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Childhood risk factors predict cardiovascular disease, impaired fasting glucose plus type 2 diabetes mellitus, and high blood pressure 26 years later at a mean age of 38 years: the Princeton–lipid research clinics follow-up study

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ABSTRACT

The objective was to assess whether pediatric risk factors predict cardiovascular disease (CVD), impaired fasting glucose (IFG) + type 2 diabetes mellitus (T2DM), and high blood pressure (HBP) in young adulthood. We performed a prospective follow-up of 909 public-parochial suburban schoolchildren first studied at ages 6 to 18 years and 26 years later at a mean age of 38 years. Pediatric triglycerides (TGs), blood pressure, low-density lipoprotein cholesterol, body mass index, and glucose above and high-density lipoprotein cholesterol below established pediatric cutoffs, along with race, cigarette smoking, family history of CVD, T2DM, and HBP, were assessed as determinants of young adult CVD, a composite variable including IFG + T2DM and HBP. By stepwise logistic regression, adult CVD (19 yes, 862 no) was associated with pediatric high TG (odds ratio [OR], 5.85; 95% confidence interval [CI], 2.3-14.7). High TG in pediatric probands with young adult CVD was familial and was associated with early CVD in their high-TG parents. Adult IFG + T2DM (114 yes, 535 no) was associated with parental T2DM (OR, 2.2; 95% CI, 1.38-3.6), high childhood glucose (OR, 4.43; 95% CI, 2-9.7), and childhood cigarette smoking (OR, 1.64; 95% CI, 1.03-2.61). Adult HBP (133 yes, 475 no) was associated with pediatric high body mass index (OR, 2.7; 95% CI, 1.7-4.3) and HBP (OR, 2.5; 95% CI, 1.5-4.3). Pediatric risk factors are significantly, independently related to young adult CVD, IFG + T2DM, and HBP. Identification of pediatric risk factors for CVD, IFG + T2DM, and HBP facilitates initiation of primary prevention programs to reduce development of adult CVD, IFG + T2DM, and HBP.

1. Introduction

Pediatric risk factors for atherosclerosis are associated with young adult atherosclerotic lesions, carotid intimal-medial thickening (CIMT) [1-4], and cardiovascular disease (CVD) events [5]. Berenson et al [6] reported that increased atherosclerotic lesions in young adults were positively correlated with the number of pediatric risk factors, hyperlipidemia, high

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blood pressure (HBP), and obesity. The Muscatine Iowa Study reported that increased CIMT was associated with high total cholesterol and hypertension in childhood [7]. The Cardiovascular Risk in Young Finns study [1] showed that CVD risk factor status in adolescence predicted increased CIMT in adulthood, independent of adult risk factors [8]. In 4 longitudinal studies in young Finns, Juonala et al [1] reported that the number of risk factors in the highest quintile of total cholesterol, triglycerides (TGs), blood pressure, and body mass index (BMI) at ages 9, 12, 15, and 18 years predicted top decile CIMT in young adulthood, but risk factors at ages 3 and 6 years did not. Assessing pooled data from the Young Finns and Bogalusa studies, Magnussen et al [9] reported that children with metabolic syndrome (MetS) were 2 to 3 times more likely than children without MetS to have high CIMT and type 2 diabetes mellitus (T2DM) as adults. We have previously reported [5] that pediatric TGs were consistently and independently associated with CVD in the fourth to fifth decade of life.

The findings from these studies [1-10] promoted extensive screening of children for high risk levels of CVD risk factors to permit early intervention, especially after the success of the Lipid Research Clinics Coronary Primary Prevention Trial [11] and the Hypertension Detection and Follow-up Studies [12]. Based on the totality of the longitudinal findings from the Bogalusa, Muscatine, and the Young Finns Study, Berenson and Pickoff [13] have advocated widespread, universal screening of children for CVD risk; but the Expert Panel on Blood Cholesterol in Children and Adolescents recommended only targeted screening of children with a family history positive for premature CVD or parental hypercholesterolemia (≥6.2 mmol/L [240 mg/dL]) [14]. The American Academy of Pediatrics endorsed using the National Cholesterol Education Program (NCEP) guidelines [15]. Yet, the effectiveness of the NCEP-Pediatrics guidelines [15] depends on several factors: (1) the parents' own pattern of health care utilization, their knowledge of their lipid levels, and their awareness of the importance of informing their children's physician or clinic about their family history; (2) consequently, the provider's knowledge of the family history; and (3) thus, the "Balkanization" of the family's health care providers.

Within the framework of these health care coverage issues, our specific aim was to evaluate the use of risk factor screening results of 5- to 19-year-old schoolchildren to predict CVD, a composite variable including impaired fasting glucose (IFG) and T2DM (IFG + T2DM), and HBP 26 years later in young adulthood.

2. Methods

In the current report, we used longitudinal data from the National Heart, Lung, and Blood Institute Princeton Follow-up Study (PFS) (1999-2003), a 22- to 30-year follow-up of black and white former schoolchildren first studied in the National Heart, Lung, and Blood Institute Lipid Research Clinics (LRC, 1973-1978) [16]. The PFS collected data following a protocol approved by the Cincinnati Children's Hospital Institutional Review Board, with signed informed consent [16].

2.1. *Princeton LRC and PFS studies*

The Princeton LRC and PFS [17] have both been described previously. Briefly, the Princeton LRC was a multistage survey of lipids and other CVD risk factors in students in grades 1 to 12 and a 50% random sample of their parents by household. The student population in LRC was 72% white and 28% black, with a mean age of 12.3 ± 3.4 years. Eighty-two percent of eligible students participated at visit 1, and 91% of eligible students participated at subsequent visits; participation rates did not differ significantly between races. At visit 1, total cholesterol and TG were measured. At visit 2, complete fasting lipid profiles, blood pressure, glucose, and BMI (kilograms per square meter) were measured on random and hyperlipidemic subsets of all visit 1 participants. At visit 3, the first-degree relatives of random and hyperlipidemic participants at visit 2 had complete fasting lipid profiles, glucose, and BMI (kilograms per square meter) measured.

The PFS was conducted to assess changes in risk factors from childhood to adulthood and changes in familial CVD risk factor correlations from the period of shared households to separate households. Hence, PFS eligibility was restricted to former students that participated at LRC visit 2 with a sibling or parent also at visit 2 plus all former students and parents participating at visit 3. There was no contact with the former schoolchildren during intervals in these studies.

2.2. *Diagnosis of CVD, IFG, T2DM, and HBP*

At PFS, information about the participants' and their parents' health history for CVD, T2DM, and HBP was obtained by direct interview of the former students, now adults, and their participating (adult) siblings and parents, a protocol shown previously [5,18] to provide accurate data. *Cardiovascular disease* was defined as myocardial infarction, coronary artery bypass graft, angioplasty, ischemic stroke, and carotid or peripheral artery bypass surgery. Diagnosis of diabetes was based on World Organization of Health criteria, fasting glucose of at least 126 mg/dL (7 mmol/L) [19], and/or self-report of diabetes with treatment by a physician. We excluded from these analyses 10 subjects who had reported diabetes mellitus as children at LRC. However, in PFS, we did not have a measurement of C-peptides or diabetes autoantibody levels, the criterion standard methods of distinguishing type 1 from type 2 DM [19]. Diagnosis of IFG was made when fasting blood glucose was at least 100 mg/dL (5.6 mmol/L). *High blood pressure* at the PFS visit was defined as a systolic (SBP) and/or diastolic blood pressure (DBP) of at least 140/90 mm Hg or taking blood pressure medication prescribed by a physician. At the PFS visit, information was obtained by interview from former schoolchildren regarding medication use, including the question "are you currently taking medicine to lower cholesterol?"

2.3. *Pediatric and young adult risk factor cutoffs*

Pediatric risk factor cutoffs included high low-density lipoprotein cholesterol (LDLC) (≥110 mg/dL [2.82 mmol/L]) [20] and cutoffs published for pediatric MetS [21]: high TG (≥110 mg/dL [1.24 mmol/L]), low high-density lipoprotein

cholesterol (HDLC) (≤50 mg/dL [1.28 mmol/L] in girls, ≤40 [1.03 mmol/L] in boys), high glucose (≥100 mg/dL [5.6 mmol/L]), high BMI (≥85th Centers for Disease Control and Prevention [CDC] 2000 age-/sex-specific percentile), and HBP (≥90th age-/height-specific percentile). The blood pressure cutoffs agree with guidelines from Fourth Report on the Diagnosis, Evaluation, and Treatment of HBP in Children and Adolescents [22].

Risk factor cutoffs at the PFS were those of the NCEP/American Heart Association MetS [23] (waist ≥102 cm men and ≥88 cm women, TG ≥150 mg/dL [1.69 mmol/L], HDLC <40 mg/dL [1.03 mmol/L] in men and <50 mg/dL [1.28 mmol/L] in women, SBP/DBP ≥130/85 mm Hg, glucose ≥100 mg/dL [5.6 mmol/L]) [23]. Body mass index and LDLC cut points at the PFS, respectively, were at least 30 kg/m^2 (CDC, US Obesity Trends, Trends by State 1985-2009) and the current cohort's sex-/race-specific 90th percentile levels.

3. Statistical methods

Cardiovascular disease risk factor measures in the cohort in childhood and adulthood were calculated. Spearman correlations between LRC and PFS values were calculated; LDLC and LDLC/HDLC correlations were calculated with and without the 31 subjects who reported taking cholesterol-lowering medicine during adulthood.

Subjects were categorized as abnormal or normal for each pediatric risk factor, using established pediatric cutoffs; childhood cigarette smoking; and family history of CVD, T2DM, and HBP. The prevalence of young adult CVD, IFG + T2DM, and HBP at PFS by risk factor category was determined. Odds ratios (OR) were calculated by pediatric risk factor category for each outcome. Sensitivity, specificity, and positive and negative predictive values of the childhood risk factors as predictors of early adult CVD, IFG + T2DM, and HBP were calculated; and the associations of CVD, IFG + T2DM, and HBP with each risk factor were assessed by χ^2 test or Fisher exact test when the expected cell size was less than 5. To deal with multiple tests, we used the Hochberg-Benjamini method controlling for false discovery rate.

Next, stepwise logistic regression analysis was used to identify significant independent pediatric risk factors for young adult CVD, IFG + T2DM, and HBP at PFS in multivariate analyses. Explanatory variables included categorical variables: race, pediatric risk factors (high vs not high) TG, LDLC, blood pressure, BMI, and glucose; HDLC (low vs not low), cigarette smoking (yes vs no), and parental history (yes vs no) of CVD, T2DM, or HBP. After explanatory variables were selected by stepwise selection, then the regression model was reevaluated using SURVEYLOGISTIC to address sibling clusters.

Cardiovascular disease–free time was determined using age at first event for subjects with an event and age at PFS as censored CVD-free time for subjects without CVD. Kaplan-Meier survival curves were plotted with strata by childhood TG (high, not high). The ratio of expected CVD-free time in TG high group vs not high group was estimated using SAS (Cary, NC) LIFEREG procedure adjusted for race.

Finally, to examine whether and to what degree familial hypertriglyceridemia underlay the observed TG levels in the 19 subjects who had CVD events, we examined TG levels in the CVD subjects, their siblings, and their parents at the LRC and later at the PFS.

4. Results

In the LRC-PFS study, after excluding 10 subjects with type 1 diabetes mellitus, there were 909 student subjects: 651 white and 258 black (Table 1).

Risk factor summary data during childhood and at follow-up are presented in Table 1. The LRC and PFS risk factor correlations were all highly significant ($P < .0001$); and the correlations for BMI, HDLC, LDLC, and the LDL/HDL ratio were all stronger than $r = 0.40$ (Table 1). The LDLC and the LDL/HDL correlations were calculated with and without the 31 subjects taking cholesterol-lowering drugs when studied in the PFS, and were comparable with these 31 subjects included or not included (Table 1). The correlation coefficients for TG, glucose, SBP, and DBP between LRC and PFS were highly significant ($r = 0.36$, 0.17, 0.28, and 0.21, respectively; Table 1).

At follow-up at a mean age of 38 years, 31 (3.6%) of 853 subjects were taking cholesterol-lowering medications (Table 1). The mean pediatric LDLC at the LRC in subjects later taking cholesterol-lowering medications as adults was higher than that in other students (132 vs 106 mg/dL [3.38 vs 2.72 mmol/L], $P < .0001$); but the mean LDLC in these participants decreased from childhood to adulthood (from 132 to 114 mg/dL [3.38 vs 2.92 mmol/L], $P = .015$), whereas, as expected, the mean LDLC increased in subjects not taking lipid-lowering drugs (106 to 121 mg/dL [2.72 vs 3.10 mmol/L], $P < .0001$; Table 1). Thus, subjects taking lipid drugs at PFS had slightly, but not significantly, lower LDLC at PFS than subjects not taking lipid drugs (114 vs 121 mg/dL [2.92 vs 3.10 mmol/L], $P = .15$; Table 1).

At PFS, 19 (2.2% of 881) former schoolchildren had sustained CVD events (Table 2A), 135 (18% of 753) had IFG + T2DM (Table 2B), and 206 (23% of 893) had HBP (Table 2C). In univariate analyses, young adult CVD associated with high childhood TG and high childhood BMI (Table 2A). At LRC, 9 (47%) of the 19 subjects with early CVD had high TG (≥110 mg/dL [1.24 mmol/L]) vs 13% of schoolchildren without CVD by PFS ($P = .0004$, Fig. 1). At PFS (mean age, 41 ± 3 years), 13 (72%) of 18 former schoolchildren with CVD had TG of at least 150 mg/dL (1.69 mmol/L) compared with 28% of subjects free of CVD at PFS ($P = .0001$, Fig. 1). Moreover, 50% of 19 former students with CVD by PFS had high BMI at LRC vs 25% of those without CVD by PFS ($P = .025$). At the PFS, 68% of former students who had CVD had high BMI vs 33% of those without CVD ($P = .0025$, Fig. 2).

Impaired fasting glucose + T2DM associated with high childhood BMI, TG, and glucose and with low HDLC and family history of T2DM (Table 2B). High blood pressure associated with high childhood BMI, BP, and family history of HBP (Table 2C). For each outcome, excepting family history of HBP, specificity was much higher than sensitivity; and negative

Table 1 – Risk factors for CVD, IFG + T2DM, and hypertension measured during childhood (LRC) and 26 years later in young adulthood in the PFS

	Mean ± SD at LRC	Mean ± SD at PFS	Spearman correlation LRC with PFS
Race	White = 651 (72%), black = 258 (28%)		
Sex	Male = 422 (46%), female = 487 (54%)		
Age (y)	12.3 ± 3.4	38.5 ± 3.7	
TG (mg/dL)	77 ± 37	134 ± 128	$r = 0.36$, $P < .0001$
HDLC (mg/dL)	55 ± 12	46 ± 15	$r = 0.47$, $P < .0001$
LDLC (mg/dL)	107 ± 30	120 ± 35	$r = 0.48$, $P < .0001$
	106 ± 29 [a]	121 ± 36 [a]	$r = 0.49$, $P < .0001$ [a]
LDL/HDL	2.04 ± 0.76	2.95 ± 1.36	$r = 0.47$, $P < .0001$
	2.02 ± 0.76 [a]	2.94 ± 1.34 [a]	$r = 0.47$, $P < .0001$ [a]
SBP (mm Hg)	104 ± 13	120 ± 15	$r = 0.28$, $P < .0001$
DBP (mm Hg)	62 ± 12	79 ± 11	$r = 0.21$, $P < .0001$
BMI (kg/m2)	20.0 ± 4.3	28.7 ± 6.9	$r = 0.40$, $P < .0001$
Glucose (mg/dL)	85 ± 8	90 ± 23	$r = 0.17$, $P < .0001$

	LDLC at LRC		LDLC at PFS		Change	Paired Wilcoxon for change
	n	Mean ± SD	n	Mean ± SD	Mean ± SD	
Took cholesterol-lowering medications	31	132 ± 39	30	114 ± 38	-17 ± 39	$P = .015$
Not taking cholesterol-lowering medications	822	106 ± 29	805	121 ± 36	+15 ± 32	$P < .0001$
Wilcoxon (took medication vs not)		$P < .0001$		$P = .15$		

[a] After removal of 31 subjects taking cholesterol lowering medications.

Table 2A – Pediatric risk factors and CVD 26 years later

Pediatric risk factor (mean age 12)	No. of subjects	Using pediatric risk factor as screening test for CVD at mean age 39						
		No. of subjects with CVD	OR 95% CI	Sensitivity	Specificity	Positive predictive value	Negative predictive value	P
BMI (≥85th CDC 2000 age-/sex-specific percentile as high)								
High	200 (25%)	9 (5%)	3.03	50%	75%	5%	98%	Fisher $P = .025$
Not high	587 (75%)	9 (2%)	1.18-7.73					
TG (≥110 mg/dL as high)								
High	124 (14%)	9 (7%)	5.85	47%	87%	7%	99%	Fisher $P = .0004$ *
Not high	757 (86%)	10 (1%)	2.33-14.7					
HDLC (≤50 female, ≤40 male as low)								
Low	213 (26%)	5 (2%)	1.03	26%	74%	2%	98%	Fisher $P = 1.0$
Not low	612 (74%)	14 (2%)	0.37-2.88					
LDLC (≥110 mg/dL as high)								
High	335 (40%)	5 (1%)	0.52	26%	59%	1%	97%	$\chi^2 = 1.60$, $P = .21$
Not high	494 (60%)	14 (3%)	0.19-1.46					
BP (≥90th age-/height-specific percentile as high)								
High	72 (12%)	4 (6%)	3.02	29%	88%	6%	98%	Fisher $P = .077$
Not high	523 (88%)	10 (2%)	0.92-9.89					
Glucose (≥100 mg/dL as high)								
High	31 (4%)	2 (6%)	3.09	11%	96%	6%	98%	Fisher $P = .16$
Not high	778 (96%)	17 (2%)	0.68-14.0					
Cigarette smoking								
Yes	237 (29%)	9 (4%)	2.84	53%	72%	4%	99%	Fisher $P = .053$
No	584 (71%)	8 (1%)	1.08-7.45					
Family CVD history								
Positive	399 (46%)	11 (3%)	1.66	58%	55%	3%	98%	$\chi^2 = 1.19$, $P = .27$
Negative	477 (54%)	8 (2%)	0.66-4.17					

* Significant using Hochberg-Benjamini controlling for false discovery rate ($P = .05$) for 8 tests.

Table 2B – Pediatric risk factors and IFG + T2DM 26 years later

Pediatric risk factor (mean age 12)	No. of subjects	Using pediatric risk factor as screening test for IFG or T2DM at mean age 39						
		No. of subjects with IFG or T2DM	OR 95% CI	Sensitivity	Specificity	Positive predictive value	Negative predictive value	P
BMI (≥85th CDC 2000 age-/sex-specific percentile as high)								
High	176 (25%)	41 (23%)	1.71	34%	76%	23%	85%	$\chi^2 = 6.17$, $P = .013$ *
Not high	516 (75%)	78 (15%)	1.12-2.61					
TG (≥110 mg/dL as high)								
High	106 (14%)	29 (27%)	1.92	21%	88%	27%	84%	$\chi^2 = 7.46$, $P = .0063$ *
Not high	647 (86%)	106 (16%)	1.20-3.09					
HDLC (≤50 female, ≤40 male as low)								
Low	182 (25%)	43 (24%)	1.63	33%	77%	24%	84%	$\chi^2 = 5.51$, $P = .019$ *
Not low	546 (75%)	87 (16%)	1.08-2.46					
LDLC (≥110 mg/dL as high)								
High	295 (40%)	51 (17%)	0.95	39%	59%	17%	82%	$\chi^2 = 0.075$ $P = .78$
Not high	437 (60%)	79 (18%)	0.64-1.40					
BP (≥90th age-/height-specific percentile as high)								
High	57 (11%)	16 (28%)	1.82	17%	90%	28%	82%	$\chi^2 = 3.62$ $P = .057$
Not high	454 (89%)	80 (18%)	0.98-3.41					
Glucose (≥100 mg/dL as high)								
High	28 (4%)	12 (43%)	3.72	9%	97%	43%	83%	$\chi^2 = 12.51$ $P = .0004$ *
Not high	697 (96%)	117 (17%)	1.71-8.07					
Cigarette smoking								
Yes	198 (29%)	42 (21%)	1.45	35%	73%	21%	84%	$\chi^2 = 3.10$ $P = .078$
No	493 (71%)	77 (16%)	0.96-2.21					
Family T2DM history								
Positive	284 (39%)	72 (25%)	2.16	54%	65%	25%	86%	$\chi^2 = 16.2$, $P < .0001$ *
Negative	449 (61%)	61 (14%)	1.48-3.16					

* Significant using Hochberg-Benjamini controlling for false discovery rate ($P = .05$) for 8 tests.

Table 2C – Pediatric risk factors and HBP 26 years later

Pediatric risk factor (mean age 12)	No. of subjects	Using pediatric risk factor as screening test for HBP at mean age 39						
		No. of subjects with HBP	OR 95% CI	Sensitivity	Specificity	Positive predictive value	Negative predictive value	P
BMI (≥85th CDC 2000 age-/sex-specific percentile as high)								
High	204 (26%)	71 (35%)	2.40	40%	79%	35%	82%	$\chi^2 = 24.2$, $P < .0001$ *
Not high	595 (74%)	108 (18%)	1.69-3.44					
TG (≥110 mg/dL as high)								
High	123 (14%)	31 (25%)	1.15	15%	87%	25%	77%	$\chi^2 = 0.37$, $P = .55$
Not high	770 (86%)	175 (23%)	0.74-1.78					
HDLC (≤50 female, ≤40 male as low)								
Low	214 (26%)	42 (20%)	0.77	22%	73%	20%	76%	$\chi^2 = 1.79$, $P = .18$
Not low	623 (74%)	150 (24%)	0.52-1.13					
LDLC (≥110 mg/dL as high)								
High	339 (40%)	79 (23%)	1.06	41%	60%	23%	78%	$\chi^2 = 0.11$, $P = .74$
Not high	502 (60%)	112 (22%)	0.76-1.47					
BP (≥90th age-/height-specific percentile as high)								
High	72 (12%)	31 (43%)	3.22	23%	91%	43%	81%	$\chi^2 = 21.4$, $P < .0001$ *
Not high	536 (88%)	102 (19%)	1.92-5.38					
Glucose (≥100 mg/dL as high)								
High	31 (4%)	5 (16%)	0.63	3%	96%	16%	77%	$\chi^2 = 0.87$, $P = .35$
Not high	789 (96%)	184 (23%)	0.24-1.67					
Cigarette smoking								
Yes	237 (29%)	61 (26%)	1.21	32%	72%	26%	78%	$\chi^2 = 1.15$, $P = .28$
No	580 (71%)	129 (22%)	0.85-1.72					
Family HBP history								
Positive	599 (70%)	163 (27%)	2.26	82%	34%	27%	86%	$\chi^2 = 17.3$, $P < .0001$ *
Negative	261 (30%)	37 (14%)	1.53-3.35					

* Significant using Hochberg-Benjamini controlling for false discovery rate ($P = .05$) for 8 tests.

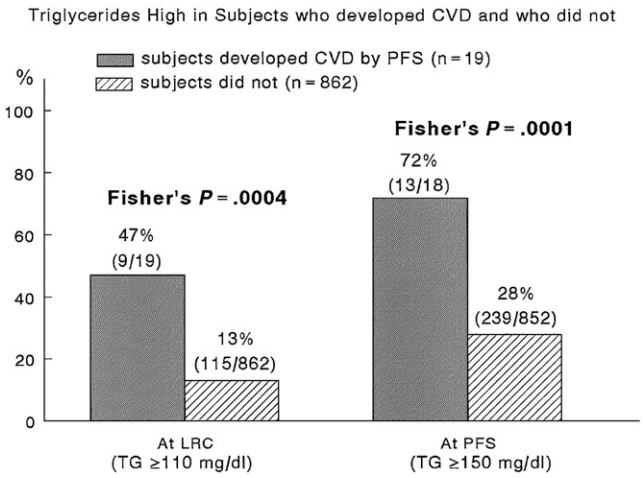

Fig. 1 – High TGs in childhood and young adulthood in subjects who developed CVD in young adulthood and those who did not.

predictive value was much higher than positive predictive value (Tables 2A, 2B, 2C). Thus, young adults who did not have high childhood TG had only a 1% chance of CVD by PFS; and those who did not have high childhood BMI had only a 2% chance of CVD by PFS (Table 2A).

In univariate analyses, high childhood LDLC was not significantly associated with CVD 26 years later (χ^2 = 1.6, P = .21, Table 2A).

In multivariate analyses, by stepwise logistic regression, high pediatric TG was the only significant independent explanatory variable for young adult CVD (Table 3). The area under the curve (AUC) was 0.670. After adjusting for race, subjects with high TG in childhood had shorter expected CVD-free time than those without high childhood TG; the ratio of expected CVD-free time was 0.84 (95% confidence interval [CI], 0.74-0.96; P = .009; Fig. 3).

Table 3 – Childhood predictors for CVD, T2DM, and HBP 26 years later

Young adult outcome	Childhood predictors	P	OR, 95% CI
CVD (19 yes, 862 no)[a] 881 observations used AUC = 0.670	TG (high vs not high)	.0002	5.85, 2.32-14.74
IFG/T2DM (114 yes, 535 no)[b] 649 observations used AUC = 0.645	Parents had T2DM (yes vs No)	.0011	2.22, 1.38-3.60
	Glucose (high vs not high)	.0002	4.43, 2.03-9.66
	Cigarette smoking (yes/no)	.036	1.64, 1.03-2.61
Hypertension (133 yes, 475 no)[c] 608 observations used AUC = 0.657	BMI (high vs not high)	<.0001	2.70, 1.71-4.27
	BP (high vs not high)	.0009	2.52, 1.46-4.34

Explanatory variables selected by stepwise selection; then model was rerun using SURVEYLOGISTIC to address sibling clusters.

[a] Stepwise logistic regression (significance level required for entry into regression equation [SLE] = .15, significance level required to stay in regression equation = .05) from categorical explanatory variables: race, childhood risk factors TG, HDLC, LDLC, BMI, glucose; cigarette smoking (yes/no), parents had CVD (yes/no), parents had CVD before age 50 (yes/no); and parents had CVD before age 60 (yes/no).

[b] Stepwise logistic regression (SLE = .15, SLS = .05) from categorical explanatory variables: race, childhood risk factors TG, HDLC, LDLC, BMI, BP, glucose; cigarette smoking (yes/no), parents had T2DM (yes/no).

[c] Stepwise logistic regression (SLE = .15, SLS = .05) from categorical explanatory variables: race, childhood risk factors TG, HDLC, LDLC, BMI, BP, glucose; cigarette smoking (yes/no), parents had HBP (yes/no).

Significant independent predictors for IFG + T2DM at PFS in multivariate analysis included parental T2DM, high childhood glucose, and childhood cigarette smoking (Table 3).

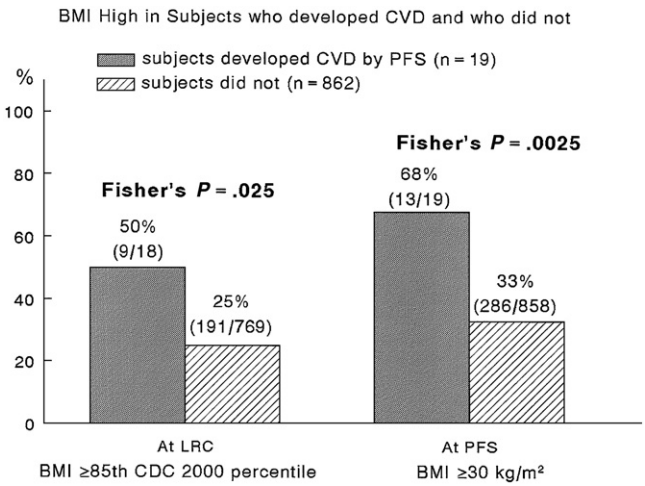

Fig. 2 – High BMI in childhood and young adulthood in subjects who developed CVD in young adulthood and those who did not.

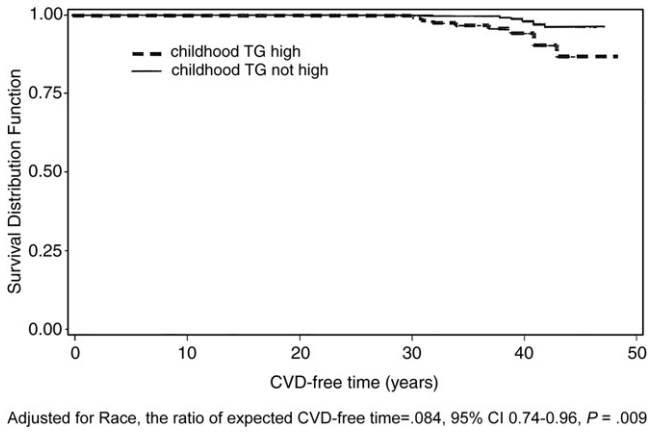

Fig. 3 – Kaplan-Meier survival curve in the group of subjects with high pediatric TG vs the group with normal childhood TG. The ratio of expected CVD-free time was estimated using SAS LIFEREG procedure.

Table 4 – Nineteen cases having cardiovascular events before the age of 42 years

	Sex	Race	Age		CVD age	BMI		TG		HDL		LDL		BP		Glucose		Waist
			LRC	PFS	(year)	LRC	PFS	LRC	PFS	LRC	PFS	LRC	PFS	LRC	PFS	LRC	PFS	PFS
			(year)			(kg/m^2)		(mg/dL)		(mg/dL)		(mg/dL)		(mm Hg)		(mg/dL)		(cm)
1	Male	White	11.2	36.9	32	**22.3**	**32.9**	**163**	**279**	**38**	**24**	**155**	132	114/70	**142/101**	91	94	**118**
2	Male	White	12.4	38.7	37	**24.2**	28.8	**120**	**237**	**32**	**37**	102	111	**128**/54	**137**/72	**109**	**179**	90
3	Male	White	12.8	40.5	38	18.7	**30.9**	90	**242**	49	**24**	109	150	–	117/78	88	75	**114**
4	Male	White	13.4	38.7	32	16.2	29.3	55	**175**	67	43	102	129	96/56	109/72	99	–	**103**
5	Male	White	13.8	39.8	34	–	**36.9**	**113**	**231**	44	42	103	157	–	**136/96**	74	**107**	**121**
6	Male	White	16.5	44.4	41	**29.7**	**43.6**	**251**	**379**	45	**29**	105	101	108/70	**169/108**	92	**100**	**134**
7	Male	White	17.2	42.2	41	**26.2**	**43.9**	92	**350**	49	**25**	108	95	108/80	128/**91**	81	**122**	**125**
8	Male	White	17.1	44.4	43	**26.6**	27.1	**285**	147	46	40	104	82	**130/86**	122/80	85	88	–
9	Male	Black	17.8	43.2	41	19.2	**31.8**	46	–	59	–	**135**	–	112/68	122/82	73	–	101
10	Male	White	18.1	45.4	30	**35.1**	**31.3**	**265**	**290**	**37**	**28**	**184**	107	**128/90**	109/78	93	**224**	**107**
11	Male	White	18.6	47.1	31	20.8	23.2	**172**	**198**	47	**36**	109	116	108/62	109/76	86	71	87
12	Male	White	20.5	44.2	42	20.7	29.7	76	91	45	**30**	95	137	–	116/73	81	**109**	97
13	Female	Black	11.3	35.6	25	16.6	**30.6**	41	38	107	72	83	73	88/58	109/74	81	81	**99**
14	Female	Black	12.5	39.5	38	21.5	23.7	70	43	62	64	107	98	108/62	124/**86**	84	80	80
15	Female	White	14.1	40.6	39	21.9	**30.1**	62	**217**	69	**46**	98	130	–	**133**/78	86	97	**102**
16	Female	White	16.2	41.8	41	**34.9**	**38.4**	**168**	**632**	**41**	**18**	**122**	67	**132**/62	**142/91**	90	**233**	**127**
17	Female	White	16.8	40.7	39	**27.4**	**37.6**	**168**	**739**	59	58	74	40	–	**149/97**	91	**107**	**134**
18	Female	Black	17.6	43.2	40	25.0	**39.6**	92	73	63	50	102	128	112/70	**138/92**	77	**188**	**128**
19	Female	Black	15.2	41.3	40	**31.2**	**41.4**	75	**165**	**50**	**46**	**125**	132	118/68	123/**93**	**101**	–	**121**
No. of abnormal (%)						9/18 (50%)	13/19 (68%)	9/19 (47%)	13/18 (72%)	5/19 (26%)	11/18 (61%)	5/19 (26%)	0/18 (0%)	4/14 (29%)	11/19 (58%)	2/19 (11%)	9/16 (56%)	13/18 (72%)

Risk factors for CVD during childhood-adolescence at the LRC and during young adulthood at the PFS. Bold, italicized numbers denote abnormal according to risk factor cutoffs used.

Significant independent explanatory variables for HBP at PFS included high pediatric BMI and BP (AUC = 0.657, Table 3).

High childhood LDLC was not an independent predictor for young adult CVD by stepwise logistic regression (Table 3).

Of the 9 students with CVD by PFS and high TG at LRC, 88% had high BMI at LRC; and 67% had high BMI at PFS (Table 4, online supplement).

4.1. *Familial hypertriglyceridemia in the 19 cases with CVD events*

Child-proband, sibling, and parental data at both the LRC and PFS revealed evidence of familial hypertriglyceridemia in the families of the 19 early CVD cases (Fig. 4). Of the 9 subjects having high TG at the LRC, 8 (89%) had high TG in PFS (Fig. 4).

Of the 19 families of child probands who later had CVD events, at least 1 parent was assessed in 13 families (18 parents) in the LRC at mean ± SD age of 41 ± 6 years when their offspring were schoolchildren; and at least 1 parent was assessed in 11 families (16 parents) at PFS at age 69 ± 5 years when their offspring were young adults (Fig. 4).

Altogether, in 14 families of the probands who had sustained CVD and had high TG either at LRC or at PFS, there was a hypertriglyceridemic parent and/or sibling in 9 (64%) of 14 families (Fig. 4). Early CVD (ages 44, 46, 48, 60, and 65 years) also occurred in hypertriglyceridemic parents of hypertriglyceridemic students.

Low HDLC was associated with high TG. Of the 19 subjects with CVD, 21% had low HDLC as children; and 61% had low HDLC as young adults (Table 4, online supplement).

5. Discussion

In the current study, high childhood TG was the sole significant independent predictor of CVD at PFS. Of the 19 CVD cases, high childhood TG persisted into young adulthood; and high TG was common in parents and in siblings, found in at least 1 parent and/or sibling in 64% of families of high TG probands, manifesting familial hypertriglyceridemia [24]. Furthermore, the association of pediatric TG with young adult CVD may reflect the underlying association of high TG with low HDLC, an association that was amplified with age in the current study. Thus, of the 19 cases who had CVD, 21% had low HDLC as children and 61% had low HDLC as young adults, with 40% more subjects with CVD manifesting atherogenic [25] low HDLC as young adults. Although the childhood lipid levels in this study were quantitated 26 years ago, likely with different assays and standards than are used today, this would, if anything, bias the results to the null outcome.

Congruent with the report by de Ferranti et al [26], 88% of children with high TG levels and CVD by young adulthood were obese, as were 67% of these subjects as young adults.

In the current study, pediatric risk factors in 5- to 19-year-old children predicted CVD, IFG + T2DM, and HBP 26 years later. Given the significant tracking of risk factors for CVD,

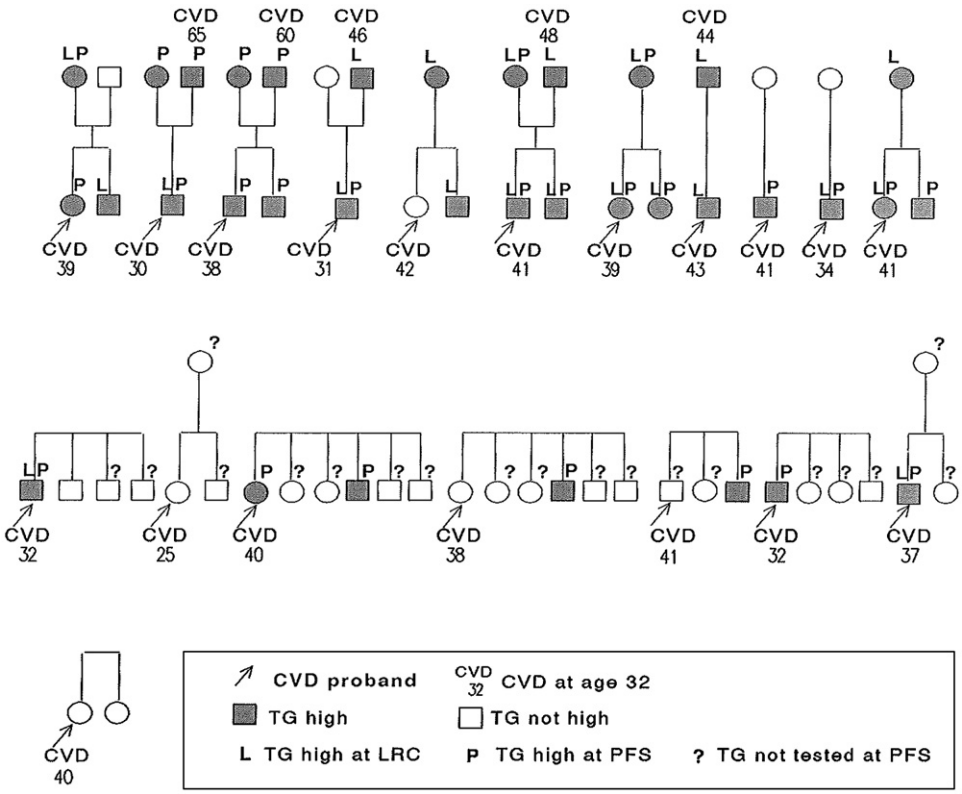

Fig. 4 – Familial high TGs in child probands, their siblings, and their parents in 19 kindreds where the probands had a CVD event before the age of 44 years.

IFG+T2DM, and HBP as observed in the current study and in previous longitudinal studies of children into young adulthood [9,27-29], failure to act on such salient childhood risk factors as TG, obesity, hyperglycemia, and hypertension means the underlying pathology continues into young adulthood. Thus, the relationship between childhood risk factors and young adult atherosclerosis [10] should support lifestyle [30] and, perhaps, pharmacologic intervention [31,32] in childhood-adolescence to prevent development of initial atherosclerotic lesions, progression to advanced lesions, and CVD.

In the Muscatine Iowa study, childhood weight, BMI, and TG levels in men were significantly related to coronary artery calcification 15 to 20 years later in young adults [33]. In the Bogalusa Louisiana study [34,35], postmortem identification of coronary artery streaks in 6- to 30-year-old subjects was significantly correlated with antecedent serum TG, very low-density lipoprotein cholesterol, blood pressure, and obesity. In the Pathobiological Determinants of Atherosclerosis in Youth postmortem study of 15- to 34-year-old men, the percentage of the right coronary arterial intima involved with atherosclerosis was correlated with age, smoking, and the combination of LDLC and very low-density lipoprotein cholesterol levels, and was negatively associated with HDLC [36]. The association of childhood TG with young adult CVD in our current report is consistent with adult studies where nonfasting TG [37-39] and fasting TG [40-43] are independent risk factors for CVD and for ischemic stroke [44].

In the current study, LDLC in childhood was not significantly associated with young adult CVD in either univariate or multivariate analyses. The predictive capability of childhood LDLC for adult CVD may have been muted by treatment of high LDLC in 31 young adult subjects, 3.6% of the adult cohort. Thus, the failure of childhood LDLC to predict adult CVD might reflect an underpowered aim, with young adult treatment to lower LDLC contributing to loss of predictive power of LDLC. Our observation that a "weaker" childhood risk factor (TG) was more likely to predict CVD than the more strongly associated LDLC may, speculatively, reflect the presence of pediatric MetS, a known predictor of adult CVD [45].

In the current study, independent pediatric explanatory variables for IFG + T2DM at a mean age of 38.5 years included high childhood glucose, parental T2DM, and childhood cigarette smoking. These findings parallel those in adults [46,47]. Our findings are congruent with those of Magnussen et al [9], Nguyen et al [30,48], and Ouyang et al [49] and should facilitate primary prevention of IFG + T2DM, starting in childhood.

In the current study, childhood independent explanatory variables for young adult HBP included childhood BMI and blood pressure. Rademacher et al [50] has reported that childhood BMI and blood pressure predicted young adult blood pressure, similar to our findings, and concluded that combined HBP and high BMI in childhood are additive in predicting young adult cardiovascular risk. In the Bogalusa Louisiana study, Srinivasan et al [51] reported that adiposity and HBP beginning in childhood, along with accelerated adverse longitudinal changes in risk variables of MetS through young adulthood, characterize the early natural history of hypertension.

Conventionally, parental history of CVD serves as an indication for screening for lipid abnormalities in children [52,53]. However, the 40-year-old ostensibly healthy parent is unlikely to have systematic [54] or practically successful [55] screening for CVD risk factors. Identification of CVD risk factors in the child can directly facilitate primary prevention [30] in the child through young adulthood and also focus diagnostic attention on the potentially high-risk parent.

Recently, the American Academy of Pediatrics issued a policy statement on lipid screening and cardiovascular health in childhood [15]. A targeted approach, reliant to a large degree on family history, was suggested. Overweight children were identified as a special risk category in need of screening irrespective of family history or other risk factors [15]. In adults, the NCEP has adopted the Framingham risk score to determine which patients are at the highest 10-year risk for CVD and would benefit from aggressive treatment [56]. In childhood, however, there is no comparable risk score; and controversy exists whether screening on the basis of family history should be done in childhood [57]. Our current study suggests that pediatric screening for risk factors for CVD, IFG + T2DM, and HBP in unselected schoolchildren has important diagnostic value for themselves 26 years later in young adulthood.

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Conflict of Interest

There are no conflicts of interest.

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