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ORIGINAL RESEARCH

Sex-Specific Parental Effects on Offspring Lipid Levels

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***Background*—**Plasma lipid levels are highly heritable traits, but known genetic loci can only explain a small portion of their heritability.

***Methods and Results*—**In this study, we analyzed the role of parental levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TGs) in explaining the values of the corresponding traits in adult offspring. We also evaluated the contribution of nongenetic factors that influence lipid traits (age, body mass index, smoking, medications, and menopause) alone and in combination with variability at the genetic loci known to associate with TC, LDL-C, HDL-C, and TG levels. We performed comparisons among different sex-specific regression models in 416 families from the Framingham Heart Study and 304 from the SardiNIA cohort. Models including parental lipid levels explain significantly more of the trait variation than models without these measures, explaining up to ≈39% of the total trait variation. Of this variation, the parent-of-origin effect explains as much as ≈15% and it does so in a sex-specific way. This observation is not owing to shared environment, given that spouse-pair correlations were negligible (<1.5% explained variation in all cases) and is distinct from previous genetic and acquired factors that are known to influence serum lipid levels.

***Conclusions*—**These findings support the concept that unknown genetic and epigenetic contributors are responsible for most of the heritable component of the plasma lipid phenotype, and that, at present, the clinical utility of knowing age-matched parental lipid levels in assessing risk of dyslipidemia supersedes individual locus effects. Our results support the clinical utility of knowing parental lipid levels in assessing future risk of dyslipidemia. **(*J Am Heart Assoc*. 2015;4:e001951 doi: 10.1161/JAHA.115.001951)**

Key Words: cholesterol • genetics • lipids • risk factors • sex

Lipid levels are highly heritable traits, with estimates of 46% to 77% for total cholesterol (TC), 22% to 48% for triglycerides (TGs), 34% to 72% for low-density lipoprotein cholesterol (LDL-C), and 37% to 82% for high-density lipoprotein cholesterol (HDL-C).[1–3] However, despite the recent improvements in technology and several large-scale genome-wide association (GWA) studies on this topic, the majority of the genetic contribution to lipid trait variation is still unexplained.[1,3–11] For example, a meta-analysis of cohorts including the Framingham Heart Study (FHS) was only able to explain 10% to 12% of total heritability in lipid concentrations when combining up to 95 relevant loci.[11] Several explanations have been proposed for the missing heritability of traits, such as lipid levels, including gene-gene and gene-environment interactions, rare variants not detected in the large GWA studies, or epigenetic influences not assessed in traditional genetic studies.[10,12,13] Based on previous observations that maternal environment influences cardiovascular (CV) outcomes in adult offspring,[14–20] that genetic associations could be sex-specific,[3] and that parent-of-origin effects (POE) influence several traits in animal models,[21–26] we hypothesized that (1) parental lipid traits explain a significant amount of the offspring lipid variation that is not accounted for by known genetic variants and (2) the effects of parental lipid traits are sex-specific.[3]

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An accompanying Tables S1 through S16 is available at http://jaha.ahajournals.org/content/4/7/e001951/suppl/DC1

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To test our hypotheses, we assessed the parent-offspring relationship of lipids in trios from 2 large, well-characterized cohorts: the FHS Offspring cohort and the SardiNIA cohort. Both studies include subjects of European ancestry and contain data from multiple generations.

Methods

Study Participants

The FHS is a prospective cohort originally designed to assess the epidemiology of CV disease (CVD).[27,28] Data have been collected from 3 generations of participants since its inception in 1948. The original cohort involved 5209 participants, 5124 were enrolled in the second generation starting in 1971, and 4095 in the third generation starting in 2002.[27,28]

Our analysis included participants from the second and third generations of the FHS for whom serum TC, TG, LDL-C (calculated using the Friedewald equation: LDL-C=TC-HDL−(TG/5)) and HDL-C were available for both generations.[29] To limit confounding of results by relatedness, we only considered the oldest offspring for each nuclear family, creating parent-offspring trios. The final study population consisted of 416 trios, with 228 females and 188 males in the offspring generation.

The SardiNIA study is a longitudinal study designed to assess the epidemiology and genetics of aging-associated conditions.[30] The study enrolled 6921 volunteers from a cluster of 4 towns on the east coast of Sardinia and represents a collection of large pedigrees, containing data from up to 5 generations. From each pedigree, we only considered parents and their oldest offspring from the 2 most recent generations.

The SardiNIA cohort had 304 families that were included in the analyses. Because this cohort included several families with only a single parent enrolled, analyses were performed on 277 mothers, 151 fathers, 168 daughters, and 136 sons. This study population included 124 complete parent-offspring trios.

For both cohorts, families in which any member had a TG level >400 mg/dL were excluded. Only individuals with at least 2 of the 4 lipid traits available were included in the analysis.

The study was approved by the institutional review boards at Vanderbilt University, Boston University, Dartmouth College, the National Institutes of Health, and the local ethical committee of Lanusei, Sardinia, in Italy. All of the included FHS and SardiNIA participants provided written informed consent, including consent to use of their DNA data in genetic analyses. For both cohorts, false paternity was assessed by genetics data management groups and the parental information was adjusted accordingly before release of data and therefore not considered in the current study.

Assessment of Risk Factors

Participants of the Framingham cohort are routinely followed up, permitting access to clinical phenotype data at multiple time points. We used first patient visit data for the offspring population, because at the time of the study only 1 visit was available for this generation.

For the parental population of the FHS, analyses were performed on values from visit 3 only, given that it had the largest number of individuals with available lipid data. The other phenotypes relevant to our study were age, body mass index (BMI), smoking status, use of lipid-lowering medications (ever treated vs. never treated), as well as the menopausal status in females. These phenotypes were used as covariates for both the offspring and parental populations. For the offspring population, we used the first adult patient visit, providing a direct adult to adult comparison.

In SardiNIA, we analyzed the same phenotypes and covariates from visit 1 in the parental and offspring population, given that both provided the largest number of patients with available lipid data.

Statistical Analysis

POE on offspring lipid traits

We examined the POE on the variation of fasting lipids in the offspring populations. To identify transmission effects, we performed a series of nested, sex-stratified linear regression analyses, modeling lipid traits in offspring. The models were generated by sequentially changing the variables included; namely, all offspring covariates and corresponding parental lipid traits (Figure – Panel A). We report the adjusted R^2 values throughout, which represent the proportion of variation explained by each model with all variables included in a given model.

The models assessed, also reported in Figure – Panel A, were the following:

$$\text{Model 1: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Corresponding Parental Lipid Trait})$$

$$\text{Model 2: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Offspring Covariate}_1) + \ldots + \beta_n(\text{Offspring Covariate}_n)$$

$$\text{Model 3: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Offspring Covariate}_1) + \ldots + \beta_n(\text{Offspring Covariate}_n) + \beta_{n+1}(\text{Corresponding Parental Lipid Trait})$$

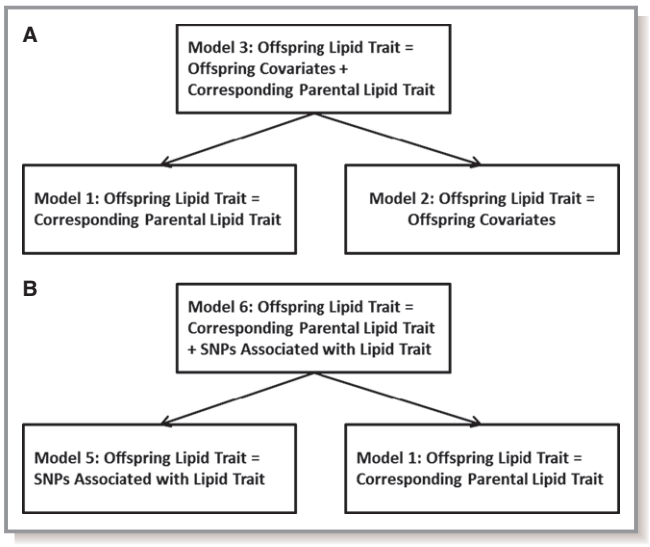

Figure. Flowchart of nested models used to determine parent of origin effects on offspring lipid traits. Parent of origin effects and relevant covariates (A) and parent of origin effects combined with SNPs previously associated with lipid traits (B). SNPs indicate single-nucleotide polymorphisms.

The summary of all analyses modeling offspring lipid traits, including the assessment of the effect of parental covariates, is provided in the Supplemental Materials (Table S1).

To evaluate the performance of each model, we compared the adjusted R^2 values for each lipid trait model using a likelihood ratio test. Pair-wise model comparisons were carried out for nested pairs, namely, Model 3 versus Model 1 (effect of offspring covariates) and Model 3 versus Model 2 (effect of parental lipid trait).

Estimating environmental effects

To estimate the effects of shared environment on lipid traits, we modeled each maternal lipid trait with the corresponding paternal lipid trait under the assumption that shared environment would be revealed by large R^2 in this regression model (Model 4).

The following model was used for all parents in the trio families and then separately stratified by the sex of their offspring, to mirror the analysis above:

$$\text{Model 4: Maternal Lipid Trait} = \beta_0 + \beta_1(\text{Corresponding Paternal Lipid Trait})$$

Additional models for the effects of maternal and paternal covariates on the adjusted R^2 produced by Model 4 are reported in Table S2.

To assess the role of early environment on lipid profiles, we compared sibling lipids in families with more than 1 offspring. Specifically, we determined the variance explained in same sex versus different sex sibling pairs.

Genetic contribution to POE

To examine whether the effects of parental lipid traits are explained by genetic variants in offspring, we analyzed the effects of the 95 previously validated single-nucleotide variants (SNPs) from Teslovich et al.[11] on the corresponding lipid levels.

To assess the dependence of offspring lipid traits on SNPs previously associated with each lipid trait, we performed nested, sex-stratified linear regression models and compared them to the variance explained only by the corresponding parental lipid traits (Figure – Panel B).

In the Framingham cohort, genotyping was performed using the 500K Affymetrix Genechip, and many of the Teslovich SNPs were not included. We therefore used proxy variants based on high linkage disequilibrium (LD) in European populations (CEU and TSI) from phase 3 of the International HapMap Project.[31–33] For each nongenotyped SNP, we chose a variant on the same chromosome in strong LD (r^2>0.75), having the highest minor allele frequency (list of SNPs used can be found in Table S3). Only 63 of the 95 SNPs were available either through direct genotyping or as proxies.

In contrast, in the SardiNIA cohort, genotyping information was available from 4 different Illumina arrays, one of which, Cardio-MetaboChip, included the majority of the Teslovich SNPs (Pistis et al.[34]). Overall, in the SardiNIA cohort, 92 of the 95 SNPs reported in Teslovich et al. were available and analyzed (Table S3). In addition, to make all analyses directly comparable between the 2 cohorts, we also evaluated the same subset of 63 SNPs, original and proxies, as in the Framingham cohort. To further assess the effects of using proxies, as opposed to the original Teslovich SNPs, in SardiNIA we also considered models using only the original 63 Teslovich SNPs for which we had either direct genotype data or proxies available in the Framingham cohort (Table S3).

We only used the subset of SNPs previously associated with each lipid trait phenotype (Table S3).

$$\text{Model 5: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Tesl. SNP}_1) + \ldots + \beta_n(\text{Tesl. SNP}_n)$$

$$\text{Model 1: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Corresponding Parental Lipid Trait})$$

$$\text{Model 6: Offspring Lipid Trait} = \beta_0 + \beta_1(\text{Tesl. SNP}_1) + \ldots + \beta_n(\text{Tesl. SNP}_n) + \beta_{n+1}(\text{Corresponding Parental Lipid Trait})$$

Because genotypes were not available for all participants, the number of observations in Model 1 included in this

comparison differs from the one above (Tables 7 and 8 vs. Tables 3 and 4, respectively). Analyses adding offspring covariates and using the other SNP sets for the SardiNIA cohort were also performed.

Effect sizes and potential redundancy among the influence of known genes and parental lipid trait measures were evaluated by comparing the results of likelihood ratio tests of Model 6 versus Model 1 (effect of offspring SNPs) and Model 6 versus Model 5 (effect of parental lipid trait).

All analyses were conducted using STATA (11.1; StataCorp LP, College Station, TX) and R software (R Foundation for Statistical Computing, Vienna, Austria). Two-sided *P* values are reported throughout.

Results

Population Characteristics

Summary statistics of lipid traits and covariates for participants are listed in Tables 1, 2, and S4, S5.

Of note, in the FHS, lipid trait measures from the offspring generation were ascertained at a younger age (mean 39.0 for daughters, 39.4 for sons) than those for parents (mean 46.4 for mothers, 48.7 for fathers). Comparisons between generations show that TC and LDL-C levels were higher in fathers than sons and higher in mothers than daughters ($P<0.001$ for all), whereas HDL was higher in sons than fathers ($P<0.001$). All comparisons are presented in Tables 1 and S4. Comparisons within each generation showed that males have higher TC, TG, and LDL, but lower HDL levels, than women. The difference between sex was statistically significant for all traits ($P<0.003$), except for TC in the parents ($P=0.06$).

In the SardiNIA cohort, lipid trait measures from offspring were ascertained at a younger age (mean 29.3 for daughters, 28.8 for sons) than those for their parents (mean 55.9 for mothers, 58.4 for fathers) (Table 2). Comparisons between generations showed that TC, TG, and LDL levels were higher in fathers than sons and higher in mothers than daughters ($P<0.002$ for all). HDL was significantly higher in fathers compared to sons ($P<0.001$) (Tables 1 and S5). Similarly, mothers had higher HDL compared to daughters, although not significantly. Comparisons within generations in the SardiNIA cohort showed that TG were higher in fathers than mothers ($P<0.001$); HDL was significantly higher in mothers compared to fathers, as well as daughters compared to sons ($P<0.001$ for both).

Parent of Origin Effects on Offspring Lipid Traits

In the FHS, models including only parental lipid traits (Model 1) explained between ≈1% and 5% of offspring variability in 7 trait combinations and more than 5% in 9 others. The highest proportion of explained variance was ≈10% for mother-son HDL (Table 3; Model 1). Maternal lipids explained at least 5% of the variation in TC, LDL, and HDL of the offspring for both sex. In general, maternal lipid values provided more information regarding offspring values than did paternal values (Table 3).

For comparison, the variation of offspring lipid traits explained by all offspring covariates was more than 5% in all 16 models. The highest proportion of variability explained was ≈15% for LDL of daughters (Model 2). When both parental lipid traits and offspring covariates were used in a single model, the explained variation ranged from ≈9% (father-son LDL) to ≈19% (father-son HDL) (Model 3). Importantly, adding

Table 1. Population Characteristics of the Framingham Heart Study Participants

	Generation 2				Generation 3			
Lipid Traits and Risk Factors	n	Females*	n	Males*	n	Females*	n	Males*
Total cholesterol	416	208.81 (41.06)	416	213.76 (34.47)	228	182.73 (30.46)	188	192.29 (35.46)
Triglycerides	416	91.32 (52.57)	416	124.55 (66.49)	228	89.07 (43.51)	188	121.40 (65.55)
LDL	413	132.43 (38.34)	416	144.23 (66.49)	228	105.19 (29.27)	188	119.43 (32.40)
HDL	413	58.28 (14.15)	416	44.62 (10.39)	228	59.73 (14.38)	188	48.58 (13.02)
Age	416	46.45 (7.48)	416	48.72 (7.67)	228	39.05 (7.45)	188	39.39 (7.56)
BMI	413	24.83 (4.93)	414	27.14 (3.30)	226	25.52 (5.58)	188	27.97 (4.71)
Anticholesterol treatment	416	5 (1.20)	416	7 (1.68)	228	5 (2.19)	188	17 (9.04)
Smoking status	415	96 (23.13)	416	91 (21.88)	228	94 (41.23)	188	61 (32.45)
Menopause	416	159 (38.22)			228	24 (10.53)		

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Mean (SD) for continuous variables, n (% total) for categorical variables.

Table 2. Population Characteristics of the SardiNIA Cohort

	Generation 2				Generation 3			
Lipid Traits and Risk Factors	n	Females*	n	Males*	n	Females*	n	Males*
Total cholesterol	277	221.90 (39.40)	151	223.13 (41.56)	168	194.43 (37.83)	136	188.54 (46.68)
Triglycerides	277	85.26 (50.44)	147	105.57 (60.87)	168	71.92 (40.14)	135	82.17 (49.91)
LDL	277	136.51 (34.28)	147	140.76 (34.98)	168	113.41 (29.86)	135	116.55 (37.99)
HDL	277	68.34 (16.05)	151	59.38 (13.23)	168	66.63 (16.29)	136	54.49 (11.83)
Age	277	55.94 (11.41)	151	58.40 (10.71)	168	29.26 (10.41)	136	28.80 (9.67)
BMI	277	27.22 (5.03)	151	27.98 (3.88)	168	22.28 (3.28)	136	24.49 (3.89)
Anticholesterol treatment	277	0	151	1 (0.06)	168	0	136	0
Smoking status	277	29 (10.47)	151	44 (29.14)	168	34 (20.24)	136	51 (37.50)
Menopause	277	175 (63.18)			168	9 (5.36)		

BMI indicates body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Mean (SD) for continuous variables, n (% total) for categorical variables.

parental lipid trait values to a model containing offspring covariates significantly increased the amount of variation explained for TC, LDL, and HDL in all parent offspring pairs (Table 3, *P* values M3/M2).

The amount of variation explained in TG models for fathers-daughters was significant, whereas all other TG parent-offspring pairs were below the significance level. This indicates that the effects of parental lipid traits and offspring covariates are significant and independent of one another, with the exception of TG measures. Parental covariates explained less of offspring lipid variability than either offspring covariates or parental lipids as can be seen by comparison of models 2, 3, S1, and S2 (Table S6).

In SardiNIA, models of offspring lipid traits using only corresponding parental lipid traits explained between 0.01% and 5% of in 6 models and more than 5% in 9 others. One

Table 3. Estimating the Parent of Origin Effects on Lipid Traits in the Framingham Heart Study

		Adjusted R^2			Likelihood Ratio Tests	
Parent-Offspring Pair	Modeled Lipid Trait	Model 1	Model 2	Model 3	*P* Value M3/M1	*P* Value M3/M2
Mothers daughters	TC (n=223)	0.0789	0.1188	0.1469	<0.001	0.004
	TG (n=223)	0.022	0.1137	0.1237	<0.001	0.059
	LDL (n=222)	0.0808	0.1307	0.1723	<0.001	<0.001
	HDL (n=222)	0.0691	0.1183	0.167	<0.001	<0.001
Fathers-daughters	TC (n=224)	0.0335	0.1314	0.1472	<0.001	0.024
	TG (n=224)	0.0207	0.1163	0.1295	<0.001	0.036
	LDL (n=224)	0.0547	0.1469	0.1722	<0.001	0.005
	HDL (n=224)	0.0762	0.1147	0.1648	<0.001	<0.001
Mothers-sons	TC (n=187)	0.0552	0.0676	0.114	0.004	0.001
	TG (n=187)	0.0182	0.1066	0.1175	<0.001	0.068
	LDL (n=185)	0.0588	0.0661	0.1247	0.002	<0.001
	HDL (n=185)	0.0963	0.1291	0.1808	<0.001	<0.001
Fathers-sons	TC (n=188)	0.0172	0.0688	0.0932	<0.001	0.014
	TG (n=188)	0.029	0.11	0.1206	<0.001	0.070
	LDL (n=188)	0.0098	0.0696	0.0884	<0.001	0.027
	HDL (n=188)	0.0784	0.1307	0.1862	<0.001	<0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

model explained less than 0.01% of the variability (TG for fathers-daughters). The highest proportion of variability explained was ≈15% for mother-son LDL (Table 4; Model 1). As in the FHS, maternal lipid traits in SardiNIA explained at least 5% of the corresponding variation for TC, LDL, and HDL of both sons and daughters and generally performed better than paternal models.

The variation of offspring lipid traits explained by offspring covariates alone was between 0.01% and 5% in 4 models and more than 5% in 12 models (Model 2). The highest proportion of variability explained was ≈36% for TC of sons (Model 2). When both parental lipid traits and offspring covariates were used in the same model, 1 model explained marginal variability (<0.01%), 1 model explained between 0.01% and 5%, and 14 models explained more than 5%. The highest proportion of variability explained was ≈39% for father-son TC (Model 3). Adding parental lipid trait values to a model containing offspring covariates explained TC significantly better when modeling sons' levels with fathers' or mothers' (Table 4, *P* values M3/M2), whereas results for daughters trended in the same direction. With the exception of fathers-sons, adding parental HDL or LDL values to Model 2 significantly improved all parent-offspring pair models (Table 4).

Maternal TG levels explained significantly more of daughters' TG, but had no effect on the other parent-offspring pairs (Table 4). As with the Framingham results, parental covariates generally explained less of the offspring lipid variability than either offspring covariates or parental lipids, as can be seen by comparison of models 2, 3, S1, and S2 (Table S7).

Environmental Effects

In the FHS, the variation of maternal lipid traits explained by the corresponding paternal lipid traits ranged from negligible (<0.01%) for TG to ≈1% for TC and LDL (Table 5). In SardiNIA, the percentage of maternal lipid traits explained by corresponding paternal lipid traits ranged from negligible (<0.01%) for TG to ≈1% for TC, LDL, and HDL (Table 6; Supplementary Results). Both results indicate that shared adult environments do not significantly impact our findings.

In the SardiNIA cohort, when only parents of daughters were considered, paternal lipid traits explained up to 2.5% of variation for HDL. When only parents of sons were considered, paternal lipid traits explained up to 2.5% of LDL variation (Table 6). These results indicate that the shared environment of parents explains very little of lipid trait variation in the unrelated parent pairs, and suggest that the effects of

Table 4. Estimating the Parent of Origin Effects on Lipid Traits in the SardiNIA Cohort

Parent-Offspring Pair	Modeled Lipid Trait	Adjusted R^2			Likelihood Ratio Tests	
		Model 1	Model 2	Model 3	*P* Value M3/M1	*P* Value M3/M2
Mothers-daughters	TC (n=152)	0.051	0.159	0.171	<0.001	0.071
	TG (n=152)	0.045	0.107	0.126	0.002	0.038
	LDL (n=152)	0.067	0.129	0.164	<0.001	0.007
	HDL (n=152)	0.102	0.053	0.157	0.008	<0.001
Fathers-daughters	TC (n=86)	0.020	0.066	0.087	0.035	0.083
	TG (n=84)	<0.001	0.002	<0.001	0.358	0.866
	LDL (n=84)	0.114	0.030	0.193	0.017	<0.001
	HDL (n=86)	0.078	0.062	0.121	0.079	0.010
Mothers-sons	TC (n=125)	0.145	0.312	0.362	<0.001	0.001
	TG (n=125)	0.024	0.188	0.185	<0.001	0.442
	LDL (n=125)	0.147	0.308	0.385	<0.001	<0.001
	HDL (n=125)	0.056	0.045	0.079	0.107	0.019
Fathers-sons	TC (n=65)	0.066	0.361	0.388	<0.001	0.050
	TG (n=63)	0.008	0.123	0.130	0.010	0.218
	LDL (n=63)	0.007	0.277	0.289	<0.001	0.144
	HDL (n=65)	0.037	0.010	0.032	0.414	0.111

The overall numbers of parents used for this analysis are lower than the numbers used in estimating parent of origin effects in Table 2 because, unlike the Framingham Heart Study, the SardiNIA cohort is comprised of more single-parent families and, consequently, fewer complete trios. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

Table 5. Estimating the Effects of Shared Environment in the Framingham Heart Study

Modeled Maternal Lipid Trait	Adjusted R^2 From Modeling With Corresponding Paternal Lipid Trait					
	n	All	n	Parents of Daughters Only	n	Parents of Sons Only
TC	416	0.014	223	0.027	187	<0.001
TG	416	<0.001	223	<0.001	187	<0.001
LDL	413	0.012	222	0.032	185	<0.001
HDL	413	0.005	222	0.004	185	0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

parental lipids on offspring are linked to factors unrelated to the shared environment.

When only parents of daughters were considered, paternal lipid traits explained between 0.02% and 3% of maternal TG and LDL, respectively. When only parents of sons were considered, paternal lipid traits only explained ≈0.1% of maternal HDL variation, with negligible variation explained for all other lipid traits (Table 5). Using maternal lipid traits to model corresponding paternal lipid traits, produced similar results to using paternal lipid traits to model maternal traits when covariates were included (Tables S8 and S9).

The role of shared early environment was also assessed by comparing variance explained for each lipid trait values in siblings of the same to those of the opposite sex. Variance explained between siblings of the same sex ranged between 5% and 12% for females and between 0.5% and 6% for males, whereas between offspring of opposite sex the results were generally smaller (0% to 5%). This supports the conclusion that the results between parents and offspring are not attributable to shared environment (Table S10).

Table 6. Estimating the Effects of Shared Environment in the SardiNIA Cohort

Modeled Maternal Lipid Trait	Adjusted R^2 From Modeling With Corresponding Paternal Lipid Trait					
	n	All	n	Parents of Daughters Only	n	Parents of Sons Only
TC	126	0.014	72	0.003	54	0.013
TG	123	<0.001	70	<0.001	53	<0.001
LDL	123	0.010	70	<0.001	53	0.025
HDL	126	0.012	72	0.025	54	<0.001

HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglycerides.

Genetic Contribution to the POE

In the FHS, SNPs previously associated with each lipid trait explained a negligible amount of variability (<0.01%) in 2 models, between 0.01% and 5% in 8 models, and more than 5% in 6 models, the highest being ≈10% for daughters' TG (Table 7; Model 5). In the offspring with available genotype data (a subset of individuals from Model 1), parental lipid traits explained between 0.01% and 5% of variability in 8 models and more than 5% in 8 models, the highest being ≈10% for sons' HDL with paternal measures (Table 7; Model 1). Adding parental lipid values to the model containing all SNPs produced significantly better models in explaining TC, LDL, and HDL in all parent-offspring pairs, except fathers-sons, where only the HDL model was significantly improved (Table 7, *P* values M6/M5). Conversely, adding all SNPs to models containing parental lipid values significantly improved HDL in the mothers-sons model and all models of TGs, with the exception of the fathers-sons comparison (Table 7, *P* values M6/M1).

In SardiNIA, models with the 92 SNPs previously associated with lipid traits (Table 8) resulted in negligible percent variance explained (<0.01%) in 8 of the 16 models (Table 8; Model 5). Four models explained between 0.01% and 5%, and 4 explained more than 5%, with the highest percentage being ≈30% for HDL in mother-son pairs (Model 5). In the subset of offspring with available genotype data, the variation of offspring measures explained by parental lipid traits only was negligible for 2 models (sons' and daughters' TG with paternal levels) (Model 1). Parental lipid traits explained between 0.01% and 5% in 4 models, and greater than 5% in 10 models, the highest being ≈16% for sons' TC with maternal levels (Table 8; Model 1). Adding parental lipid values to the model containing all SNPs significantly improved the models for TC, LDL, and HDL in mother-daughter and father-daughter models, for all lipid traits in mother-son models, and for TC and HDL in father-son models (Table 8, *P* values M6/M5). Adding all SNPs to a model containing parental lipid values produced significant results for HDL in mother-daughter models, for TC and HDL in father-daughter models, for HDL in mother-son models, and for TC, TG, and HDL in father-son models (Table 8, *P* values M6/M1). These results were generally consistent when the alternative SNP sets were used; namely, the subset of 63 original and proxy SNPs from the Framingham analysis, and also when all nonproxy 63 SNPs (Tables S11 through S16).

Discussion

We investigated how parental serum levels of TC, TG, LDL, and HDL can be used to model lipid traits of the offspring, using sex-stratified analyses. We also compared the effect of

Table 7. Comparing Lipid Trait Relevant SNPs to Parent of Origin Effects in the Framingham Heart Study

Parent-Offspring Pair	Modeled Lipid Trait	Adjusted R^2			Likelihood Ratio Tests	
		Model 5	Model 1	Model 6	*P* Value M6/M5	*P* Value M6/M1
Mothers-daughters	TC (n=186)	0.005	0.079	0.089	<0.001	0.237
	TG (n=186)	0.102	0.023	0.111	0.091	0.008
	LDL (n=185)	0.024	0.091	0.125	<0.001	0.094
	HDL (n=184)	<0.001	0.095	0.107	<0.001	0.216
Fathers-daughters	TC (n=186)	0.005	0.015	0.023	0.033	0.261
	TG (n=186)	0.102	0.017	0.105	0.182	0.008
	LDL (n=186)	0.025	0.036	0.077	0.001	0.076
	HDL (n=185)	<0.001	0.101	0.068	<0.001	0.101
Mothers-sons	TC (n=153)	0.039	0.064	0.079	0.006	0.199
	TG (n=153)	0.079	0.013	0.074	0.607	0.050
	LDL (n=152)	0.003	0.068	0.064	0.001	0.404
	HDL (n=152)	0.061	0.091	0.166	<0.001	0.025
Fathers-sons	TC (n=153)	0.040	0.004	0.040	0.251	0.116
	TG (n=153)	0.079	0.020	0.080	0.249	0.052
	LDL (n=153)	0.007	0.003	0.019	0.087	0.236
	HDL (n=151)	0.064	0.104	0.155	<0.001	0.059

For models 5 and 6, there are 4 original, 25 proxy for TC; 4 original, 17 proxy for TG; 3 original, 15 proxy for LDL; 5 original, 25 proxy for HDL. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; SNP, single-nucleotide polymorphism; TC, total cholesterol; TG, triglycerides.

Table 8. Comparing Lipid Trait Relevant SNPs to Parent of Origin Effects in the SardiNIA Cohort

Parent-Offspring Pair	Modeled Lipid Trait	Adjusted R^2			Likelihood Ratio Tests	
		Model 5	Model 1	Model 6	*P* Value M6/M5	*P* Value M6/M1
Mothers-daughters	TC (n=133)	0.037	0.055	0.069	0.015	0.100
	TG (n=133)	<0.001	0.046	<0.001	0.063	0.740
	LDL (n=133)	0.061	0.081	0.102	0.007	0.158
	HDL (n=133)	0.041	0.072	0.158	<0.001	0.014
Fathers-daughters	TC (n=78)	0.054	0.007	0.153	0.001	0.001
	TG (n=76)	<0.001	<0.001	<0.001	0.686	0.455
	LDL (n=76)	<0.001	0.095	0.068	0.008	0.168
	HDL (n=78)	0.003	0.077	0.163	<0.001	0.003
Mothers-sons	TC (n=109)	<0.001	0.169	0.059	<0.001	0.494
	TG (n=109)	<0.001	0.032	0.022	0.038	0.240
	LDL (n=109)	<0.001	0.152	0.119	<0.001	0.403
	HDL (n=109)	0.304	0.069	0.353	0.002	<0.001
Fathers-sons	TC (n=60)	<0.001	0.062	<0.001	0.001	0.006
	TG (n=59)	0.151	<0.001	0.138	0.253	0.004
	LDL (n=59)	<0.001	<0.001	<0.001	0.383	0.681
	HDL (n=60)	0.009	0.057	0.198	<0.001	<0.001

For models 5 and 6, there are 51 SNPs for TC, 32 SNPs for TG, 37 SNPs for LDL, and 47 SNPs for HDL. HDL indicates high-density lipoprotein; LDL, low-density lipoprotein; SNP, single-nucleotide polymorphism; TC, total cholesterol; TG, triglycerides.

parental lipids with that of known and validated genetic variants in loci previously associated with plasma lipid levels.[11] These analyses were performed in 2 well-characterized and large prospective cohorts, the FHS (inclusive of Offspring and Generation 3 cohorts) and the SardiNIA Study.

The most important finding from our study is that, in general, parental serum lipid levels explain a higher proportion of variability in the offspring than do the 95 loci described in the work by Teslovich et al.[11] This effect was not owing to shared environment and was independent of nongenetic factors known to modulate lipid levels. These results were generally consistent between the Framingham and SardiNIA cohorts (Tables 3 through 8). Given the independence from other variables and from the currently known genetic loci, these results suggest the presence of unknown variants or mechanisms responsible for the missing heritability of lipid traits[12,13] and serve to emphasize the size of the gap in our knowledge of factors that affect lipid levels. However, because we do not yet have an understanding of these other determinants, we argue that parental lipid levels explain those of adult offspring better than do the validated variants in 95 genes. Thus, knowledge of parental lipid levels provides information to predict future lipid levels in the offspring and should be used as a tool to target pediatric lipid testing.

With the exception of Mendelian forms of dyslipidemia, serum lipids are complex traits influenced by multiple genetic and nongenetic factors. Therefore, the use of single-gene variants is of little utility in the prediction of this complex phenotype. To date, GWA studies have identified risk loci that have high statistical significance, but low biological effect sizes, and such markers are not generally practical for predictive purposes.[35–38] As a consequence, genetics-based predictions using multilocus modeling thus far provide marginal clinical utility in prevention because they have low predictive power.[35,39] The value of a genetic test depends on several factors, including the number of genes influencing the trait, frequency of the associating allele, and strength of association between genotype and phenotype, making accurate predictions from simple models extremely difficult.[35] In contrast, the results of our study show that family history and nongenetic covariates better explain lipid levels in adult offspring than does variation in the loci known to influence lipids across study populations. Our findings are in agreement with what has been shown in other complex phenotypes, such as type II diabetes, where risk scores not including genetic variant data were virtually identical to those incorporating validated genes for type II diabetes risk.[37,38] Similar results were also found in a previous study where a gene-based score did not significantly improve the association between canonical risk factors and CVD.[39] Recently, 62 additional lipid-associated loci were identified, but their effects were small, explaining <2% of the total phenotype variance and therefore should not substantially impact our conclusions.[40] Furthermore, we demonstrate the existence of parent-of-origin effects on lipid levels, which are sex-specific and likely owing to both genetic and epigenetic factors. Such effects have been shown to modulate some of the risk factors for dyslipidemia. For example, a recent GWA study has demonstrated parent-of-origin effects in the degree to which SNPs in 2 genes, *SLC2A10* and *KCNK9*, affect BMI, a major factor affecting lipids. These SNPs showed "polar overdominance," where homozygotes of either SNP had the same average BMI, whereas heterozygotes differed as a function of parent of origin.[41]

We also found that maternal traits generally explain more of the offspring's TC, HDL, and LDL. Maternal lipid traits explained at least 5% of the offspring variability in TC, HDL, and LDL of both sons and daughters in both cohorts. Paternal traits were less consistent, given that their effects ranged from nonsignificant in multiple traits to relatively high in explaining the daughter's LDL and HDL (5% to 8% of explained variability in Framingham and 7% to 11% in SardiNIA). The finding of stronger maternal influences on offspring lipid traits is consistent with epidemiological data demonstrating that maternal lifestyle and environment (such as nutritional status, stress level, insulin resistance, diabetes, hypertension, hypercholesterolemia, obesity, and smoking), both at time of conception and during pregnancy, influence the offspring's phenotypes, such as adiposity, blood pressure, fatty streak formation, or diabetes.[15,17,42–50] This is consistent with the Barker hypothesis, that is, that early exposure, both pre- and postnatal, can affect risk of adult-onset disease.[51,52]

Interestingly, small or nonexistent parent-of-origin effects were generally observed for TG (Tables 3 and 4). TGs also provided the most variable results when using genetic models (Tables 5 and 6). TG levels have a smaller parent-of-origin effect than the other lipid traits, and a bigger part of their heritability may be determined by other factors, such as rare variants. It has been recently demonstrated that rare APOC3 mutations have a strong influence on plasma TG levels in aggregate.[53,54]

Our study has several limitations. Although we were able to identify models that account for a significant portion of lipid variation explained, we were not able to provide a mechanism for this effect. We can only speculate that our observations may forecast discovery of additional genes, gene-gene interactions, or epigenetic effects that regulate lipid levels. Furthermore, in our analyses, we did not account for specific environmental variables, such as diet, alcohol, exercise, socioeconomic status, and use of specific medications. However, it is of note that the 2 cohorts we studied would be expected to have different environmental exposures and the results were still mostly concordant. This discrepancy is not likely to have influenced the results, and it would have had

an attenuating effect even if it did. Both cohorts are prospective studies analyzing populations of European ancestry, but Framingham's residents are from multiple European origins, whereas the participants in SardiNIA are part of a genetic isolate. This may be the basis for the minor discrepancies we observed (seen in Tables 3 through 6). Dietary habits were not directly quantified and, consequently, were not represented in our models in either cohort, although BMI and lipid medication covariates can be considered partial proxies for diet and lifestyle. However, the similarities of results between cohorts provide additional strength to our main claim.

In conclusion, we have determined that parent-of-origin effects explain more variability in the adult offspring's lipid levels than do common variants in the loci known to modulate lipid metabolism. Knowledge of the parent's lipid levels may provide an inexpensive and practical means to predict future lipid levels in their children.

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Disclosures

None.

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