LDL cholesterol level in fifth-grade schoolchildren associates with stature

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Abstract **Short stature is associated with increased LDL-cholesterol levels and coronary artery disease in adults. We investigated the relationship of stature to LDL levels in children in the West Virginia Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project to determine whether the genetically determined inverse relationship observed in adults would be evident in fifth graders. A cross-sectional survey of schoolchildren was assessed for cardiovascular risk factors. Data collected at school screenings over 18 years in WV schools were analyzed for 63,152 fifth-graders to determine relationship of LDL to stature with consideration of age, gender, and BMI. The first (shortest) quartile showed an LDL level of 93.6 mg/dl compared with an LDL level of 89.7 mg/dl for the fourth (tallest) quartile. Each incremental increase of 1 SD of height lowered LDL by 0.049 mg/dl ($P < 0.0001$). Multivariate analysis showed LDL to vary inversely as a function of the first (lowest) quartile of height after controlling for gender, median age, BMI percentile for age and gender, and year of screening. The odds ratio for LDL ⩾ 130 mg/dl for shortest versus tallest quartile is 1.266 (95% CL 1.162–1.380). The odds ratio for LDL ⩾ 160 mg/dl is 1.456 (95% CL 1.163–1.822).** **The relationship between short stature and LDL, noted in adults, is confirmed in childhood.**—Pyles, L. A., C. L. Lilly, C. J. Mullett, E. S. Polak, E. M. Elliott, and W. A. Neal. **LDL cholesterol level in fifth grade school children associates with stature.** ***J. Lipid Res.*** **2017.** 58: **2197–2201.**

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A cardiovascular risk screening program for children in West Virginia, Coronary Artery Risk Detection in Appalachian Children (CARDIAC), has collected lipid data from West Virginia fifth-grade schoolchildren for nearly two decades. A recent report by Nelson et al. (1) demonstrated increased coronary events in short-stature adults associated with higher LDL levels and genes that determine both LDL and height. Nelson et al. noted that many of the SNPs responsible for short stature also drive (or are associated with) a higher LDL level in adults (1). That work was performed by a combination of different registries, allowing data from 200,000 persons, including genotype data from 18,249 persons to be examined. Spurred by this association of short-stature genes with higher LDL and CVD, we have investigated our CARDIAC database to question whether the inverse relationship between stature and LDL will be observed in childhood.

A meta-analysis of the relationship between height and coronary heart disease (CHD) by Paajanen et al. provides the best empiric evidence of the predictive effect of height on CHD (2). A review by Batty et al. in 2009 noted an inverse relationship between height and CVD in most studies (3). However, the meta-analyses have not considered BMI or family history of CHD in relation to cholesterol (LDL or non-HDL levels). Henriksson et al. demonstrated a negative correlation between height and non-HDL cholesterol even after adjustment for BMI or for waist/height ratio (4).

The relationships of cholesterol or CVD to height have not been explored in the major cohorts that study cardiovascular risk factors in children, such as Bogalusa Heart Study, Muscatine or in analyses of the National Health and Education Nutrition Examination Survey other than to note that a greater change in height predicts a larger LDL decrease over time (5–7). Shimizu et al. showed lower LDL levels in taller adult Japanese males, unless the BMI was ⩾ 25 kg/m^2 (8). The odds ratio of dyslipidemia (LDL > 140 mg/dl or triglycerides ⩾150 mg/dl) fell from the first (shortest) to fourth (tallest) quartile in those under 25 kg/m^2, but was nonsignificant for those ⩾25 kg/m^2. Fujita et al. measured lipids in 2,515 students in public schools in Fukeroi, Japan, from 2008 to 2010 and then again in the eighth grade with follow-up in 2,225 students (9). Lipid levels decreased in association with largest increased height over 3 years, but this was attenuated in the group with a larger weight increment. There was no assessment of developmental stage, but it was inferred that the subjects were peripubertal based on age. Eissa (14) showed a peripubertal fall in non-HDL cholesterol in a group from Chicago in Project

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HeartBeat! Responses varied by male and female and by black and white, but there was little change in Tanner Stage 1 to 2. The majority of 11-year-olds were in those stages in that report. No mention was made of height or BMI.

These studies and gaps have prompted us to review our experience and data in the CARDIAC Project with respect to lipid levels and height to determine whether this relationship can provide guidance for evaluation of the genetics of cholesterol levels in our cohort.

METHODS

The CARDIAC project was developed in 1998 to identify children and families at risk for coronary artery disease. Fifth-grade children who were enrolled in West Virginia schools received an information packet and were invited to participate in the CARDIAC Project. The information packet included an explanation of the project and the procedures to take place on screening day, parental consent/child assent forms, and a parental self-report family history questionnaire. The study protocol was approved by the West Virginia University Institutional Review Board (WVU IRB). Screenings were conducted within the school setting by trained health professionals, health science students, and volunteer trained phlebotomists. Beginning with CARDIAC yearly screenings of fifth-graders in 2003, cholesterol levels, family history of CVD, and anthropomorphic measurements were systematically obtained from 63,152 school children whose parents signed a WVU IRB-approved consent to gather the child's data, including lipid panel by venipuncture. In the consent process, the parents were asked to agree to the blood draw and given the option to have their family doctor contacted with the test results. Lipid panels were evaluated by LabCorp of America or by local chemistry laboratories. Height was obtained by using a SECA Road Rod stadiometer. Weight was measured by using a SECA 840 digital scale (10). BMI is defined as weight in kilograms divided by height squared (square centimeter). The Centers for Disease Control and Prevention Epi Info software 3.5 was used to calculate height for age and gender percentiles, weight for age and gender percentiles, BMI, and BMI percentiles. Detailed family history was obtained, but for the purposes of this project was considered as positive or negative for CVD in a first- or second-degree relative.

Statistical analysis

Data was managed with Microsoft products, stored on an Access spreadsheet, exported to Excel, and analyzed with SAS 9.4 (SAS, Cary, NC). Missing data was assumed to be either missing completely at random or missing at random, and dealt with by using pairwise deletion. The relationship of height percentile (first vs. fourth quartile) to LDL was considered for the group of fifth graders, for boys only and girls only, and for older and younger (median-split) fifth graders to investigate whether any significant effect of advancing sexual maturity could be assessed by comparing younger to older children. This was accomplished by using independent sample *t*-tests (two-tailed) to test for unadjusted differences in mean LDL overall and among all stratified groups, with Cohen's d reported as an effect size measure. Alpha was set to 0.05. A generalized linear model (GLM) for adjusted multivariate differences in mean LDL cholesterol, controlling for year of screening, BMI percentile, with gender, median age, and stature, type I model reported. Least-square means for significant categorical predictors are also reported, with *P*-values adjusted for using Bonferroni correction for multiple comparisons. R-square and eta-square values are reported as effect size measures. Finally, logistic regression models for LDL clinical cutoffs (130, 160, 175, and 190) by height top and bottom quartile and then stratified by gender, and then adjusting for BMI percentile were conducted, reporting Fisher's exact *P*-values given small cell sizes, and both adjusted and unadjusted odds ratios based on parameter estimates reported as effect size measures.

RESULTS

This study included 63,152 West Virginia fifth-grade children who had a fasting lipid profile and completed the family history questionnaire between September 2003 and April 2016. The children were 93.3% white and 53.6% female. The mean age was 10.97 years (SD: 0.51 years). These data, as well as the numbers of children in the first (shortest) and fourth (tallest) quartiles and the numbers above and below median age, are provided in **Table 1**. Each incremental increase of 1 SD of height lowered LDL by 0.049 mg/dl ($P < 0.0001$). The data for children in the second and third quartiles follow the general trends and are excluded from further analysis. **Table 2** shows the mean LDL value for the top and bottom quartiles for all subjects and then by male and female. LDL for the top quartile is 89.7 mg/dl and for the first (lowest) quartile this value is 93.6 mg/dl with a significant difference of 3.84 mg/dl ($P < 0.0001$). The aggregate data is shown in Table 2 which also shows information for top and bottom height quartiles split into older and younger groups. In Table 2, each of the groups was consistent with our hypothesis that shorter height was associated with higher LDL, except for males below median age.

The higher LDL for taller, younger males prompted consideration of BMI and thus analysis with a GLM that calculated a least-squares mean value for LDL, as given in **Table 3**. Table 3 shows that year of screening, median age, BMI percentile, gender, and stature (first vs. fourth quartile) is each a significant factor in predicting LDL. Adjusted LDL is 0.57 mg/dl higher for males and 6.89 mg/dl higher for the first (shortest) quartile. Of note, the adjusted LDL is nearly 2 mg/dl lower for the older half of the fifth graders. The difference of least-squares means for first versus fourth quartile was approximately 10 mg/dl in females and 4 mg/dl in males (Table 3).

TABLE 1. Descriptive statistics and demographics

Variable	N	Mean (SD)
LDL	63,152	91.66 (25.23)
Age	86,733	10.97 (0.51)
Gender		
BMI percentile	85,697	71.47 (28.46)
Weight percentile	85,810	68.77 (29.58)
Height percentile	85,765	59.54 (28.82)
	Frequency	(Valid percent)
Height percentile quartiles		
Top quartile (≥85.23)	21,543	(51.3%)
Bottom quartile (≤36.08)	22,682	(48.7%)
Age median (10.93) split		
Below median	43,479	(50%)
Above median	43,608	(50%)

TABLE 2. Independent sample *t*-tests for LDL overall, by stature, stratified by gender, and then by median age

Group	N	Mean (SD)	t-value	DF	*P*	Cohen's d
Top quartile	16,248	89.74 (24.88)	13.52	31,577	<0.0001	0.15
Bottom quartile	15,331	93.58 (25.69)				
For females only						
Top quartile	9,019	88.00 (24.29)	17.31	17,006	<0.0001	0.27
Bottom quartile	7,989	94.60 (25.38)				
For males only						
Top quartile	7,229	91.90 (25.44)	1.36	14,569	0.175	0.02
Bottom quartile	7,342	92.48 (25.98)				
For females below median age						
Top quartile	5,091	88.96 (24.65)	12.37	8,957	<0.0001	0.26
Bottom quartile	3,868	95.49 (24.85)				
For females above median age						
Top quartile	3,928	86.75 (23.76)	12.64	8,047	<0.0001	0.28
Bottom quartile	4,121	93.76 (25.85)				
For males below median age						
Top quartile	3,442	93.51 (25.47)	−1.01	6,617	0.315	0.02
Bottom quartile	3,177	92.88 (25.41)				
For males above median age						
Top quartile	3,787	90.44 (25.33)	2.98	7,950	0.0029	0.07
Bottom quartile	4,165	92.17 (26.40)				

In addition to consider mean values by quartile, we considered the odds of exhibiting an elevated LDL in the shortest (first) versus tallest (fourth) quartiles for various clinically significant cutoff levels of LDL: 130 mg/dl up to 190 mg/dl and with or without adjustment for BMI. The largest odds ratio in the table is 6.2 (95% confidence limit 2.4–16.2) for shortest versus tallest males with LDL over 190 mg/dl after adjustment for BMI. All confidence intervals for odds after adjustment for BMI at different LDL levels are significant. **Table 4** shows 7.94% of children (n = 1,217 of 14,114) with LDL > 130 mg/dl for the shortest quartile of subjects.

DISCUSSION

This report is driven by the observation that CVD presents a major burden of loss of life, economic costs, and a decrement in quality of life for West Virginians (11). Seven percent of fifth-grade children in the statewide cholesterol screening program CARDIAC exhibited a LDL level > 130

TABLE 3. GLM for LDL, controlling for year of screening, BMI percentile, with gender, median age, and stature, Type I model reported

Source	df	F	*P*	R-square	Eta-square	
Model	9	153.34	<0.0001	0.042	0.04	
Corrected total	31,198					
Predictors	df	F	*P*	Partial eta-square	LS means	Adjusted *P*
Median age	1	34.27	<0.0001	0.0011		
Below median					92.75	<0.0001
Above median					90.81	
Year of screening	1	382.14	<0.0001	0.0121		
BMI percentile	1	322.81	<0.0001	0.0102		
Gender	1	12.65	0.0004	0.0004		
Female					91.49	0.0442
Male					92.06	
Stature	1	504.90	<0.0001	0.0159		
Bottom quartile					95.22	<0.0001
Top quartile					88.33	
Gender*Stature	1	112.12	<0.0001	0.0036		
Female, bottom quartile					96.47	All < 0.0001
Female, top quartile					86.51	
Male, bottom quartile					93.98	
Male, top quartile					90.15	
Median Age*Gender*Stature	3	3.72	0.0109	0.0004		
Below median age, female, bottom height quartile					97.46	All < 0.05 unless
Below median age, female, top height quartile					87.68[a]	superscript
Below median age, male, bottom height quartile					94.16[b]	
Below median age, male, top height quartile					91.67	
Above median age, female, bottom height quartile					95.48	
Above median age, female, top height quartile					85.33	
Above median age, male, bottom height quartile					93.79[b]	
Above median age, male, top height quartile					88.62[a]	

Least-squares (LS) mean for significant categorical predictors also reported, with *P*-values adjusted for using Bonferroni.
[a]*P* = 0.051.
[b]*P* = 0.74.

TABLE 4. LDL cutoffs by height top and bottom quartile (N = 44,225) and then stratified by female (N = 17,008) and male (N = 14,571) gender, and then adjusting for BMI percentile

Outcome		N (%) high risk	N (%) not at risk	Fisher's exact *P*	OR	95% CI OR		Adjusted[a] OR	95% CI AOR	
LDL ⩾130										
Height-for-age and gender percentile	Bottom quartile	1,217 (7.94)	14,114 (92.06)	<0.0001	1.266	1.162	1.380	1.856	1.687	2.042
	Top quartile	1,036 (6.38)	15,212 (93.62)							
Female	Bottom quartile	662 (8.29)	7,327 (91.71)	<0.0001	1.705	1.507	1.929	2.352	2.052	2.696
	Top quartile	454 (5.03)	8,565 (94.97)							
Male	Bottom quartile	555 (7.56)	6,787 (92.44)	0.280	0.934	0.827	1.054	1.464	1.278	1.676
	Top quartile	582 (8.05)	6,647 (91.95)							
LDL ⩾160										
Height-for-age and gender percentile	Bottom quartile	182 (1.19)	15,149 (98.81)	0.001	1.456	1.163	1.822	2.347	1.839	2.995
	Top quartile	133 (0.82)	16,115 (99.18)							
Female	Bottom quartile	96 (1.20)	7,893 (98.80)	0.0007	1.601	1.172	2.188	2.362	1.681	3.321
	Top quartile	68 (0.75)	8,951 (99.25)							
Male	Bottom quartile	86 (1.17)	7,256 (98.83)	0.120	1.306	0.945	1.806	2.343	1.652	3.324
	Top quartile	65 (0.90)	7,164 (99.10)							
LDL ⩾175										
Height-for-age and gender percentile	Bottom quartile	77 (0.50)	15,254 (99.50)	0.004	1.704	1.187	2.445	2.819	1.913	4.154
	Top quartile	48 (0.30)	16,200 (99.70)							
Female	Bottom quartile	42 (0.53)	7,947 (99.47)	0.058	1.584	0.990	2.532	2.437	1.466	4.051
	Top quartile	30 (0.33)	8,989 (99.67)							
Male	Bottom quartile	35 (0.48)	7,307 (99.52)	0.027	1.919	1.086	3.391	3.541	1.935	6.480
	Top quartile	18 (0.25)	7,211 (99.75)							
LDL ⩾190										
Height-for-age and gender percentile	Bottom quartile	40 (0.26)	15,291 (99.74)	0.033	1.768	1.066	2.934	3.009	1.752	5.167
	Top quartile	24 (0.15)	16,224 (99.85)							
Female	Bottom quartile	21 (0.26)	7,968 (99.74)	0.088	1.318	0.702	2.475	2.034	1.028	4.026
	Top quartile	18 (0.20)	9,001 (99.80)							
Male	Bottom quartile	19 (0.26)	7,323 (99.74)	0.015	3.123	1.247	7.825	6.22	2.391	16.182
	Top quartile	6 (0.08)	7,223 (99.92)							

AOR, adjusted odds ratio; OR, odds ratio.
[a]Adjusted for BMI percentile.

mg/dl (12). We have shown that LDL varies in association with several factors including BMI, age, year of screen, and, most importantly, height quartile. The data show a small decrease in LDL with older age, consistent with a decrease in cholesterol with advancing sexual development. The absolute difference in LDL with regard to age, gender, and year of screening were not as great as those related to tallest versus shortest quartiles. Finally, with regard to the high levels of LDL, the shortest compared with tallest quartile had a higher odds ratio of elevated LDL at each cutoff level and the odds ratios were higher at each advanced level including the largest odds ratio of 5.46:1 for males with LDL > 190 mg/dl.

Despite the recent notation of Eissa et al. that the non-HDL levels decrease with advancing Tanner stage, we find little effect in older versus younger girls (13). The older fifth-grade boys had a higher LDL level, opposite of the expected effect if advanced puberty in the older versus younger cohort were significantly depressing LDL (13). The overall least-squares mean adjusted difference between older and younger age was <1/3 of the difference by shortest versus tallest height quartile.

Some limitations of this study include the voluntary sample of fifth graders that varied between 20% and 42% of eligible children over the 18 years of the CARDIAC Project and the lack of consideration of Tanner Stage categorization. The fifth grade is specifically chosen to provide a prepubertal sample of schoolchildren, and this is considered in national guidelines for child cholesterol screening. Tanner staging is impractical in a large-scale school screening. In addition, our analysis of the younger and older half of fifth graders allows us to consider whether any significant effect of onset of puberty is observed. West Virginia includes only 7% blacks and Hispanics, as does the CARDIAC sample, and thus no attempt was made to differentiate the effect by race that was seen in the Bogalusa Heart Project (6). The strength of our study, the inclusion of more than 60,000 fifth graders with lipid panels, decreases the concern for the possibility that we chose a nonrandom sample. The prevalence of positive family history for CVD was not discussed in this report, but is consistent with overall findings in West Virginia, suggesting a nonbiased sample.

The adult relationship of CVD prevalence to height is well established, with several reports plus meta-analysis. However, the relationship between genetics of height and of cholesterol in Nelson's report was not previously established, and the height-to-cholesterol relationship has only been considered in a few papers. In our report, we confirm that this relationship can be observed in fifth-grade children and delineate BMI as an important mitigating cofactor. Inclusion of BMI in the analysis clarified several observations such as the odds ratios for short versus tall stature at various levels of LDL (Table 4) and the higher unadjusted LDL level in the older, taller boys.

The observations support the contention that factors in addition to diet, physical activity, and BMI determine serum

cholesterol. Screening studies for familial hypercholesterolemia (FH) show a higher rate of identified genetic defect when children rather than adults are investigated, suggesting that the genetically determined relationship between height and LDL may actually be more apparent in childhood (14–16). The seminal report by Ritchie et al. and the CARDIAC team showed that as many as 1/3 of children with FH would be missed if only positive family history of CVD were used to consider cholesterol screening (12). Our odds-ratio analysis suggests that shorter stature could be added to a screening paradigm if universal screening is not employed (17). The first quartile included fifth graders up to the 36th percentile for height. A strong genetic control of LDL is suggested by this report. This highlights the need for consideration of hyperlipidemia, specifically increased LDL as a multifactorial marker for CVD risk influenced by not only environment but also genetics. The relationship between short stature and LDL, noted in adults, is confirmed in childhood.

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