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Cardiometabolic risk factors in siblings from a statewide screening program

Lee A. Pyles, MD, MS*,

Department of Pediatrics and WVU Children's Hospital, West Virginia University School of Medicine, Morgantown, WV, USA

Christa L. Lilly, PhD,

Department of Biostatistics, WVU School of Public Health, Morgantown, WV, USA

Amy Joseph, MD,

Department of Pediatrics and WVU Children's Hospital, West Virginia University School of Medicine, Morgantown, WV, USA

Charles J. Mullett, MD, PhD,

Department of Pediatrics and WVU Children's Hospital, West Virginia University School of Medicine, Morgantown, WV, USA

WV Clinical and Translational Science Institute Bioinformatics Core, Morgantown, WV, USA

William A. Neal, MD

Department of Pediatrics and WVU Children's Hospital, West Virginia University School of Medicine, Morgantown, WV, USA

Abstract

BACKGROUND: The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project is a state-wide risk factor screening program that operated in West Virginia for 19 years and screened more than 100,000 5th graders for obesity, hypertension, and dyslipidemia.

OBJECTIVES: We investigated siblings in the CARDIAC Project to assess whether cardiometabolic risk factors (CMRFs) correlate in siblings.

METHODS: We identified 12,053 children from 5752 families with lipid panel, blood pressure, and anthropometric data. A linkage application (LinkPlus from the U.S. Centers for Disease Control and Prevention) matched siblings based on parent names, addresses, telephone numbers, and school to generate a linkage probability curve. Graphical and statistical analyses demonstrate the relationships between CMRFs in siblings.

*Corresponding author. Department of Pediatrics, WVU School of Medicine, Box 9214 1 Medical Center Drive, Morgantown, WV 26506, USA. lpyles@hsc.wvu.edu.

Authors' contributions: L.A.P. conceptualized and designed the study, performed sibling data linkages, analyzed data and reviewed analyses from C.L.L., prepared figures and tables, drafted the initial manuscript, and reviewed and revised the manuscript; A.J. helped develop figures and draft the initial manuscript; C.L.L. analyzed the data and reviewed the initial and subsequent manuscripts; C.J.M. reviewed the data, helped develop figures and tables, and reviewed the initial and subsequent manuscripts; and W.A.N. helped conceptualize and design the study, drafted the initial manuscript, and reviewed and revised the manuscript.

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RESULTS: Siblings showed moderate intraclass correlation coefficient of 0.375 for low-density lipoprotein cholesterol (LDL-C), 0.34 for high-density lipoprotein cholesterol (HDL-C), and 0.22 for triglyceride levels. The body mass index (BMI) intraclass correlation coefficient (0.383) is slightly better (2%) than LDL-C or HDL-C, but the standardized beta values from linear regression suggest a 3-fold impact of sibling LDL-C over the child's own BMI. The odds ratio of a second sibling having LDL-C < 110 mg/dL with a first sibling at that level is 3.444:1 (Confidence Limit 3.031–3.915, $P < .05$). The odds ratio of a sibling showing an LDL-C $\geq$ 160 mg/dL, given a first sibling with that degree of elevated LDL-C is 29.6:1 (95% Confidence Limit: 15.54–56.36). The individual LDL-C level correlated more strongly with sibling LDL-C than with the individual's own BMI. Seventy-eight children with LDL-C $\geq$ 160 mg/dL and negative family history would have been missed, which represents more than half of those with LDL-C $\geq$ 160 mg/dL (78 vs 67 or 54%).

CONCLUSIONS: Sibling HDL-C levels, LDL-C levels, and BMIs correlate within a family. Triglyceride and blood pressure levels are less well correlated. The identified CMRF relationships strengthen the main findings of the overall CARDIAC Project: an elevated BMI is not predictive of elevated LDL-C and family history of coronary artery disease poorly predicts cholesterol abnormality at screening. Family history does not adequately identify children who should be screened for cholesterol abnormality. Elevated LDL-C ($\geq$ 160 mg/dL) in a child strongly suggests that additional siblings and parents be screened if universal screening is not practiced.

Table of contents summary:

Sibling LDL-C and HDL-C levels as well as the BMI are highly correlated. A 5th grader's LDL-C correlates better to LDL-C of a sibling rather than the child's own BMI.

Keywords

Cholesterol; Low-density lipoprotein cholesterol; Body mass index; Familial hypercholesterolemia; Cardiometabolic risk factors; Cholesterol screening; Siblings

The Coronary Artery Risk Detection in Appalachian Communities (CARDIAC) Project in West Virginia (WV) has studied the incidence of risk factors for coronary artery disease (CAD) in fifth grade children for 19 years to identify hypercholesterolemia, hypertriglyceridemia, insulin resistance, hypertension, and obesity in childhood.^{1–3} The American Academy of Pediatrics (AAP) recommends universal cholesterol screening at age 9–11 years in its Bright Futures Guidelines consistent with information from the National Institutes of Health and from the CARDIAC Project that 37% of elevated low-density lipoprotein cholesterol (LDL-C) levels in children would have been missed if targeted screening based on positive family history of CAD was used.^{4–6} Conversely, a recent statement from the U.S. Public Health Service Preventive Services Task Force reports that evidence is insufficient to recommend universal screening for familial hypercholesterolemia (FH).⁷ The screening controversy pivots on the question of whether hyperlipidemia should be discovered and treated because the task force questioned the downstream impact of childhood treatment of FH. Given the morbidity and mortality of coronary vascular disease in our state's adult population, we concur with the AAP that screening should be used in children and all available treatment measures undertaken.

For childhood CAD risk factor screening, a family history of cardiac disease has not been found discriminatory.⁴ Therefore, we have undertaken this investigation of sibships in our CARDIAC data set to either strengthen the understanding of familial associations of cardiometabolic risk factors (CMRFs) and therefore, ease of screening, or, conversely, bolster the evidence for a need for universal screening in children for CMRFs and for FH.

More than 100,000 fifth graders have enrolled in the CARDIAC Project, and generating fasted, venipuncture lipid panels for nearly 60,000 of these children now forms year 6 to 19 of the program. The purpose of this study is to (1) find sets of siblings in the CARDIAC database and (2) determine if any CMRF in the first sibling screened can adequately predict CMRFs in the second sibling screened.

Secondarily, we seek to determine if these family analyses will support our finding that universal screening is appropriate, at least in a setting of high incidence of CAD such as WV.⁸ Empiric analysis of risk factors allows consideration of management of family risk for CAD in the absence of knowledge of an identified genetic abnormality. Empiric management has become especially important as mounting evidence suggests that childhood marks the beginning of the cumulative impact of LDL-C over time (the LDL-C time integral) that imparts major risk of atherosclerosis.⁹

Less than 10% of FH cases are diagnosed in the United States, in comparison with 70% in the Netherlands with well-established screening including cascade screening.¹⁰ All too frequently, patients and parents are erroneously instructed that high cholesterol is not important in children and that the children should not be treated with statins. Parents with a monogenic abnormality of a lipid gene exhibit a 50% probability of passing the autosomal dominant trait to an offspring. Many parents will possess an ill-defined polygenic abnormality of LDL-C metabolism.¹¹ With unclear genotypic inheritance possible within families, it is important to have an idea of whether a normal or a markedly abnormal lipid level in a first sibling can help guide parents and providers to the priority level of CMRF screening for a child. The question of congruence of lipid levels in siblings has been investigated in the Bogalusa Heart Study but with a smaller cohort of siblings and without consideration of the body mass index (BMI) or blood pressure.¹²

Based on the lack of recent or detailed information regarding cardiometabolic risk factor grouping in siblings, we considered it worthwhile to establish and investigate family relationships in our CARDIAC database. Thus, we have embarked on this study to link siblings in the CARDIAC Project and correlate their cardiometabolic risk factors as identified in the fifth grader screenings.

Patients and methods

Families and guardians of WV fifth grade schoolchildren were approached for informed consent and the students approached for assent using a protocol and consent form approved by the West Virginia University Committee for the Protection of Human Subjects. The forms included a family history questionnaire with the consent and were returned in advance of the screening day at the school. The screening was approved by the superintendent of each

county school system and the screening date and site details approved and arranged by the principal of each school. Fifty to 55 of the counties allowed screening in the various years of the study.² The fasting blood lipid panel, height, weight, and blood pressure plus inspection for acanthosis nigricans were obtained for each fifth grade student subject. Glucose and insulin were only checked for children who showed acanthosis nigricans at the time of school screening. Blood pressures were measured with automated oscillometric cuff and results interpreted with reference to the 2017 Pediatric blood pressure guideline.¹³ Calculated LDL-C was used. Further details of screening protocol are provided in other reports.⁴

Sibships were determined by matching demographic materials in the database. LinkPlus 2.0 software application from the U.S. Centers for Disease Control and Prevention was obtained by download of freeware from the Centers for Disease Control and Prevention website.¹⁴ Customized settings in LinkPlus took advantage of availability of telephone numbers in addition to addresses and names. LinkPlus generates a probability of match that includes the relative frequency of a surname from the U.S. Census. The software includes extensive entry error compensation programming using regular expressions and reflects the error compensation by lowering the likelihood score generated. The LinkPlus program was configured to find a match of father and/or mother first and last names, address, and telephone number for 2 or more children. The county was used as a blocking variable, meaning that the match was effectively conducted within each county, and a mistaken county designation would result in a nonmatch. Figure 1 shows the accuracy of the match as a function of the probability score calculated for each potential match. Matches with the highest 5000 probability scores were spot checked approximately every 100 entries and then accepted as accurate. As the error-correction features of LinkPlus were used, the probability score decreased. Matches with descending probability score ranging from numbers 5001 to 7500 were visually inspected by the lead author, and Figure 1 was generated from groupings of 50 matches. A cutoff of 96% sensitivity was chosen as a result of this analysis to establish the curve in Figure 1. Children with a nonmatch for either parent name were discarded as were children with a discrepancy in one parent and no first name for a second parent. Above the 96% cutoff, the visually identified erroneous matches were also discarded. No children with a different last name were matched even with identical addresses and telephone numbers. Sibling 1 was the first sibling screened irrespective of the age.

Analysis after establishment of sibships included analysis of correlations in cardiometabolic risk factors in childhood including lipids (total cholesterol, high-density lipoprotein cholesterol [HDL-C], LDL-C, very-low-density lipoprotein cholesterol, triglycerides [TGs]), blood pressure (systolic blood pressure and diastolic blood pressure), and BMI that was indexed to sex and a z-score calculated. The analysis of variance (ANOVA) was used to analyze the relationship of LDL-C to the BMI in sibling pairs. The ANOVA and nonadjusted odds ratios (ORs) were calculated, and heat maps showing frequency of correlated values were constructed using JMP 13.0 statistical application from SAS, Inc SAS 9.4 (Cary, NC) was used to determine overall intraclass correlation coefficient (ICC) within families for the different variables from a list of all 12,053 children with siblings that included a family ID code.

Results

The analysis for siblings was performed for 57,499 children enrolled in the CARDIAC Project from years 6 to 16 of the study (for whom a venipuncture 8-hour fasting lipid panel with LDL-C was available). Table 1 shows that the group of siblings did not differ clinically from the overall CARDIAC population for the BMI, blood pressures, lipids or glucose, and insulin, although statistical differences were observed.

No significant differences were observed in any of the parameters between the overall CARDIAC cross-sectional sample group ($n = 57,499$), the group of siblings ($n = 12,053$), or male (5699) vs female (6354) (Table 1). Figure 1 depicts the decrement in the LinkPlus matching algorithm that identified a total of 6921 pairs of siblings.

To consider the relationship between multiple siblings, analysis of ICC was undertaken. A list of 12,053 children with at least one enrolled sibling (2 or more enrolled children per family) was transferred to SAS (Cary, NC) to determine the ICC for each of the variables of interest to be able to assess the multiple correlations including the 509 families with 3 or more (4 families with 5 siblings each) enrolled siblings plus the pairs. In Table 2, the means, ranges of variables, and ICCs are considered. The best ICC levels are found for LDL-C and BMI, compared with the other analyzed factors.

Next, various gradation of LDL-C and TG levels are considered and ORs constructed for likelihood of determination of an elevated LDL-C, given an elevated level in the first sibling. For an LDL-C level of > 175 mg/dL, 7 sets of siblings both exhibited a level greater than the threshold and thus showed an extreme likelihood of FH in the family (Table 3). At this level, the OR for elevated LDL-C > 175 mg/dL for the second sibling in addition to the first sibling is 79-fold that of the overall group of siblings and the odds for LDL-C 160 mg/dL is 29.6 (95% CL: 15.54–56.36) as in Table 3. For an LDL-C level less than 110 mg/dL ($n = 5380$ first siblings), the odds of the second sibling also exhibiting an LDL-C level less than 100 mg/dL is 3.44:1 (95% CL: 3.031–3.915). Five hundred seventy-three pairs both had LDL-C levels greater than 110 mg/dL (Table 3).

This grouping of sib matches was used to construct graphs of relationships of the BMI z score, systolic blood pressure, LDL-C, and TG levels for the sets of siblings (Fig. 2). Sibships with 3, 4, or 5 children enrolled in the study are overrepresented in these graphs of 1:1 matching. The various heat maps that depict the degree of agreement between sibs visually show the best agreement for the BMI z-score and LDL-C.

From Table 3, 13 children with LDL-C > 190 mg/dL (38% of all 34 greater than 190 mg/dL) and negative family history of coronary disease would have evaded screening based on family history. Seventy-eight children with LDL-C > 160 mg/dL and negative family history would have been missed, which represents more than half of those with LDL-C > 160 mg/dL (78 vs 67 or 54%). The OR (Table 3) of the second sib showing LDL-C > 160 mg/dL, given the first sib with that level is 29:1 (95% CL: 15.54–56.36) and the OR rises to 42 (95% CL: 17.84–100.7) with positive family history of CAD. The 130 mg/dL cutoff for family history shows 413 with positive family history of and 553 negative, indicating 57% of

subjects with LDL-C > 130 mg/dL would be missed if only subjects with positive family history were screened.

Other cardiometabolic risk factors are also analyzed. TG levels are not as predictive of the correlated behavior as the LDL-C as is demonstrated in the Figure 2C heat map. This is also identified with the ANOVA. Of the 691 first siblings with a TG level greater than or equal to 150 mg/dL, 137 of the second sibs had an abnormally elevated level for an OR of 2.53:1 (95% CL: 2.06–3.11). However, the majority of elevated TG levels in the second siblings, 691 (9.98% of 6917 total), followed normal TG levels in the older sibling. The BMI was available for 6911 sets of siblings. Of these, 4340 were both nonobese (62.8%) and 662 (9.6%) were both obese (BMI > 95%ile). The OR of the second sibling showing obesity, given an obese first sibling, was 3.21 (95% CL: 2.91–3.71). Sibling pairs with only one obese child numbered 1882 (28%).

Thirteen hundred eighty-two first siblings showed systolic hypertension (greater than 95%ile value) compared with 2017 AAP guideline values (Table 3) along with 1441 second siblings for an OR of 1.616 (95% CL: 1.411–1.851).¹³ Also from Table 3, slightly more children showed diastolic hypertension, but the OR for second sibling was lower (1.53, 95% CL: 1.352–1.732). From Table 2, ICC levels for blood pressure were lower than for any lipid level or BMI, also suggesting a weaker between-sibling correlation.

A regression equation for the second sibling LDL-C was generated from the analysis that shows the relative contribution of different variables (Table 4). Table 4 shows standardized beta values for the variables and indicates the strongest contribution to the second sibling LDL-C is from the first sibling LDL-C (LDL-1) rather than the BMI of either the second sibling screened or the first sibling screened. Thus, the only major impact from the older sibling (1) is from the LDL-1 level. As indicated by the magnitude of the standardized beta levels, LDL-1 from the first sibling is 3 times as impactful as the second child's own BMI z score, and 6 times as impactful as the child's own TG level. Other factors such as the year of screening, HDL-C, family history of CVD, and race were nonsignificant and dropped from preliminary models.

In summary, the several analyses demonstrate a strong association between LDL-C levels within sibships and between BMIs within sibships. The ANOVA demonstrates a weak relationship between LDL-C and the BMI z score that does not produce an adequate predictive model to foretell the LDL-C level in the second sibling. Although the predictive value of a normal or abnormal BMI, LDL-C, or TG level is insufficient to guide clinical decisions to screen, the strong relationships demonstrated by ORs in Table 3 provide a great deal of information that informs attempts to create predictive models of lipid levels in families.

Discussion

Recent studies have reinforced the need to empirically describe family correlation of cholesterol, especially LDL-C that primarily imparts significant risks of CAD in adults.^{15,16} LDL-C-driven risk is related both to FH and to familial combined hyperlipidemia but the

more significant risk occurs in FH in which untreated adult men exhibit a 50% risk of CAD by the age of 50 years and 50% of females by the age of 60 years.¹⁷ Khera, in a recent multicenter study, showed that only a small percentage of adults with clinical FH (<5%) had an identified monogenic defect, in contrast with 57% of children in Klancar's study.^{15,18} The persons with clinical FH and a presumably polygenic etiology seem to show more variability in lipid levels as they age and represent a challenge to detect and manage. These persons likely represent the discrepancy of findings between Khera and Klancar's reports. Lipid levels that drive the development of atherosclerosis and elevated BMI that drives the metabolic syndrome and type II diabetes are probably under polygenic control for most persons and also responsive to a major degree to lifestyle influences.

In Bogalusa, ICCs were calculated for LDL-C (0.32), Apolipoprotein B, and HDL-C (0.21 for both after adjustment) for black and white children. The children were slightly older at 12–13 years of age than 11 years for the CARDIAC Project, and approximately 1300 sibling pairs were analyzed rather than more than 5000 pairs. The Ponderal index defined as weight/height³ was used to adjust for obesity. In 1997, the BMI was not commonly considered. There was no statistical difference in the ICC for LDL-C between blacks and whites after adjustment for obesity, age, and sex.

A limitation of this study is the homogeneity of the WV population and the CARDIAC Project subjects who are 93% Caucasian. With the high concentration of Caucasian subjects in WV, we could not reach any conclusions by race. This along with the high rate of obesity in WV limits the generalizability of our findings to other populations. An additional limitation is the post hoc determination of family relationships. We did not include fifth graders at the same address unless last names matched and the first names of both parents matched, but we still have potentially included half siblings. Adopted children including those adopted by relatives may have been included. This would impact any of the analyses. Children from the same address with questionable relationships were not included in analysis. Abnormalities of thyroid metabolism were not sought by screening or history. In addition, only children exhibiting acanthosis nigricans were screened with fasting blood sugar or insulin level. The use of error-detection capabilities in Match Plus allowed us to find sibships with one child with a telephone number off by 1 digit or a parental familiar name in one child and parent's formal name used to register the second child.

The overall objective of the CARDIAC Project is to identify and raise awareness of cardiovascular risk factors in families. In this sibling study, we attempt to find empiric relationships that can improve detection of increased risk for cardiovascular disease from its origin in childhood. Mounting evidence confirms the importance of early aggressive management of elevated LDL-C blood levels to prevent coronary atherosclerosis. Recent reports of long-term follow-up from the Framingham study suggest that LDL-C control from ages 20–40 years can lower the risk of CVD in later years.¹⁹ We extrapolate to extend the paradigm to LDL-C lowering in childhood as no recent evidence *contradicts* the hypothesis that an elevated LDL-C level causes atherosclerosis and should be lowered to limit the cumulative dose in persons with increased risk. The U.S. Army autopsy series and studies such as Pathological Determinants of Atherosclerosis in Youth have suggested for some time that atherosclerosis begins in childhood (16–19).^{20–23} Recent studies that compare the

phenotype with genotype continue to suggest increased complexity of genetic control of lipid metabolism. In essence, the aggregate exposure to LDL-C (LDL-C time integral) drives atherosclerosis. Lurink in the Netherlands has recently presented definitive data regarding favorable outcome of childhood treatment of FH.²⁴

In our present study, we have shown that the correlation of CMRFs between the first and second siblings although strong cannot adequately replace actual screening. These results support the AAP's policy recommendation for universal screening.²⁵ The ORs for CMRF values in the second sibling, given their presence in the first sibling, suggest that abnormalities of LDL-C, especially greater than 160 mg/dl in sibling 1, strongly predict an association. The ORs for LDL-C $\geq$ 130 mg/dL, the BMI in an obese range, and HDL-C levels, TG levels, and systolic and diastolic blood pressures, all in the 1.5 to 4 range less, strongly indicate an abnormal value in the second sibling. Positive family history of CAD strengthens the predictive value of LDL-C $\geq$ 160 mg/dL as would be expected. In fact, one of the most important overall findings of the CARDIAC Project is that markedly elevated LDL-C is a genetic abnormality minimally related to the BMI, and the conclusion is confirmed in the sibling study.⁴ In the absence of universal screening, an elevated LDL-C $\geq$ 160 mg/dL in any child should prompt a clinician to be insistent for lipid screening in siblings and parents in the alternative model known as Cascade FH Screening.²⁶

Conclusion

In summary, total cholesterol, LDL-C, HDL-C, and BMI show good correlation between siblings. The BMI only vaguely relates to sibling LDL-C. The ORs for normal or abnormal LDL-C levels demonstrate a high likelihood of the levels grouping within families. None of these associations, just like family history from the Ritchie report from the CARDIAC Project, avoids universal lipid screening.⁴ Again, from ANOVA standardized beta values in Table 4, the LDL-C value for the second sibling is most strongly explained by sibling 1 LDL-C value rather than the second child's own BMI. The reported results will stimulate us to investigate models of increasing complexity to empirically explain family relationships of LDL-C levels. This study can be considered a precursor to the understanding of phenotypes of polygenic lipid disorders because it will support hypothesis generation regarding the importance of the various genes that have been observed in other investigations. These and other observations of familial manifestation of dyslipidemia will help improve our understanding of how dyslipidemia leads to CAD.

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References

1. Pyles LA, Lilly CL, Mullett CJ, Polak ES, Elliott EM, Neal WA. LDL cholesterol level in fifth-grade schoolchildren associates with stature. *J Lipid Res.* 2017;58(11):2197–2201. [PubMed: 28870972]
2. Elliott E, C L, Pyles L, L C, Neal W. Coronary Artery Risk Detection In Appalachian Communities (CARDIAC): an 18 year review. *Curr Pediatr Rev.* 2017;18(1):265–276.
3. Lilly CL, Gebremariam YD, Cottrell L, John C, Neal W. Trends in serum lipids among 5th grade CARDIAC participants, 2002–2012. *J Epidemiol Community Health.* 2014;68(3):218–223. [PubMed: 24218074]
4. Ritchie SK, Murphy EC, Ice C, et al. Universal versus targeted blood cholesterol screening among youth: The CARDIAC project. *Pediatrics.* 2010;126(2):260–265. [PubMed: 20624798]
5. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents. 2014 Available at: https://www.nhlbi.nih.gov/sites/default/files/media/docs/peds_guidelines_sum-1.pdf. Accessed July 7, 2020.
6. Bright futures american academy of pediatrics recommendations for pediatric preventive health care; 2020. Available at: https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf. Accessed July 7, 2020.
7. Lozano P, Henrikson NB, Dunn J, et al. Lipid screening in childhood and adolescence for detection of familial hypercholesterolemia: evidence report and systematic review for the US Preventive Services Task Force. *JAMA.* 2016;316(6):645–655. [PubMed: 27532919]
8. The Burden of Cardiovascular Disease in West Virginia; 2011. Available at: http://www.wvdhhr.org/bph/hsc/pubs/other/burdenofcvd2010/cvh_burden_2010.pdf. Accessed January 29, 2017.
9. Elis A, Zhou R, Stein EA. Effect of lipid-lowering treatment on natural history of heterozygous familial hypercholesterolemia in past three decades. *Am J Cardiol.* 2011;108(2):223–226. [PubMed: 21545982]
10. Nordestgaard BG, Chapman MJ, Humphries SE. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. *Eur Heart J.* 2013;34(45):3478–90a. [PubMed: 23956253]
11. Talmud PJ, Shah S, Whittall R. Use of low-density lipoprotein cholesterol gene score to distinguish patients with polygenic and monogenic familial hypercholesterolaemia: a case-control study. *Lancet.* 2013;381(9874):1293–1301. [PubMed: 23433573]
12. Chen W, Srinivasan S, Bao W, Wattigney W, Berenson G. Sibling aggregation of low- and high-density lipoprotein cholesterol and Apolipoprotein B and A-I levels in black and white children: the Bogalusa heart study. *Ethn Dis.* 1997;7:241–249. [PubMed: 9467707]
13. Flynn J, Kaelber D, Baker-Smith C, Blowey D, Carroll A. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. *Pediatrics.* 2017;140(3):e20171904. [PubMed: 28827377]
14. LinkPlus, Centers for Disease Control and Prevention; 2017. Available at: https://www.cdc.gov/cancer/npcr/tools/registryplus/lp_tech_info.htm. Accessed October 21, 2017.
15. Khera AV, Won HH, Peloso GM, et al. Diagnostic yield and clinical utility of sequencing familial hypercholesterolemia genes in patients with severe hypercholesterolemia. *J Am Coll Cardiol.* 2016;67(22):2578–2589. [PubMed: 27050191]

16. Abul-Husn NS, Manickam K, Jones LK, et al. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. *Science*. 2016;354(6319):aaf7000. [PubMed: 28008010]
17. Slack J. Risk of ischaemic heart-disease in familial hyperlipoproteinaemic states. *Lancet*. 1969;294(7635):1380–1382.
18. Klancar G, Groselj U, Kovac J, et al. Universal screening for familial hypercholesterolemia in children. *J Am Coll Cardiol*. 2015;66(11):1250–1257. [PubMed: 26361156]
19. Pletcher MJ, Vittinghoff E, Thanataveerat A, Bibbins-Domingo K, Moran AE. Young adult exposure to cardiovascular risk factors and risk of events later in life: the framingham offspring study. *PLoS One*. 2016;11(5):e0154288. [PubMed: 27138014]
20. Homma S, Ishii T, Malcom G, et al. Histopathological modifications of early atherosclerotic lesions by risk factors—findings in PDAY subject. *Atherosclerosis*. 2001;156(2):389–399. [PubMed: 11395036]
21. Enos W, Holmes R, Beyer J. Coronary disease among United States soldiers killed in action in Korea. *JAMA*. 1953;152(12): 1090–1093.
22. McNamara J, Molot M, Strempel J, Cutting R. Coronary artery disease in combat casualties in Vietnam. *JAMA*. 1971;216(7):1185–1187. [PubMed: 5108403]
23. Tracy RE, Newman WP, Wattigney WA, Berenson GS. Risk factors and atherosclerosis in youth autopsy findings of the Bogalusa heart study. *Am J Med Sci*. 1995;310:S37–S41. [PubMed: 7503122]
24. Luirink IK, Wiegman A, Kusters DM, et al. 20-year follow-up of statins in children with familial hypercholesterolemia. *N Engl J Med*. 2019;381(16):1547–1556. [PubMed: 31618540]
25. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents, National Heart, Lung, and Blood Institute. Expert panel on integrated guidelines for cardiovascular health and risk reduction in children and adolescents: summary report. *Pediatrics*. 2011;128(Suppl 5):S213–S256. [PubMed: 22084329]
26. Neal W, Knowles J, Wilemon K. Underutilization of cascade screening for Familial Hypercholesterolemia. *Clin Lipidol*. 2014;9(3):291–293.

What is known on this subject:

The CARDIAC Project has established the usefulness of universal cholesterol screening to detect FH and shown poor correlation of high LDL-C to a high BMI. Sibling lipid levels were correlated in the Bogalusa Heart Study, but the BMI and blood pressure were not considered.

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What this study adds:

The LDL-C level correlates 3-fold more strongly to sibling LDL-C than the child's own BMI. HDL-C and the BMI correlate between siblings, but TG and BP only weakly correlate. No correlation is sufficiently strong to exempt sibling screening.

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Figure 1.

Percent sensitivity by the match probability score (X-axis, ranging from 62 to 14) generated by LinkPlus. Each sensitivity data point represents a sample of 50 matches and the curve depicts high sensitivity to a probability score of 25.3. The probability score is a relative scale determined by LinkPlus.

Figure 2.

Heat maps of sib 1 and sib 2 pairings. Findings for the first sibling screened are displayed on the x-axis and those for the second sibling on the y-axis. (A) Low-density lipoprotein (mg/dL), (B) BMI z score (SD), (C) triglyceride levels (mg/dL), (D) high-density lipoprotein (mg/dL), and (E) total cholesterol (mg/dL).

Table 1

Cardiometabolic risk factors for CARDIAC and for siblings and siblings by gender

	All CARDIAC				All Siblings				Male			Female			<i>P</i> male vs female	
	Mean	N	SD	<i>P</i> all vs siblings	Mean	N	SD	<i>P</i> male vs siblings	Mean	N	SD	<i>P</i> female vs siblings	Mean	N		SD
BMI	21.4	57,174	5.2	<.001	20.7	12,008	4.8		20.8	5678	4.8		20.7	6330	4.8	
BMI z-score	0.83	57,154	1.144	<.001	0.71	12,008	1.10	<.001	0.78	5678	1.10	<.001	0.65	6330	1.10	<.001
Blood pressure systolic	108.5	56,779	11.9	<.001	108.0	11,930	11.8	.04	108.4	5638	11.8		107.6	6292	11.8	<.001
Blood pressure diastolic	68.2	56,734	9.4	<.001	67.7	11,920	9.5	.05	68.0	5635	9.4		67.5	6285	9.6	<.001
Total cholesterol	160.1	57,498	28.3		159.8	12,053	28.1		160.2	5699	28.5		159.4	6354	27.8	
High-density lipoprotein	50.7	57,496	12.3	<.001	51.3	12,053	12.2	<.001	52.4	5699	12.4		50.3	6354	11.8	<.001
Low-density lipoprotein	91.7	57,499	25.2		91.5	12,053	25.4		91.7	5699	25.8		91.4	6354	25.0	
Very-low-density lipoprotein	17.8	51,145	10.9	<.001	17.1	10,777	10.3	<.001	16.2	5110	10.3	<.001	17.8	5667	10.3	<.001
Triglycerides	91.5	57,485	53.8	<.001	87.5	12,050	50.7	<.001	83.0	5698	50.7	<.001	91.6	6352	50.4	<.001
Glucose *	89.3	4454	12.8		89.3	799	9.5		89.2	362	9.4		89.4	437	9.7	
Insulin *	24.4	2407	27.1		21.8	428	26.6		19.3	186	31.2		23.7	242	22.3	

BMI, body mass index; CARDIAC, Coronary Artery Risk Detection in Appalachian Communities.

CARDIAC subjects who underwent lipid screening were matched for siblings. Gender was reported by the family.

Statistically significant difference by the *t*-test.

* Glucose and insulin were generally only measured if acanthosis nigricans was present.

Table 2

Intraclass correlation coefficients for cardiometabolic risk factors

Variable	Mean	SD	Range	ICC
Total Cholesterol	159.8	28.1	465	0.356
HDL	51.3	12.2	115	0.34
LDL	91.6	25.4	404	0.375
Triglyceride	87.5	50.7	984	0.217
BMI percentile greater than the median	15.6	21.4	180	0.383
Systolic BP	108.0	11.8	198	0.166
Diastolic BP	67.7	9.47	120	0.143

BMI, body mass index; ICC, intraclass correlation coefficient; HDL, high-density lipoprotein; LDL, low-density lipoprotein; BP, blood pressure.

The intraclass correlation coefficient without adjustment for the BMI, gender, or race was calculated considering each sibship to account for variable sibship sizes. The number of siblings varied from 2 to 5.

Table 3

Correlation of CMRF levels in pairs of siblings (n = 6921)

LDL (mg/dL)	Sib 1 (n, %)	Sib 2 (n, %)	Both (n, %)	Odds ratio for value of interest in sib 2	95% CL
<110	5380	5559	4591	3.444	3.031–3.915
>110	1541	1362	573	3.444	3.031–3.915
130	557 (8.0)	409 (5.9)	116 (1.67)	5.45	4.31–6.90
130 + Pos FHx	239 (8.6)	174 (6.3)	49 (1.8)	4.962	3.455–7.125
130 + negative FHx	318 (7.7)	235 (5.7)	67 (1.6)	5.85	4.290–7.986
Odds for both > 130 for FHx positive vs negative (49/2720)/(67/4085)				1.098	0.7575–1.593
160	87 (1.3%)	58 (0.84)	14 (0.20)	29.59	15.54–56.36
160 + FHx positive	37 (1.3)	30 (1.1)	9 (0.32)	42.38	17.84–100.7
160 + FHx negative	50 (1.2)	28 (0.67)	5 (0.12)	19.70	7.171–54.14
Odds for both > 160 for FHx positive vs negative (9/2760)/(5/4147)				2.705	0.9054–8.0787
175	36 (0.52)	28 (0.40)	7 (0.10)	78.89	31.13–199.9
175 + FHx positive	18 (0.65)	17 (0.61)	6 (0.22)	124.5	39.63–391.4
175 + FHx negative	18 (0.43)	11 (0.26)	1 (0.02)	24.25	2.941–200.1
Odds for both > 175 for FHx positive vs negative (29/2740)/(28/4124)				9.014	1.086–74.92
190	17 (0.25)	17 (0.61)	5 (0.07)	236.8	72.76–776.2
190 + FHx positive	10 (0.36)	11 (0.40)	4 (0.14)	262.1	60.47–1136
190 + FHx negative	7 (0.17)	6 (0.14)	1 (0.02)	138	13.95–1365
Odds for both > 190 for FHx positive vs negative (4/2765)/(1/4151)				6.005	0.6708–53.76
HDL 40	1274	1267	441	3.090	2.94–3.544
Triglyceride (mg/dl)					
>110	1628 (23.5)	1561 (22.5)	559 (8.1)	2.24	1.98–2.53
>150	691 (9.98)	691 (9.98)	137 (2.0)	2.53	2.06–3.11
BMI > 95%ile	1592 (23.0)	1614 (23.3)	662 (9.6)	3.21	2.91–3.71
SBP > 95%ile	1382 (19.97)	1441 (20.8)	382 (5.52)	1.616	1.411–1.851
DBP > 95%ile	1699 (24.6)	1601 (23.1)	495 (7.15)	1.530	1.352–1.732

BMI, body mass index; HDL, high-density lipoprotein; CMRF, cardiometabolic risk factor; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Low-density lipoprotein cholesterol (LDL-C) for pairs of siblings. Sibling pairs were analyzed for the presence of LDL greater than and less than critical values. Sibling 1 was the child with the first screening and sib 2 was the more recent screen (irrespective of the subject age). Unadjusted odds ratios for various LDL levels are shown. Family history (FHx-as opposed to familial hypercholesterolemia

[FH]) of coronary artery disease (CAD) was obtained from the parent who signed consent. Total FHx positive for CAD (including heart attack, coronary angioplasty or coronary bypass grafting) 2769; FHx negative = 4152.

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Table 4

Multivariable regression analysis of low-density lipoprotein correlation for sibling 2

Term	Estimate	Standard error	t Ratio	Prob> t	Lower 95%	Upper 95%	Std Beta
Intercept	52.091287	1.120516	46.49	<.0001*	49.894729	54.287845	0
TG-2	0.0324908	0.006057	5.36	<.0001*	0.0206178	0.0443638	0.064275
LDL-1	0.354507	0.010604	33.43	<.0001*	0.333719	0.3752949	0.372559
TG-1	0.0186331	0.005929	3.14	0.0017*	0.0070107	0.0302555	0.037968
BMI z score-1	-1.074999	0.283461	-3.79	0.0002*	-1.630671	-0.519327	-0.04794
BMI z score-2	2.9374787	0.282597	10.39	<.0001*	2.3835005	3.491457	0.130002

BMI, body mass index; TG, triglyceride.

The standardized estimate (standardized beta) for the regression on LDL-2 shows the largest contribution from LDL-1 *from the sibling*, followed by the BMI from the subject (BMI z score-2), TG-2 (from the subject), BMI z score-1 (from the first sibling), TG-1 from the first sibling.

LDL-1, low-density lipoprotein (mg/dL) for the first screened sibling; BMI z score is the body mass index standard deviation for either sibling.

* Two-tailed t-test p value.