis, JAMA Cardiol. 5 (5) (2020) 557–566.
[7] L.R. Pool, A.E. Krefman, D.R. Labarthe, P. Greenland, M. Juonala, M. Kähönen, et al., The timing and sequence of cardiovascular health decline, Am. J. Prev. Med. 61 (4) (2021) 545–553.
[8] M.K. Armstrong, B.J. Fraser, O. Hartiala, M.J. Buscot, M. Juonala, F. Wu, et al., Association of non-high-density lipoprotein cholesterol measured in adolescence, young adulthood, and mid-adulthood with coronary artery calcification measured in mid-adulthood, JAMA Cardiol. 6 (6) (2021) 661–668.
[9] A.O. Agbaje, A.R. Barker, T.-P. Tuomainen, Effects of arterial stiffness and carotid intima- media thickness progression on the risk of overweight/obesity and elevated blood pressure/hypertension: a cross-lagged cohort study, Hypertension 79 (1) (2022) 159–169.
[10] A.O. Agbaje, A.R. Barker, G.F. Mitchell, T.-P. Tuomainen, Effect of arterial stiffness and carotid intima-media thickness progression on the risk of dysglycemia, insulin resistance, and dyslipidaemia: a temporal causal longitudinal study, Hypertension 79 (3) (2022) 667–678.
[11] A.O. Agbaje, Arterial stiffness precedes hypertension and metabolic risks in youth: a review, J. Hypertens. 40 (10) (2022) 1887–1896.
[12] M.J. Domanski, X. Tian, C.O. Wu, J.P. Reis, A.K. Dey, Y. Gu, et al., Time course of LDL cholesterol exposure and cardiovascular disease event risk, J. Am. Coll. Cardiol. 76 (13) (2020) 1507–1516.
[13] O. Raitakari, K. Pahkala, C.G. Magnussen, Prevention of atherosclerosis from childhood, Nat. Rev. Cardiol. 19 (8) (2022) 543–554.
[14] A. Wiegman, E. de Groot, B.A. Hutten, J. Rodenburg, J. Gort, H.D. Bakker, et al., Arterial intima-media thickness in children heterozygous for familial hypercholesterolaemia, Lancet (London, England) 363 (9406) (2004 Jan) 369–370.
[15] I.K. Luirink, A. Wiegman, D.M. Kusters, M.H. Hof, J.W. Groothoff, E. de Groot, et al., 20-Year follow-up of statins in children with familial hypercholesterolemia, N. Engl. J. Med. 381 (16) (2019 Oct 16) 1547–1556.
[16] R.A. Mekary, W.C. Willett, F.B. Hu, E.L. Ding, Isotemporal substitution paradigm for physical activity epidemiology and weight change, Am. J. Epidemiol. 170 (4) (2009) 519–527.
[17] P.A. Harris, R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, et al., The REDCap consortium: building an international community of software platform partners, J. Biomed. Inf. 95 (2019), 103208.
[18] A. Boyd, J. Golding, J. Macleod, D.A. Lawlor, A. Fraser, J. Henderson, et al., Cohort profile: the 'Children of the 90s'-The index offspring of the avon longitudinal study of parents and children, Int. J. Epidemiol. 42 (1) (2013) 111–127.
[19] A. Fraser, C. Macdonald-wallis, K. Tilling, A. Boyd, J. Golding, G. Davey smith, et al., Cohort profile: the avon longitudinal study of parents and children: ALSPAC mothers cohort, Int. J. Epidemiol. 42 (1) (2013) 97–110.
[20] K. Northstone, M. Lewcock, A. Groom, A. Boyd, J. Macleod, N. Timpson, et al., The Avon Longitudinal Study of Parents and Children (ALSPAC): an update on the enrolled sample of index children in 2019, Wellcome Open Res. 4 (2019) 51.
[21] A.O. Agbaje, A.R. Barker, T.-P. Tuomainen, Cumulative muscle mass and blood pressure but not fat mass drives arterial stiffness and carotid intima-media thickness progression in the young population and is unrelated to vascular organ damage, Hypertens. Res. (2022 Oct), https://doi.org/10.1038/s41440-022-01065-1.
[22] M. Frysz, L.D. Howe, J.H. Tobias, L. Paternoster, Using SITAR (SuperImposition by translation and rotation) to estimate age at peak height velocity in avon longitudinal study of parents and children, Wellcome Open Res. 3 (2018) 90.
[23] A.O. Agbaje, A.R. Barker, T.-P. Tuomainen, Cardiorespiratory fitness, fat mass, and cardiometabolic health with endothelial function, arterial elasticity, and stiffness, Med. Sci. Sports Exerc. 54 (1) (2022) 141–152.
[24] A.O. Agbaje, Mediating role of body composition and insulin resistance on the association of arterial stiffness with blood pressure among adolescents: the ALSPAC study, Front. Cardiovasc. Med. 9 (2022), 939125.
[25] Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents; national heart, Lung and BI. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report, Pediatrics 128 (Suppl 5) (2011) S213–S256.
[26] H. Mikola, K. Pahkala, H. Niinikoski, T. Rönnemaa, J.S.A. Viikari, A. Jula, et al., Cardiometabolic determinants of carotid and aortic distensibility from childhood to early adulthood, Hypertension 70 (2) (2017) 452–460.
[27] G. Golding, P. Pembrey, J. Jones, ALSPAC - the avon longitudinal study of parents and children I. Study methodology, Paediatr. Perinat. Epidemiol. 15 (1) (2001) 74–87.
[28] C. Vlachopoulos, K. Aznaouridis, C. Stefanadis, Prediction of cardiovascular events and all-cause mortality with arterial stiffness. A systematic review and meta-analysis, J. Am. Coll. Cardiol. 55 (13) (2010) 1318–1327.
[29] S.J. Kiechl, A. Staudt, K. Stock, N. Gande, B. Bernar, C. Hochmayr, et al., Predictors of carotid intima-media thickness progression in adolescents—the eva-tyrol study, J. Am. Heart Assoc. 10 (18) (2021), e020233.
[30] L. D'elia, E. La Fata, A. Iannuzzi, P.O. Rubba, Effect of statin therapy on pulse wave velocity: a meta-analysis of randomized controlled trials, Clin. Exp. Hypertens. 40 (7) (2018) 601–608.
[31] K. Bibbins-Domingo, D.C. Grossman, S.J. Curry, K.W. Davidson, J.W. Epling, F.A. R. García, et al., Screening for lipid disorders in children and adolescents US Preventive Services Task Force recommendation statement, J. Am. Med. Assoc. 316 (6) (2016) 625–633.
[32] K. Liu, J.T. Wilkins, L.A. Colangelo, D.M. Lloyd-Jones, Does lowering low-density lipoprotein cholesterol with statin restore low risk in middle-aged adults? Analysis of the observational mesa study, J. Am. Heart Assoc. 10 (11) (2021), e019695.
[33] K. Pahkala, T.T. Laitinen, H. Niinikoski, N. Kartiosuo, S.P. Rovio, H. Lagström, et al., Effects of 20-year infancy-onset dietary counselling on cardiometabolic risk factors in the Special Turku Coronary Risk Factor Intervention Project (STRIP): 6-year post-intervention follow-up, Lancet Child Adolesc. Health 4 (5) (2020) 359–369.
[34] B.A. Ference, W. Yoo, I. Alesh, N. Mahajan, K.K. Mirowska, A. Mewada, et al., Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a mendelian randomization analysis, J. Am. Coll. Cardiol. 60 (25) (2012) 2631–2639.
[35] M.J. Buscot, C.G. Magnussen, M. Juonala, N. Pitkänen, T. Lehtimäki, J.S.A. Viikari, et al., The combined effect of common genetic risk variants on circulating lipoproteins is evident in childhood: a longitudinal analysis of the cardiovascular risk in Young Finns Study, PLoS One 11 (1) (2016), e0146081.
[36] M.J. Pencina, K.M. Pencina, D. Lloyd-Jones, A.L. Catapano, G. Thanassoulis, A. D. Sniderman, The expected 30-year benefits of early versus delayed primary prevention of cardiovascular disease by lipid lowering, Circulation 142 (9) (2020) 827–837.
[37] P. Willeit, L. Tschiderer, E. Allara, K. Reuber, L. Seekircher, L. Gao, et al., Carotid intima-media thickness progression as surrogate marker for cardiovascular risk, Circulation 142 (7) (2020) 621–642.