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Pediatric triglycerides predict cardiovascular disease events in the fourth to fifth decade of life

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Abstract

To assess relationships between pediatric lipids and subsequent cardiovascular disease (CVD) in the fourth to fifth decades, we conducted 22- to 31-year follow-up studies (1998-2003) in former schoolchildren first studied in 1973-1976. The follow-up included 53% of eligible former subjects. We compared pediatric and adult body mass (in kilograms per square meter) and lipids in 19 cases with at least 1 CVD event and in 789 CVD event-free subjects. Mean ± SD age was 12.3 ± 3.3 years at entry and 38.5 ± 3.8 years at follow-up. Mean age at the first CVD event was 37.1 ± 4.9 years. The major novel finding of our study was that childhood triglycerides (TG) were consistently and independently associated with young adult CVD. The distributions of both childhood and adult TG were shifted to higher levels in the cases than controls. Of the 19 cases, 7 (37%) had childhood TG greater than the pediatric 95th percentile (153 mg/dL); and 6 of these 7 had high TG (≥150 mg/dL) at adult follow-up. Overall, 61% of cases had high TG as adults. After adjusting for age, sex, and race, by analysis of variance, cases had higher TG levels both in childhood and in young adulthood. A bootstrapping method and the Cox proportional hazard analysis were used to predict CVD in the cohort with explanatory variables sex; race; childhood body mass index, low-density lipoprotein, log high-density lipoprotein cholesterol, and log TG; and adult cigarette smoking and type 2 diabetes mellitus. Childhood TG level was a significant, independent explanatory variable for young adult CVD hazard (hazard ratio, 5.35; 95% confidence interval, 1.69-20.0 for each 1-unit increase in natural logarithm scale) along with adult type 2 diabetes mellitus (hazard ratio, 19.4; 95% confidence interval, 4.24-114.2). Pediatric hypertriglyceridemia appears to be a significant, independent, potentially reversible correlate of young adult CVD.

1. Introduction

The role of triglycerides (TG) in the constellation of cardiovascular disease (CVD) risk factors has been somewhat controversial because of their strong, inverse correlation with high-density lipoprotein cholesterol (HDLC), a major CVD risk factor [1,2]. In univariate analyses, high adult TG predict CVD; but the TG-CVD relationship weakens after adjustment for plasma HDLC [1]. Nevertheless, even after adjustment for HDLC, a significant, independent relationship between TG and CVD events remains [2]. In addition, nonfasting hypertriglyceridemia (HTG) [3-5] and fasting HTG [2,6] are independent risk factors for CVD, particularly for women. Hypertriglyceridemia is often concurrent with centripetal obesity, hyperglycemia, hypertension, and low HDLC, metabolic syndrome [4] components associated with increased CVD events [7]. Heterogeneity in lipoprotein lipase, with reduced degradation of TG, is associated with increased CVD [8]. The question remains, however, whether HTG alone or CVD risk factors associated with HTG (obesity, hyperglycemia, hypertension, hyperinsulinemia [9]) are most important [4] in predicting CVD.

Lowering TG and raising HDLC by fibric acids have been associated with significant reductions in cardiovascular event rates [10-14]. After acute coronary syndrome, on-treatment TG level less than 150 mg/dL was independently associated with reduced risk of recurrent CVD events [15].

As the number of childhood CVD risk factors increases, so does the severity of asymptomatic coronary and aortic

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atherosclerosis in young adulthood [16]. Atherosclerosis begins to develop in early life [17]. Childhood obesity is associated with young adult carotid intimal-medial thickness (CIMT), a surrogate marker of CVD [18]. In Finnish children aged 12 to 18 years at baseline, with follow-up 23 years later [19], apolipoprotein (apo) B and the apo B/apo A-I ratio were directly ($P < .001$) related and apo A-I was inversely ($P = .01$) related with adulthood CIMT. Juonala et al [20] have reported that cardiovascular risk factors identified in childhood and adolescence predict decreased carotid artery elasticity in adulthood and suggested that risk factors operating in early life may have sustained deleterious effects on arterial elasticity [20,21]. Childhood obesity predicts adult metabolic syndrome [22], which is associated with increased CVD events [7]. In the Muscatine, IA, study [23], total cholesterol was a significant childhood predictor of CIMT.

None of the longitudinal follow-up studies from childhood to young adulthood [18-20,23] has focused on relationships of childhood CVD risk factors to CVD events in adults. For the current report, we conducted 22- to 31-year follow-up studies (1998-2003) in former schoolchildren first studied in 1973-1976 to assess relationships between pediatric body mass index (BMI) and lipids and subsequent CVD in the fourth to fifth decades using participants in the Princeton Follow-up Study (PFS) population [24].

2. Materials and methods

2.1. Princeton Follow-up Study

This study was carried out following a protocol approved by the Children's Hospital Institutional Review Board, with signed informed consent.

The PFS was a 22- to 31-year follow-up (1998-2003) [24] of former schoolchildren and their parents from the Cincinnati Clinic of the National Institutes of Health (NIH)–National Heart, Lung, and Blood Institute Lipid Research Clinics (LRC) Prevalence Program (1973-1978). The LRC [25,26] and PFS [24] have both been described previously. Briefly, the LRC was a multistage survey of lipids and other (CVD) risk factors [25,26]. At the first stage of the LRC (visit 1), total cholesterol and TG were measured, basic demographic data were collected, and family relationships among participating members from the same family were determined. At stage 2 (visit 2), randomly selected and hyperlipidemic visit 1 subjects were recalled, independent of other members of the family, for a second screening, at which complete lipid profiles and anthropometric data were recorded. At stage 3 (family study), complete lipid profiles were measured on all first-degree relatives of a random and hyperlipidemic subset of stage 2 subjects. Eighty-four percent of eligible students participated at the initial LRC study visit, and 91% participated at subsequent visits; participation rates did not differ significantly between races.

The PFS was conducted to assess changes in the family lipoprotein cholesterol correlations from the period of shared households to that of separate households [24]. Hence, eligibility for PFS required participation in stage 3 (LRC family study), or stage 2 (visit 2) along with either a sibling or a parent. The student population from which participants came was 73% white and 27% black, and 52% male and 48% female [26]. The interval between LRC study and PFS visits ranged between 22 and 31 years, depending on when the subjects attended their LRC study and PFS visits. In 1998, eligible former schoolchildren who had participated in the LRC family study or at visit 2, along with either a sibling or a parent, were invited by mail and by follow-up phone call to participate in the PFS, 22 to 31 years after their initial LRC sampling. There had been no contacts with these eligible former schoolchildren for the 22- to 31-year interval from their LRC studies.

In the LRC, data were collected according to the collaborative NIH–National Heart, Lung, and Blood Institute protocol [27]. In the PFS, data were collected using standard protocols [25,28]. In the LRC and PFS, fasting blood was drawn into Vacutainers containing EDTA, kept on ice (LRC) or cold packs (PFS), and delivered to the laboratory within 3 hours for processing. A detailed medical history was obtained at PFS, including information on angioplasty, coronary artery bypass grafts, myocardial infarction, other vascular surgery (carotid or femoral bypass), ischemic stroke, diabetes, and cigarette smoking.

2.2. Statistical methods

All analyses were done using SAS 9.1 (SAS, Cary, NC). If PFS participants had data for these analyses from more than one stage of the LRC (visits 2 and/or 3), data from the last LRC examination were used. Percentile distributions of TG in the analysis cohort of 808 children were calculated. The distribution of TG in the 19 CVD cases and 789 CVD-free controls were plotted for both childhood (Fig. 1) and adulthood (Fig. 2).

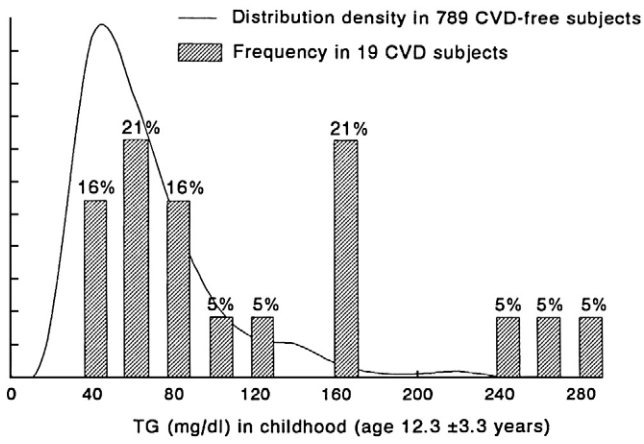

Fig. 1. The distribution density functions of TG in subsequent CVD cases and subsequent CVD-free subjects during childhood (mean age, 12.3 ± 3.3 years).

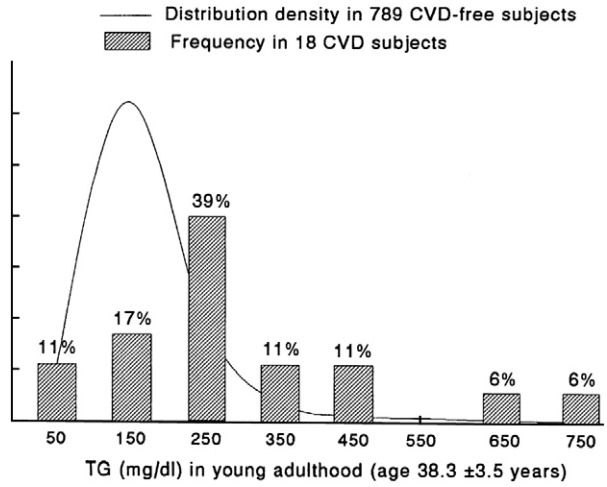

Fig. 2. The distribution density functions of TG in CVD cases and CVD-free subjects during young adulthood (mean age, 38.5 ± 3.7 years).

Childhood entry and young adult follow-up characteristics of the 19 former schoolchildren who sustained CVD events are displayed in Table 1. Table 2 summarizes the number of cardiovascular events (1, 2, or 3 per subject), cross tabulated by the nature of the cardiovascular events.

Differences between CVD cases and all CVD-free subjects, both at childhood entry and at young adult follow-up, were assessed by analysis of variance (ANOVA) after adjusting for race, sex, and age (Table 3).

To improve upon the estimates given by the Cox proportional hazard model with backward selection (α = .5), we followed the guidelines of Austin [29], using a zero-corrected bootstrap model selection method. In the 808 subjects, the bootstrap method samples, with replacement, 1000 times with the full analysis size = 808 each time [29]. The parameter estimate was set to zero if the candidate explanatory variable was removed from the selection [29]. Afterward, the mean of all the parameter estimations from the 1000 resultant models was used for the parameter estimate, whereas the 2.5th and 97.5th percentiles were used for the 95% confidence interval (CI). Childhood explanatory variables included race, sex, BMI, low-density lipoprotein cholesterol (LDLC), log HDLC, and log TG. Adult explanatory variables included type 2 diabetes mellitus and cigarette smoking. Analyses of cigarette smoking included 3 levels: 1 = never, 2 = quit, 3 = current smoking; and thus, 2 dummy variables for cigarette smoking (never smoke vs rest, current smoking vs rest) were used.

To assess for differences between eligible former schoolchildren studied in the PFS and those not studied in the PFS, Wilcoxon tests were first done of childhood age, childhood BMI, total cholesterol, LDLC, HDLC, and TG, followed by ANOVA adjusting for age, sex, race, and BMI.

3. Results

3.1. Follow-up of the schoolchild cohort

There were 1756 LRC student-participants who met eligibility criteria for the PFS; and 22- to 31-year follow-up data were obtained on 933 (53%) in PFS, including 18 who had died before PFS. By review of autopsy reports, physicians' records, and interviews with family members, 1 subject (with second-generation familial HTG) had had a lethal myocardial infarction, 6 subjects had deaths unrelated to CVD, and 11 subjects could not be classified with regard to cause of death. After excluding 18 former schoolchildren who had died and 107 subjects because of missing data on one or more childhood explanatory variables, the analysis

Table 1
Nineteen former schoolchildren who sustained cardiovascular events during young adulthood: childhood and young adulthood lipids and BMI

ID	Sex	Race	Age (y)		BMI (kg/m^2)		TG (mg/dL)		HDLC (mg/dL)		LDLC (mg/dL)	
			Initial	Event	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up
1	F	B	11.3	25	16.5	30.6	41	38	107	72	83	73
2	M	B	17.8	41	19.2	31.8	46	–	59	–	135	–
3	M	W	13.4	32	16.2	29.2	55	175	67	43	102	129
4	F	W	14.1	39	21.9	30.0	62	217	69	46	97	130
5	F	B	12.4	38	21.5	23.7	70	43	62	64	107	98
6	F	B	15.1	40	31.2	41.4	75	165	50	46	125	132
7	M	W	17.3	42	20.7	29.7	76	91	45	30	94	137
8	M	W	12.7	38	18.6	30.8	90	242	49	24	109	150
9	F	B	17.5	40	24.9	39.5	92	73	63	50	102	128
10	M	W	17.2	41	26.1	43.8	92	350	49	25	108	95
11	M	W	13.7	34	–	36.8	113	231	44	42	103	157
12	M	W	12.3	37	24.1	28.8	120	237	32	37	102	111
13	M	W	11.1	32	22.3	32.9	163	279	38	24	155	132
14	F	W	16.2	41	34.8	38.3	168	632	41	18	122	67
15	F	W	16.7	39	27.3	37.5	168	739	59	58	74	40
16	M	W	18.6	31	20.7	23.2	172	198	47	35	109	115
17	M	W	16.5	41	29.6	43.5	251	379	45	29	105	101
18	M	W	18.1	30	35.1	31.2	265	290	37	28	184	107
19	M	W	17.0	43	26.5	27.1	285	147	46	40	104	82

Table 2
Nineteen former schoolchildren who sustained cardiovascular events during young adulthood: nature of and age at the cardiovascular event

ID	Diabetes	Cigarette smoke[a]	Event age	Angioplasty	CABG	Myocardial infarction	Carotid or femoral bypass	Stroke	No. of events	Medication to lower cholesterol
1	No	1	25	–	No	No	Yes	No	1	No
2	No	3	41	–	–	–	Yes	–	1	Yes
3	No	1	32	No	No	Yes	No	No	1	No
4	No	3	39	No	No	No	Yes	–	1	No
5	No	3	38	No	No	No	Yes	No	1	No
6	Yes	2	40	Yes	No	No	No	No	1	Yes
7	No	2	42	Yes	No	Yes	No	No	2	No
8	No	3	38	No	No	Yes	Yes	No	2	No
9	Yes	1	40	No	No	No	Yes	No	1	No
10	No	3	41	No	No	No	No	Yes	1	Yes
11	No	1	34	No	No	Yes	Yes	No	2	No
12	Yes	1	37	Yes	Yes	No	No	No	2	Yes
13	No	3	32	Yes	No	Yes	No	–	2	No
14	Yes	3	41	Yes	No	Yes	No	No	2	Yes
15	Yes	3	39	Yes	No	Yes	Yes	No	3	Yes
16	No	1	31	No	No	No	Yes	No	1	No
17	No	3	41	No	No	No	Yes	No	1	No
18	Yes	1	30	No	No	No	Yes	Yes	2	No
19	No	2	43	Yes	No	Yes	No	No	2	Yes
total				7	1	8	11	2	29	

CABG indicates coronary artery bypass graft.
[a] Cigarette smoke code: 1 = never, 2 = quit, 3 = current smoking.

sample included 808 former schoolchildren, 19 with morbid CVD events (Tables 1 and 2) and 789 CVD event-free (Table 3, Figs. 1 and 2). These 808 participants came from 556 families as follows: there were 384 families (69%) with 1 student-participant, 118 families with 2 student-participants, 38 families with 3 student-participants, 11 families with 4 student-participants, 2 families with 5 student-participants, 1 family with 6 student-participants, and 2 families with 7

Table 3
Nineteen former schoolchildren who developed CVD as young adults (mean age, 37.1 ± 4.9), compared with 789 former schoolchildren without young adult CVD, at childhood study entry baseline and at follow-up

	CVD cases (n = 19)	Subjects without CVD (n = 789)	*P* (ANOVA)
	Event age, 37.1 ± 4.9		
Baseline (age, 12.3 ± 3.3)	Age, 15.3 ± 2.5	Age, 12.3 ± 3.3	
BMI (kg/m^2)	24.3 ± 5.7	20.0 ± 4.3	.012
TC (mg/dL)	186 ± 25	174 ± 33	.094
TG (mg/dL)	127 ± 75	76 ± 45	<.0001
HDLC (mg/dL)	53 ± 17	55 ± 12	.93
LDLC (mg/dL)	112 ± 25	107 ± 30	.40
Diastolic BP (mm Hg)	68 ± 11	62 ± 12	.75
Systolic BP (mm Hg)	114 ± 13	104 ± 13	.27
Glucose (mg/dL)	87 ± 9	86 ± 8	.60
Follow-up (age, 38.5 ± 3.8)	Age, 40.7 ± 2.8	Age, 38.5 ± 3.8	
BMI (kg/m^2)	33.2 ± 6.2	28.6 ± 6.8	.0078
TC (mg/dL)	196 ± 24	194 ± 42	.79
TG (mg/dL)	251 ± 186	135 ± 133	.0016
HDLC (mg/dL)	40 ± 15	46 ± 15	.16
LDLC (mg/dL)	110 ± 31	121 ± 36	.098
Diastolic BP (mm Hg)	85 ± 11	79 ± 11	.080
Systolic BP (mm Hg)	128 ± 16	120 ± 15	.062
Glucose (mg/dL)	122 ± 53	90 ± 26	<.0001
Cigarette smoking, n (%)	7 (37%) Never	482 (61%) Never	Mantel-Haenszel
	3 (16%) Quit	118 (15%) Quit	$\chi^2 = 5.84$,
	9 (47%) Current smoke	189 (24%) Current smoke	$P = .016$
Type 2 diabetes mellitus, n (%)	6 (32%)	31 (4%)	.0001 (Fisher)

P values were by ANOVA adjusted for race, sex, and age. TC indicates total cholesterol; BP, blood pressure.

student-participants. Each of the 19 CVD cases came from separate families; 8 of the 19 cases had 1 sibling as a noncase. There were 438 girls (54%) and 370 boys (46%), and 585 white (72%) and 223 black participants (28%). Thus, the racial makeup of the cohort was similar at the LRC and PFS (73%-27% and 72%-28%, respectively). Comparisons of LRC summary data on the 933 follow-up subjects and the 823 eligible LRC subjects not in the PFS indicated that the ages of the 2 groups were similar, but PFS subjects had higher BMI than nonparticipants (19.4 vs 18.7 kg/m^2, $P = .0006$). There were no differences ($P > .2$) between PFS participants and nonparticipants at the original LRC study in mean total cholesterol, HDL-C, LDL-C, or TG after adjustment for age, sex, race, and BMI.

3.2. Characteristics of the CVD case population

The mean (±SD) age of the analysis cohort was 12.3 ± 3.3 years in the LRC and 38.5 ± 3.8 years at PFS (Table 3). At the time of the PFS, 19 participants (cases) had sustained at least 1 CVD event. Seven were women, and 12 were men; 5 were black, and 14 were white (Table 1). Event ages ranged from 25 to 43 years, with mean ± SD age of 37 ± 5 years (Table 1). Of the 19 subjects, 7 (37%) had childhood TG greater than the schoolchild 95th percentile (153 mg/dL, Table 1). Of these 7 hypertriglyceridemic children (2 girls, 5 boys), follow-up TG were high (≥150 mg/dL) in 6 (86%, Table 1). Of the 18 cases with adult lipids (venipuncture was not successful for 1 case subject), 11 (61%) of 18 had high TG (≥150 mg/dL) as adults (Table 1).

The 19 cases had had 29 CVD events including 7 angioplasties, 1 coronary artery bypass grafting, 8 myocardial infarctions, 11 carotid or femoral bypasses, and 2 ischemic strokes (Table 2). Eight of 19 subjects had 2 CVD events, and 1 had 3 events (Table 2). In the 7 subjects where carotid-femoral artery events were the sole CVD event, 4 of the 7 cases were current smokers (Table 2).

At PFS follow-up, the 19 cases had higher TG than former schoolchildren without CVD events (251 vs 135 mg/dL, $P = .0016$). Low-density lipoprotein cholesterol was 110 mg/dL in cases vs 121 mg/dL in noncases ($P = .098$), but 7 (37%) of 19 cases reported taking lipid-lowering drugs vs 3% (24 of 789) of noncases ($P < .05$).

3.3. CVD cases vs CVD-free subjects: risk factor comparisons

The TG distributions of cases and CVD-free comparison subjects in both childhood (Fig. 1) and adulthood (Fig. 2) were skewed to the right (higher values), but the shift was markedly greater in the cases in both childhood and adulthood. Of the 19 cases, 7 (37%) had childhood TG greater than the schoolchild population 95th percentile TG (153 mg/dL, Table 1). Comparing CVD risk factors in cases and CVD-free subjects after adjusting for age, sex, and race, cases had higher least square mean TG ($P < .0001$) and higher BMI ($P = .012$) in both childhood and adulthood ($P = .0016$ and .0078, respectively; Table 3). In addition, plasma glucose was higher in adult CVD cases than CVD-free subjects ($P < .0001$, Table 3). At adult follow-up, cigarette smoking was more prevalent in cases than CVD-free subjects: 9 (47%) of the 19 cases reported smoking cigarettes and 3 (16%) reported being ex-smokers vs 24% (189 of 789) of CVD-free subjects reporting smoking and 15% (n = 118) reporting being ex-smokers (Mantel-Haenszel $\chi^2 = 5.84$, $P = .016$, Table 3). Type 2 diabetes mellitus was more prevalent in cases (6 [32%] of 19 cases vs 31 [4%] of 789 CVD-free subjects, Fisher $P = .0001$, Table 3).

3.4. Pediatric determinants of CVD events

Using the Austin [29] bootstrapping method and the Cox proportional hazard model, significant, independent explanatory variables for CVD included adult type 2 diabetes mellitus (hazard ratio, 19.4; 95% CI, 4.24-114.2) and childhood TG (hazard ratio, 5.35; 95% CI, 1.69-20.0 for each 1-unit increase in natural logarithm scale).

4. Discussion

Prospective studies of the relationships of childhood CVD risk factors to CVD in young adulthood have relied on the CVD surrogate CIMT. The following childhood CVD risk factors have been associated with CIMT and other vascular surrogates (carotid artery compliance, Young elastic modulus, and stiffness index) in young adulthood: total cholesterol [23], obesity [18,20], and the ratio of apo B to apo A-I [19,21]. Subjects with type IIB hyperlipidemia in childhood had increased CIMT 21 years later in young adulthood [21].

None of the longitudinal follow-up studies from childhood to young adulthood to date [18-21] has focused on relationships of childhood CVD risk factors to CVD events in adults. By virtue of having a longer follow-up (22-31 years) than the previous childhood risk factor → adult CVD studies [18-21], our study allowed direct examination of the relationship of childhood BMI and lipids to young adult CVD events including angioplasty; coronary, carotid, and femoral artery bypass surgery; myocardial infarction; and ischemic stroke. The major novel and original finding in the current study was that childhood TG level was consistently and independently associated with young adult CVD. The distribution of both childhood and adult TG shifted to higher levels in the 19 CVD cases than in CVD-free subjects. Of the 19 subjects, 7 (37%) had childhood TG greater than 153 mg/dL, the schoolchild 95th percentile. Of the 7 hypertriglyceridemic children, 6 (86%) had high TG (≥150 mg/dL) as adults. Overall, 13 (72%) of the 18 CVD cases who had TG measured as young adults had high TG (≥150 mg/dL). Mean adult TG level in the CVD cases was 251 mg/dL as adults compared with 135 mg/dL in CVD-free subjects. After adjusting for sex, race, and age by ANOVA, children who subsequently

sustained CVD events had higher TG levels both in childhood and in young adulthood than CVD-free subjects. Moreover, by the Cox proportional hazard analysis, childhood TG level was a significant, independent explanatory variable for young adult CVD hazard (hazard ratio, 5.35; 95% CI, 1.69-20.0 for each 1-unit increase in natural logarithm scale). An additional significant explanatory variable in the Cox model included adult type 2 diabetes mellitus (hazard ratio, 19.4; 95% CI, 4.24-114.2).

Our finding that 7 of the 19 CVD events in former schoolchildren were femoral and/or carotid bypass as the only CVD event raised the question of TG as an etiology for femoral and/or carotid disease. Four of these 7 carotid-femoral event cases were current smokers, a known association with carotid [30,31] and peripheral vascular disease [32,33]. Beyond cigarette smoking, Genoud et al [34] reported that TG and HDLC were major contributors to peripheral atherosclerosis in 120 overweight cases. In 21-year follow-up in the Young Finns Study that started in 1980 in children then aged 3 to 18 years, type IIB dyslipidemia was related to CIMT [21]. Mori et al [35] have reported a significant association between postprandial TG levels and CIMT in Japanese patients with type 2 diabetes mellitus. Shoji et al [36] reported that small dense LDL was the best marker of CIMT, along with TG. Because small dense LDL is commonly high in hypertriglyceridemic subjects [36], the findings of Shoji et al may also point to high TG associated with CIMT. In subjects with carotid atherosclerosis, reduction in TG on Crestor (Astra Zeneca, London, UK) 10 mg was a significant predictor of change in CIMT after adjustment for established CVD risk factors [37]. Rizzo et al [38] have reported that the concomitant presence of high TG, low HDLC, and high small dense LDL was 26% in patients with peripheral arterial disease vs 0% in controls (P = .0024). Vaudo et al [39] have reported that femoral IMT was associated with TG, among other CVD risk factors.

To the best of our knowledge, previous prospective studies of CVD risk factors in childhood and expression of surrogates for CVD in young adulthood [19,20] have not identified TG as a significant, independent explanatory variable. Our current study is congruent with studies in adults where nonfasting TG [3-5] and fasting TG [2,6] are independent risk factors for CVD.

The major limitation of the current study is the small number of CVD cases (n = 19). A general recommendation for proportional hazards regression is that the number of cases (if this is the smaller outcome group) should be at least 10 times larger than the number of "potential" predictors [40,41]. The initial Cox proportional hazards model had 8 explanatory variables and 19 cases. The conventional backward elimination method may filter out explanatory variable "winners," and may result in effect estimates that are too high and P values that are too small because of the numerous statistical tests that are performed [29,42-44]. To deal with this issue in our data set, we used the Austin [29] bootstrapping method with the Cox model. However, in a simulation study, Austin [45] noted that "… bootstrap model selection tended to result in an approximately equal proportion of selected models being equal to the true regression model compared with the use of conventional backward variable elimination." In the final model, there were 2 explanatory variables (log childhood TG and adult type 2 diabetes mellitus) that were significantly associated with CVD. Low-density lipoprotein cholesterol was not higher in cases than controls at follow-up in the PFS; but lipid-lowering drugs were reported by 37% of cases vs 3% of controls. The interaction of BMI, diabetes, and both TG and HDL cholesterol may be difficult to dissect in 19 cases with CVD and in 789 subjects free of CVD. An additional limitation of our study was that we used self-identified and interviewer-recorded history of CVD, without direct validation by review of physician-hospital records. Family history of CVD has, however, been shown by Murabito et al [46] to provide accurate data.

We are able to restudy 53% of our childhood cohort as young adults, 22 to 31 years after their initial assessment in the LRC family studies. Comparing eligible former schoolchildren who were and were not studied as young adults, the participants had higher pediatric BMI; but there were no differences in childhood LDLC and HDLC or TG after covariance adjusting for age, sex, race, and BMI. Hence, the PFS participants might reflect some bias toward somewhat higher BMI as children.

Triglyceride-rich lipoproteins and their associated atherogenic remnants [47] produce a proinflammatory and oxidative state that may enhance adhesion molecule and foam cell production, and adversely affect smooth muscles [48]. High TG are associated with an increased population of small dense LDL particles that are highly atherogenic and can be oxidatively modified [49,50].

In the blinded, placebo-controlled Helsinki Heart Study [10] in asymptomatic middle-aged men, there was a 34% reduction in the incidence of CVD in the gemfibrozil treatment group. In the blinded, placebo-controlled Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (HIT) secondary prevention study [51], CVD events were reduced by 11% with gemfibrozil for every 5-mg/dL increase in HDLC (P = .02). Because high TG track from childhood to young adulthood [52-54] and because TG are an independent risk factor for CVD [2], recognition of high TG in childhood and treatment may offer a pediatric approach to primary prevention of CVD in adults.

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