Trends of Lipoprotein Variables From Childhood to Adulthood in Offspring of Parents With Coronary Heart Disease: The Bogalusa Heart Study

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Although dyslipidemia among offspring of parents with coronary heart disease (CHD) has been known, the development of this adverse relationship with respect to specific lipoprotein variables from childhood to young adulthood has not been elucidated. This aspect was examined in a young adult cohort with (n = 271) and without (n = 805) a parental history of CHD followed longitudinally since childhood by repeated surveys from 1973 to 1991. Trends in fasting lipoprotein variables by parental CHD status were assessed by Lowess smoothing curve and Generalized Estimating Equations (GEE). In multivariate analyses adjusted for race and sex, parental CHD associated positively with low-density lipoprotein cholesterol (LDL-C, $P < .01$) and triglycerides ($P < .05$) mainly at the young adulthood age, whereas a positive association was noted with very-low-density lipoprotein cholesterol (VLDL-C) during both childhood and young adulthood ($P < .05$). The positive association between parental CHD and LDL-C in young adulthood persisted independently of body mass index (BMI) and fasting insulin, but disappeared when fasting glucose was added to the model. With respect to triglycerides and VLDL-C, inclusion of BMI, insulin, and/or glucose eliminated the adverse association with parental CHD. These observations suggest that parental CHD is just one more explanatory variable that loses its partial contribution to lipoprotein profiles in their offspring when other strongly interrelated contributory variables such as age, body fatness, and measures of glucose homeostasis are taken into account. Information on these risk variables in conjunction with parental or family history of CHD may enhance the potential of CHD risk assessment in youth.

IT HAS BEEN ESTABLISHED that atherosclerosis begins in childhood and that the initial stages of atherosclerosis relate strongly to adverse levels of lipoproteins.[1-5] Since coronary heart disease (CHD) aggregates in families,[6-9] a positive parental history can be considered a precursor or a useful predictor of CHD risk in the offspring.[10,11] Further, an association of parental history of CHD has been demonstrated with unfavorable cardiovascular risk factor variables in their offspring.[12-18] Recent studies from the Bogalusa Heart Study cohort showed that offspring of parents with early CHD were overweight beginning in childhood and developed an adverse cardiovascular risk factor profile at an increased rate from childhood to adulthood.[17] However, in this regard the trends over time of lipoprotein variables and their correlates during the periods of childhood and young adulthood still need elucidation. The objectives of the present work are to examine (1) the relationship between parental CHD and the longitudinal trends of lipoprotein profiles in their offspring from childhood to adulthood, and (2) the influence of age, body fatness and measures of glucose homeostasis on this relationship.

MATERIALS AND METHODS

Population

The Bogalusa Heart Study, which began in 1973 in the semi-rural, biracial community of Bogalusa, LA, is a long-term epidemiologic study of cardiovascular disease risk factors in children and young adults.[1] Six cross-sectional surveys of children aged 5 to 17 years were conducted between 1973 and 1988. In addition, 4 cross-sectional surveys of young adults who have been previously examined as children and accessible were conducted between 1979 and 1991. The age of young adults ranged from 18 to 20 years in the 1979 to 1980 survey and from 18 to 32 years in the 1988 to 1991 survey. The above panel design, based on repeated cross-sectional examinations conducted approximately every 3 years resulted in multiple observations during childhood and young adulthood required for the longitudinal analyses. However, since this was not a prospective cohort study by design, not every participant has been examined in all surveys. The distribution of the study cohort by age at the 1988 to 1991 survey and number of screenings between childhood and adulthood are given in Table 1. Of the 1,076 young adult offspring, 3.4%, 7.8%, 16.3%, 43.5%, and 29.0% were examined 2, 3, 4, 5, and 6 times, respectively, since childhood.

Parental history of CHD was obtained from the study cohort as part of the examination. Confirmation of parental CHD was made on these self-reports (n = 371) obtained in the 1988 to 1991 young adult survey, as detailed previously.[19] Briefly, the subject's parents or close relatives (if the parent was deceased) or a physician were contacted to confirm symptoms, specific procedures or treatments related to CHD (eg, angina, myocardial infarction, balloon angioplasty, bypass surgery, or medication) that the parent might have undergone. Medical records were reviewed to verify the occurrence of CHD in cases where the interview did not provide a clear answer regarding disease and treatment. During a telephone interview, the interviewer also confirmed whether the parents were the biological parents. Parental CHD was confirmed in 271 individuals. Parents with no CHD history were included in the study only if offspring consistently acknowledged no history of parental CHD in previous surveys. Of those with no parental history of CHD in the 1988 to 1991 survey (n = 894), 89 reported positive parental CHD in a subsequent 1995 to 1996 survey. These 89 individuals were excluded from the current analysis, resulting in 805 individuals with no parental CHD to make the classification of controls more specific. The number of observations totaling 5,241 made on this 1,076 study cohort from childhood to adulthood by age at the time of examination and status of parental CHD are listed in Table 2. Careful control to adhere to a common protocol and to procedures in all surveys should limit bias by pooling data from the different surveys.

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Table 1. Distribution of the Study Cohort by Age at 1988 to 1991 Survey and Number of Screenings Between Childhood and Adulthood: The Bogalusa Heart Study

Age (yr)	No. of Screenings*					
	2	3	4	5	6	Total
≤20	9	17	30	28	9	93
21-23	11	38	72	95	78	294
24-26	8	14	45	168	126	361
27-29	6	8	11	141	67	233
>29	2	7	17	37	32	95
Total	36	84	175	469	312	1,076

* Since childhood.

General Examination

Subjects were examined according to previously published protocols.[20] They were instructed to fast for 12 hours and compliance with fasting was determined by interview on the morning of the examination. Blood was obtained by venipuncture for serum and plasma (EDTA). Height and weight were measured twice to ±0.1 cm and ±0.1 kg, respectively. As a measure of general body fatness, body mass index (BMI = weight in kilograms divided by the square of height in meters) was used. Means of replicates were used in all analyses.

Laboratory Analysis

From 1973 to 1986, total serum cholesterol and triglyceride levels were measured using chemical procedures on Technicon AutoAnalyzer II (Technicon Instrument Corp, Tarrytown, NY), according to the protocol developed by the Lipid Research Clinics Program.[21] Later analyses of these variables were determined using enzymatic procedures on the Abbott VP instrument (Abbott Laboratories, North Chicago, IL).[22,23] Both chemical and enzymatic procedures met the performance requirements of the Lipid Standardization Program sponsored by the Centers for Disease Control and Prevention (CDC), Atlanta, GA. Serum levels of very-low-density lipoprotein cholesterol (VLDL-C), low-density lipoprotein (LDL-C), and high-density lipoprotein (HDL-C) cholesterols were analyzed by a combination of heparin-calcium precipitation and agar-agarose gel electrophoresis procedures.[24] Plasma immunoreactive insulin levels were measured by a commercial radioimmunoassay kit (Phadebas; Pharmacia Diagnostics, Piscataway, NJ). From 1981 to 1986, plasma glucose levels were measured using a Beckman glucose analyzer (Beckman Instrument Corp, Fullerton, CA) by a glucose oxidase method. From 1987 to 1991, glucose levels were determined as part of a multiple chemistry profile.

Statistical Analysis

A curve fitting method, Lowess smoothing,[25] was used to highlight the change in lipoprotein variables over different ages by parental history of CHD. Lowess smoothing is a nonparametric regression method where weighted least-squares line is fitted for multiple windows (groups) of the data. More weight is given to observations close to the middle of the window, and less weight is given to outliers. In order to investigate the association and change over years of follow-up of different risk factors by parental history of CHD, Generalized Estimating Equations (GEE) analysis was used.[26-28] GEE analysis adjusts for the correlation between observations taken on the same individual repeatedly. Since the main interest is in evaluating the change of the effect of parental CHD on offspring while they grow from childhood to adulthood, multivariate models including interaction with age were fitted to the data. Age, race, and sex were always included in the models. To study the role of body fatness, and insulin and glucose levels in this association, other models were used where BMI, followed by insulin and then glucose, were forced in the model sequentially. Due to nonlinearity of the lipoprotein pattern with age, terms such as age square and age cube and their interaction terms with parental CHD history were tested. Beta coefficients and confidence intervals for each of these models were presented. A margin for statistical significance was established at $P \leq .05$. Stata Statistical Software (STATA) were used for these analyses.[29]

RESULTS

Longitudinal trends in levels of serum lipoprotein variables from childhood to young adulthood by parental CHD status are shown in Fig 1. (These trends are descriptive in nature and no statistical comparisons were made.) Offspring of parents with CHD history showed higher LDL-C level than those without such history between the ages of 4 and 15. At age 15, a steep increase in LDL-C level in both groups occurred, although with a higher rate for offspring with parental history of CHD was noted. This difference in rate of increase resulted in higher LDL-C levels in young adults with parental history of CHD after age 20. Both triglycerides and VLDL-C showed continuous increases with age during the periods of childhood and adulthood in both groups. The age-related increase was more marked for triglycerides in the group with parental CHD, particularly after age 20. For VLDL-C, small but consistently higher values were seen in those with parental CHD during childhood and adulthood, probably reflecting the occurrence of relatively cholesterol-poor and triglyceride-rich VLDL-C particles in this group. Regarding HDL-C, an inverse association with age was noted between the ages of 4 and 20 in both groups, although at later ages a slight trend for lower values was noted for offspring with parental CHD history compared to those without a history of CHD.

A multivariate analysis adjusted for race and sex was used to determine the association of parental CHD with longitudinal changes in lipoprotein variables utilizing GEE (Table 3). Parental CHD showed significant interaction with age in predicting triglycerides ($P = .045$) and with age and age square in predicting LDL-C ($P = .032$ and .003, respectively). Parental CHD was associated with consistently higher values of

Table 2. Number of Observations on the Study Cohort by Age, and Parental CHD Status: The Bogalusa Heart Study

Age (yr)	No. of Examinations*		
	With Parental CHD	Without Parental CHD	Total
<7	20	129	149
7-9	53	254	307
9-11	86	362	448
11-13	114	413	527
13-15	157	482	639
15-17	156	480	636
17-19	129	406	535
19-21	92	333	425
21-23	106	338	444
23-25	92	304	396
25-27	88	229	317
>27	141	277	418
Total	1,234	4,007	5,241

* Values represent multiple observations made on 271 individuals with parental CHD and 805 without parental CHD from childhood to young adulthood.

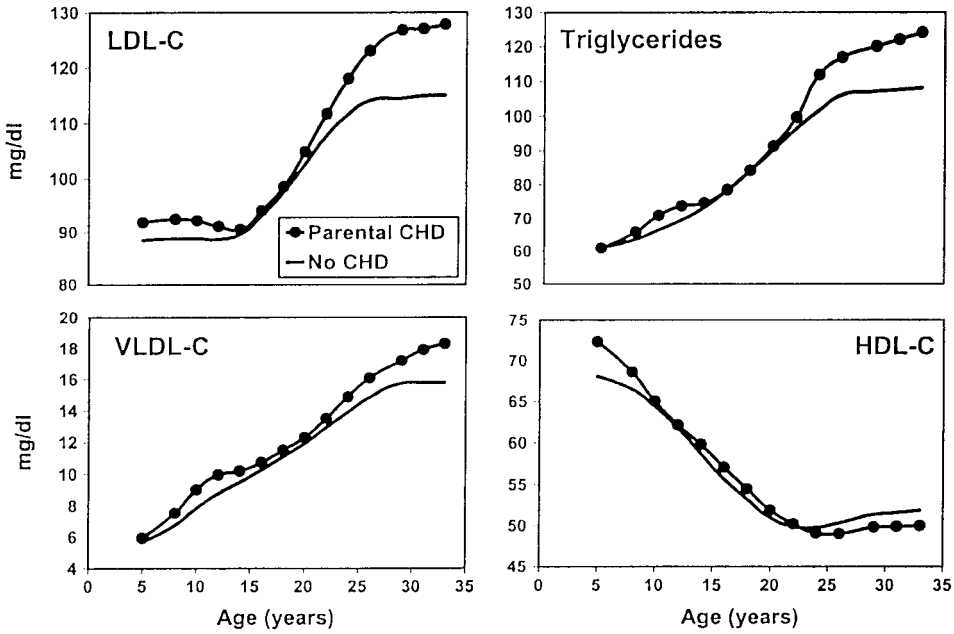

Fig 1. Longitudinal trends in serum lipoprotein variables in the offspring from childhood to young adulthood by parental CHD status: The Bogalusa Heart Study.

VLDL-C in their offspring with no interaction with age. With regard to HDL-C, parental history of CHD showed a negative interaction with age that was not significant ($P = .08$). When the results of multivariate analysis were viewed in conjunction with the longitudinal trends shown in Fig 1, the interaction in the LDL-C model of parental CHD history with age and age square indicated that there was a smaller difference in LDL-C between children around puberty with and without parental CHD history, as might be expected from dynamic lipoprotein changes occurring at this age period.[30] However, this difference increased in adulthood (after age 20 years). The presence of a positive interaction with age only in the triglycerides model indicated an increasing difference in triglycerides between groups as they become older. This increase became more evident above age 20. For VLDL-C, parental history was significant but without an interaction with age, indicating that offspring of parents with CHD had consistently higher values, as they grow older. Regarding HDL-C, even though the interaction with age was nonsignificant, young adults with parental history of CHD tend to have lower values of HDL-C compared to those without such history. When BMI, insulin, and/or glucose were added in the models, the adverse association of VLDL-C and serum triglycerides with parental CHD was no longer significant. With respect to LDL-C, the adverse relationship remained significant when BMI and/or insulin were included in the model, but disappeared when glucose was added to the model. Moreover, BMI and insulin were independent predictors of VLDL-C, LDL-C, HDL-C, and triglycerides; in addition, glucose was a predictor for VLDL-C and triglycerides.

For all of the analyses there were no significant interaction with race and sex, denoting that all associations between parental CHD history and the different lipoprotein variables were consistent regardless of race and sex.

DISCUSSION

Analysis of longitudinal trends over time, beginning during childhood and extending into adulthood, between parental CHD and lipoprotein patterns in their offspring showed accentuated levels of serum LDL-C and triglycerides after their maturation into adulthood, whereas a small but consistent positive association was noted with VLDL-C in offspring with parental CHD history during both childhood and young adulthood. Earlier studies found that levels of lipoprotein cholesterol and triglycerides in childhood were similar between those with and without parental CHD.[16,17,31] However, childhood dyslipidemia at extreme levels (LDL-C above 95th percentile and/or HDL-C below 5th percentile) was associated with higher prevalence of parental CHD.[12-15] Such associations reflect the familial aggregation of dyslipidemia and related CHD in the first degree adult relatives.[13,15,32-34] The current longitudinal observations indicate that the trend of adverse patterns in LDL-C and triglycerides in the offspring with parental CHD is more accentuated in adulthood than during childhood, probably reflecting the burden of various genes and lifestyle-related factors with age.

In the present study, body fatness and measures of glucose homeostasis (fasting insulin and glucose) were independent predictors of adverse changes over time in the lipoprotein variables in the offspring. These effects were noted irrespective of the status of parental CHD. Of particular interest is the finding that the association between parental CHD and changes in VLDL-C and triglycerides in the offspring disappeared when adjusted for body fatness, insulin, and/or glucose. Likewise, parental CHD was no longer a predictor of adverse changes in LDL-C in the offspring when adjusted for glucose. This suggests that parental history is just one more explanatory variable that loses its partial contribution to lipoprotein profiles in their offspring when adjusted for other strongly interrelated contributory variables. These observations are in accordance with the

Table 3. Independent Correlates of Longitudinal Changes of Lipoprotein Variables in the Study Cohort: The Bogalusa Heart Study

	Model 1[a]		Model 2[b]		Model 3[c]		Model 4[d]	
	β*	95% CI	β	95% CI	β	95% CI	β	95% CI
LDL-C (mg/dL)								
Parental CHD	10.1	−1.18 to 21.39	11.80	0.74 to 22.86	8.99	−4.84 to 22.83	−2.45	−44.21 to 39.25
Parental CHD × age	−1.34	−2.57 to −0.11†	−1.68	−2.88 to −0.47‡	−1.17	−2.69 to 0.34	−0.03	−3.92 to 3.87
Parental CHD × age^2	0.05	0.02 to 0.08‡	0.06	0.02 to 0.88‡	0.04	0.00 to 0.08†	0.01	−0.08 to 0.10
BMI	—	—	1.66	1.44 to 1.88‡	1.50	1.24 to 1.76‡	1.65	1.34 to 1.96‡
Insulin	—	—	—	—	0.14	0.05 to 0.23‡	0.14	0.03 to 0.25†
Glucose	—	—	—	—	—	—	−0.03	−0.10 to 0.04
Triglyceride (mg/dL)								
Parental CHD	12.28	−12.59 to 37.15	13.78	−10.68 to 38.22	23.39	1.16 to 45.63	11.24	−24.30 to 46.79
Parental CHD × age	0.75	0.02 to 1.48†	0.59	−0.14 to 1.32	−0.08	−0.76 to 0.59	0.47	−0.79 to 1.72
BMI	—	—	3.66	3.02 to 4.28‡	2.92	2.37 to 3.47‡	2.34	1.72 to 2.97‡
Insulin	—	—	—	—	0.91	0.70 to 1.13‡	0.65	0.41 to 0.89‡
Glucose	—	—	—	—	—	—	1.19	1.03 to 1.35‡
VLDL-C (mg/dL)								
Parental CHD	1.42	0.41 to 2.43†	0.79	−0.18 to 1.75	0.86	−0.18 to 1.90	0.46	−0.70 to 1.62
Parental CHD × age	0.40	−0.05 to 0.13	0.03	−0.05 to 0.12	−0.02	−0.12 to 0.08	−0.07	−0.26 to 0.13
BMI	—	—	0.63	0.56 to 0.71‡	0.54	0.45 to 0.63	0.51	0.40 to 0.61‡
Insulin	—	—	—	—	0.1	0.07 to 0.23	0.01	0.06 to 0.14‡
Glucose	—	—	—	—	—	—	0.09	0.07 to 0.12‡
HDL-C (mg/dL)								
Parental CHD	3.06	−0.66 to 6.79	3.27	−0.41 to 6.95	1.23	−3.31 to 5.77	3.12	−5.15 to 11.38
Parental CHD × age	−0.16	−0.33 to 0.02	−0.12	−0.29 to 0.06	−0.04	−0.25 to 0.16	−0.12	−0.49 to 0.24
BMI	—	—	−0.89	−1.04 to −0.73‡	−0.67	−0.84 to −0.49‡	−0.66	−0.85 to −0.47‡
Insulin	—	—	—	—	−0.20	−0.26 to −0.13‡	−0.18	−0.25 to −0.11‡
Glucose	—	—	—	—	—	—	0.01	−0.05 to 0.05

* GEE regression coefficient. † $P < .05$; ‡ $P < .01$.

Abbreviation: 95% CI, 95% confidence interval.

[a] Model 1: Parental CHD × race, sex, age, or age^2 interaction.

[b] Model 2: Model 1 + BMI as independent.

[c] Model 3: Model 2 + insulin as independent.

[d] Model 4: Model 3 + glucose as independent.

known interrelationship, based on both clinical and epidemiologic studies, between body fatness, measures of glucose homeostasis, and lipoproteins.[35-42]

The more apparent associations of abnormal LDL-C and triglycerides in the offspring with parental CHD during adulthood suggest that excess body fatness and alterations in measures of glucose homeostasis while beginning in childhood are increasing in individuals with genetic predisposition to CHD. Earlier analyses in this cohort revealed that in the offspring with parental CHD the only significant risk factor in childhood was relative overweight.[16] Since childhood obesity persists into adulthood,[43-47] controlling obesity in early life may be a prudent preventive approach to limiting cardiovascular risk later in life.

Parental history of CHD is recommended as a powerful marker for identifying children with dyslipidemia and cardiovascular risk, as might be expected.[48] However, studies including the present one, indicated that parental history alone is not sufficient at the relatively young age of children. Their parents generally are too young to manifest CHD.[15,16,48,49] It should be noted that the lack of verification of negative parental history of CHD and the low occurrence in parents at a young age are limitations of the current study. Associations at an older age of offspring are to be expected. With regards to this specific study an incomplete case ascertainment, however, generally reduces rather than increases the risk estimate.

In summary, the association between parental CHD and longitudinal adverse trends in lipoprotein variables during childhood and adulthood are dependent on age, body fatness, and measures of glucose homeostasis. Information on these risk variables in conjunction with parental (or family) history of CHD may enhance the potential of evaluating CHD risk assessment in youth.

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