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ORIGINAL RESEARCH

Twenty-Five Year Secular Trends in Lipids and Modifiable Risk Factors in a Population-Based Biracial Cohort: The Coronary Artery Risk Development in Young Adults (CARDIA) Study, 1985–2011

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***Background*—**Cross-sectional analyses suggest that total and low-density lipoprotein cholesterol (LDL-c) trends that had been declining are now reversing. We examined longitudinal data from the Coronary Artery Risk Development in Young Adults (CARDIA) study to examine secular trends in total cholesterol, LDL-c, high-density lipoprotein cholesterol (HDL-c), and triglycerides over 25 years. We also assessed whether modifiable lifestyle factors (body mass index, physical activity, alcohol consumption, smoking, and lipid-lowering medications) are associated with these trends.

***Methods and Results*—**CARDIA recruited 5115 black and white men and women ages 18 to 30 years from 4 US communities in 1985–1986, and re-examined them 5, 10, 15, 20, and 25 years later. Secular trends, modeled as age-matched time trends, were estimated using repeated-measures regression stratified on race and sex. Total cholesterol and LDL-c initially decreased ≈5 to 8 mg/dL between visits before plateauing and moving toward adverse trends in all groups, except black women, by year 25. HDL-c showed an upward secular trend of 1 to 3 mg/dL between visits starting at year 15 in all groups; triglyceride trends were largely flat. Obesity and use of lipid-lowering medications, which both increased over follow-up, had strong independent, but opposite, associations with lipid trends over time. In aggregate, associations of modifiable lifestyle factors counterbalanced one another, minimally influencing secular trends.

***Conclusions*—**Over 25 years, initially favorable trends in total cholesterol and LDL-c have leveled off and may be reversing, persisting after control for modifiable risk factors. Factors such as dietary changes over 25 years and poor adherence to medications are candidates for additional investigation. **(*J Am Heart Assoc*. 2016;5:e003384 doi: 10.1161/JAHA.116.003384)**

Key Words: epidemiology • lipids • population • risk factor

Elevated levels of total cholesterol, low-density lipoprotein cholesterol (LDL-c), and triglycerides and low levels of high-density lipoprotein cholesterol (HDL-c) have been linked with cardiovascular disease morbidity and mortality in numerous population-based and clinical studies.[1–4] Individuals with elevated lipid values have high relative risk of future cardiovascular events and often benefit from antihyperlipidemic medication therapy. Individuals with only mildly elevated lipid levels have lower relative risks, but comprise the majority of abnormal values; these individuals may respond to lifestyle modification and therefore offer opportunities for primary prevention.

Secular trend data based on serial cross-sectional data from the National Health and Nutrition Examination Survey (NHANES) have suggested that total and LDL-c levels have declined in most race/ethnic and sex groups over the past 20 years.[5] These favorable trends in total and LDL-c have been replicated in many Western countries during the same time period, whereas trends in HDL-c and triglycerides have exhibited less-consistent patterns. A recent report by Carroll et al.,[6] extending NHANES data through 2010, suggests that favorable trends continue among most subgroups, regardless of lipid-lowering medication status. Other serial cross-sectional data suggest that the favorable secular trends have either flattened out or are reversing.[7–9]

However, longitudinal data, as opposed to serial cross-sectional data, allow for a better understanding of the effects of both time and aging while accounting for changes in potential correlates, such as obesity on lipid profiles. Given the strong association of adverse lipid levels with

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cardiovascular disease morbidity and mortality, we used data from the community-based Coronary Artery Risk Development in Young Adults (CARDIA) study to examine secular and aging trends in total cholesterol, LDL-c, HDL-c, and triglycerides over 25 years of follow-up in a fixed biracial cohort of men and women who were 18 to 30 years old at baseline. We also assessed whether the observed lipid trends were confounded by modifiable risk factors—body mass index (BMI), physical activity, ethanol consumption, and smoking—after controlling for age, education, and study center. Our goal was to identify risk factors that may have attenuated observed favorable lipid trends or contributed to adverse lipid trends in a cohort that has moved from young adulthood to middle age during the obesity epidemic.

Methods

Study Population

Participants for this study were from the CARDIA study, a multicenter, longitudinal study of the development of cardiovascular risk factors in black and white adults ages 18 to 30 years in 1985–1986 recruited from 4 US cities: Birmingham, Alabama; Chicago, Illinois; Minneapolis, Minnesota; and Oakland, California. The CARDIA study cohort included 5115 participants free of cardiovascular disease at baseline recruited to be balanced within each center on race, sex, age, and education.[10] Follow-up examinations were conducted 2, 5, 7, 10, 15, 20, and 25 years after baseline with response rates of 91%, 86%, 81%, 79%, 74%, 72%, and 72% of the surviving cohort, respectively. Data for the current study are based on participants attending examinations that were 5 years apart: year 0 (baseline), year 5, year 10, year 15, year 20, and year 25 examinations. The CARDIA study was approved by the institutional review boards of the coordinating center and the 4 participating field centers, and written informed consent was obtained from participants at all examinations.

Measurements

Age and race were self-reported using standardized questionnaires, as were years of education completed, use of cholesterol-lowering medication, smoking status (current, former, or never), and ethanol consumption in milliliters per day based on the quantity and type of alcoholic beverages consumed. BMI was calculated as weight in kilograms divided by height in meters squared. Physical activity was estimated from an interviewer-administered questionnaire based on the amount of moderate and heavy physical activity performed during the past year[11]—a score of 300 exercise units (EU) is roughly equivalent to 150 minutes of moderate physical activity per week, or five 30-minute sessions.[12] Diet was only assessed at years 0, 7, and 20 in CARDIA, with saturated fat intake and total caloric intake derived from an interviewer-administered diet history questionnaire developed for the CARDIA study.[13]

All participants were asked to fast for 12 hours before each clinic visit. Serum and plasma blood samples were drawn from the antecubital vein and stored at −70°C until analyzed. Plasma total cholesterol, HDL-c, and triglyceride levels were measured using enzymatic methods[14]; HDL-c levels were measured after dextran-sulfate-magnesium precipitation of other lipoproteins.[15] LDL-c levels were estimated with the Friedewald equation for individuals with fasting triglyceride values less than 400 mg/dL.[16] Extensive quality control has been implemented by CARDIA to reduce variability in longitudinal laboratory data; the test-retest correlation for total cholesterol, HDL-c, LDL-c, and triglycerides was 0.98 to 0.99.[17]

Statistical Analyses

Means and frequencies of covariates of interest were obtained at time points modeled as class variables corresponding with clinic visits conducted 5 years apart—years 0, 5, 10, 15, 20, and 25. Repeated-measures regression was performed on fixed effects models using a Toeplitz covariance structure and stratified by race and sex. Whereas the age ranges across all 6 exams considered here do not completely overlap, sensitivity analyses showed little difference when analyses were limited to subsamples with overlapping age ranges longitudinally; therefore, we retained the 5-year interval approach. All available data were included at each time point under the assumption that missing data were missing at random.

Mean secular trends in lipids were generated by adjusting crude values at each time point with age. Specifically, time was modeled as a class variable and current age was modeled continuously using a quadratic fit. We assumed no birth cohort effect given the narrow age range of the cohort. By treating time as a homogenous variable at each clinic visit and age continuously, the period and age effects are algebraically separated. Therefore, the period effect was considered an age-matched time trend, comparing mean levels in groups of people who achieved a given age at 1 calendar time to the mean levels in groups who achieved the same age at a different calendar time. The period effect was then modeled as a calendar time trend in these age-matched values.[18]

Multivariable longitudinal models were further adjusted for clinic site, education, BMI, physical activity, smoking status, amount of alcohol consumed, and antihyperlipidemic medication use. Though these covariates were included at each categorical time point, interactions of covariates with time

were not consistently statistically significantly associated with different lipid outcomes. Therefore, all covariate adjustment in these models represents pooled averages across time. When we included dietary saturated fat and total caloric intake in additional multivariable-adjusted models to assess confounding of the secular trend data, we observed no changes in secular trends in lipids by these dietary factors. We therefore chose not to include diet in our analyses.

Interactions of time with race and sex were examined as additive interaction terms based on differences we observed in mean levels of lipids for these groups. Both interactions were statistically significant for all lipid outcomes, so we consequently presented analyses stratified by both race and sex. All analyses were 2-sided with a type 1 error of 0.05 considered as statistically significant. Analyses were conducted using SAS software (v.9.3; SAS Institute, Inc., Cary, NC).

Results

Table 1 shows means and frequencies of population demographics across time. Mean age at year 0 was 24.8 years and increased to 50.2 years at year 25. Mean BMI increased over time from 24.5 to 30.2 kg/m^2; educational attainment increased as well. Physical activity decreased with time, and prevalence of current smoking also was less common at year 25 compared to year 0, decreasing from 30.4% to 17.1%. Alcohol use decreased from year 0 to year 5 and then remained relatively stable through year 25. White participants and women were slightly more likely to attend exams after year 0. Use of antihyperlipidemic medications also increased over time in all race-sex groups, with no reported use of these medications at baseline when the cohort was ages 18 to 30 years and between 10% and 20% using these medications by year 25. Men were more likely to be using lipid-lowering medications, with white men reporting the highest use by year 25 (20.0%).

Unadjusted mean lipid values across follow-up are presented stratified by race and sex in Figure 1. Total cholesterol tended to increase in all groups, whereas triglycerides consistently increased in all race and sex groups with some evidence of plateauing by year 25, and LDL-c remained relatively constant across time. HDL-c also exhibited a mostly flat trend across time, with all 4 race-sex groups showing an increase in years 20 and 25 that exceeded baseline values.

Secular trends—time trends adjusted for aging—for lipids are presented by race and sex in Figure 2. Compared to the unadjusted means presented in Figure 1, secular trends in total cholesterol decreased over the 25 years of follow-up, largely in the period from 1985 to 1995 (year 0 to year 10), with the suggestion of an upward trend between years 20 and 25 in all except black women. Similar trends were observed for LDL-c. Controlling for age had little effect on HDL-c trends, whereas the increasing mean triglyceride trends observed in the crude data were attenuated with control for age, particularly among blacks; whites, particularly women, exhib-

Table 1. Means (SD) and Frequencies of Selected Demographic Characteristics Over 25 Years of Follow-up: the CARDIA Study, 1985–2011

	Year 0	Year 5	Year 10	Year 15	Year 20	Year 25
N (range)*	5034 to 5115	4302 to 4352	3838 to 3944	3605 to 3672	3467 to 3549	3478 to 3497
Age, y	24.8±3.7	30.0±3.6	35.0±3.7	40.2±3.6	45.2±3.6	50.2±3.6
BMI, kg/m^2	24.5±5.0	26.1±5.9	27.5±6.5	28.8±6.8	29.4±7.0	30.2±7.2
Education, yr	13.8±2.3	14.4±2.4	14.7±3.2	14.9±2.5	15.0±2.6	15.1±2.7
Physical activity (EU)	420.2±300.7	379.4±292.5	331.0±275.0	347.3±283.6	335.9±274.1	337.9±275.7
Alcohol, mL/day	12.1±21.9	11.2±25.6	10.9±22.1	11.0±24.9	10.8±22.2	11.7±23.4
Current smokers (%)	30.4	28.6	25.6	22.0	19.4	17.1
Former smokers (%)	13.3	14.1	16.5	18.1	19.4	21.8
White (%)	48.5	51.3	51.3	52.9	53.5	53.1
Men (%)	45.5	45.0	44.5	44.1	43.3	43.4
Lipid-lowering medication use (%)						
Black men	0	0	0.5	2.4	8.5	15.6
Black women	0	0.2	0.2	1.4	7.7	17.2
White men	0	0.4	0.6	4.8	15.0	20.0
White women	0	0.4	0.7	1.3	4.9	10.4

*N varies because of small numbers of missing values for the demographic data. BMI indicates body mass index; EU, exercise units.

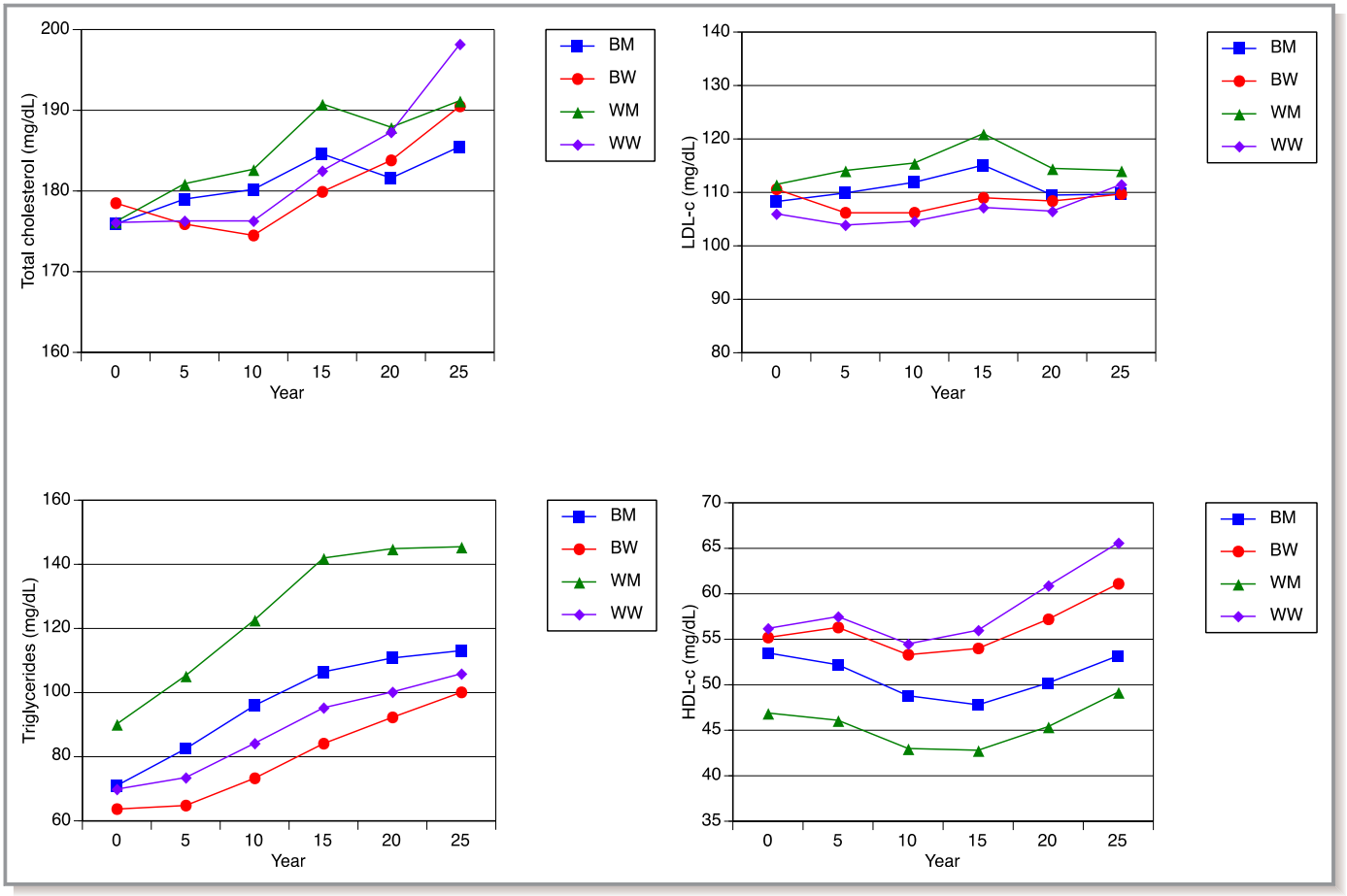

Figure 1. Unadjusted mean plasma lipid values by race and sex across 25 years of follow-up: the CARDIA study, 1985–2011. BM indicates black men; BW, black women; CARDIA, Coronary Artery Risk Development in Young Adults; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; WM, white men; WW, white women.

ited increasing trends in triglycerides for both crude and age-adjusted models.

Table 2 shows mean changes in lipids for men by race in 5-year intervals from baseline after controlling for age, education, and clinic site (model 1) and modifiable lifestyle factors (model 2). Multivariable-adjusted secular trends differed by race (P interaction <0.05 for time×race for all lipids; results not shown). LDL-c decreased across most time periods, from −7.3 mg/dL in black men between years 0 and 5 to 0.67 mg/dL in white men between years 20 and 25, with smaller decreases in white men compared to black men, consistent with the age-adjusted trends shown in Figure 2. The decline in LDL-c ended after year 20, with no statistically significant differences between years 20 and 25 for either race group.

Whereas other risk factors, such as smoking status, were inconsistently associated with LDL-c in each race group, BMI was one of the strongest predictors of increases in LDL-c levels independent of secular trend. Obesity, here modeled as BMI ≥30 kg/m^2 pooled across time, was associated with a 7.74-mg/dL increase in LDL-c over 25 years among black men and a 2.41-mg/dL increase among white men compared to being overweight or normal weight. Use of antihyperlipidemic medications was associated with large decreases in mean LDL-c over time; however, after including medications and modifiable lifestyle factors, the secular trends changed minimally, as reflected in the modest differences in the point estimates for the 5-year changes in lipids between models 1 and 2. In aggregate, the positive and inverse associations of the modifiable lifestyle factors examined counterbalanced each other, leading to the modest changes described above. Total cholesterol mirrored the trends observed for LDL-c.

Declines in HDL-c levels were observed early in follow-up with increases in the later examination years, reflecting the nonlinear patterns observed in the crude and age-adjusted figures. After controlling for lifestyle and demographic factors, the HDL-c trends across time were not uniformly statistically significant in either race group but reflected the trends observed in model 1. Similar to the LDL-c and total cholesterol findings, the risk factor most strongly associated

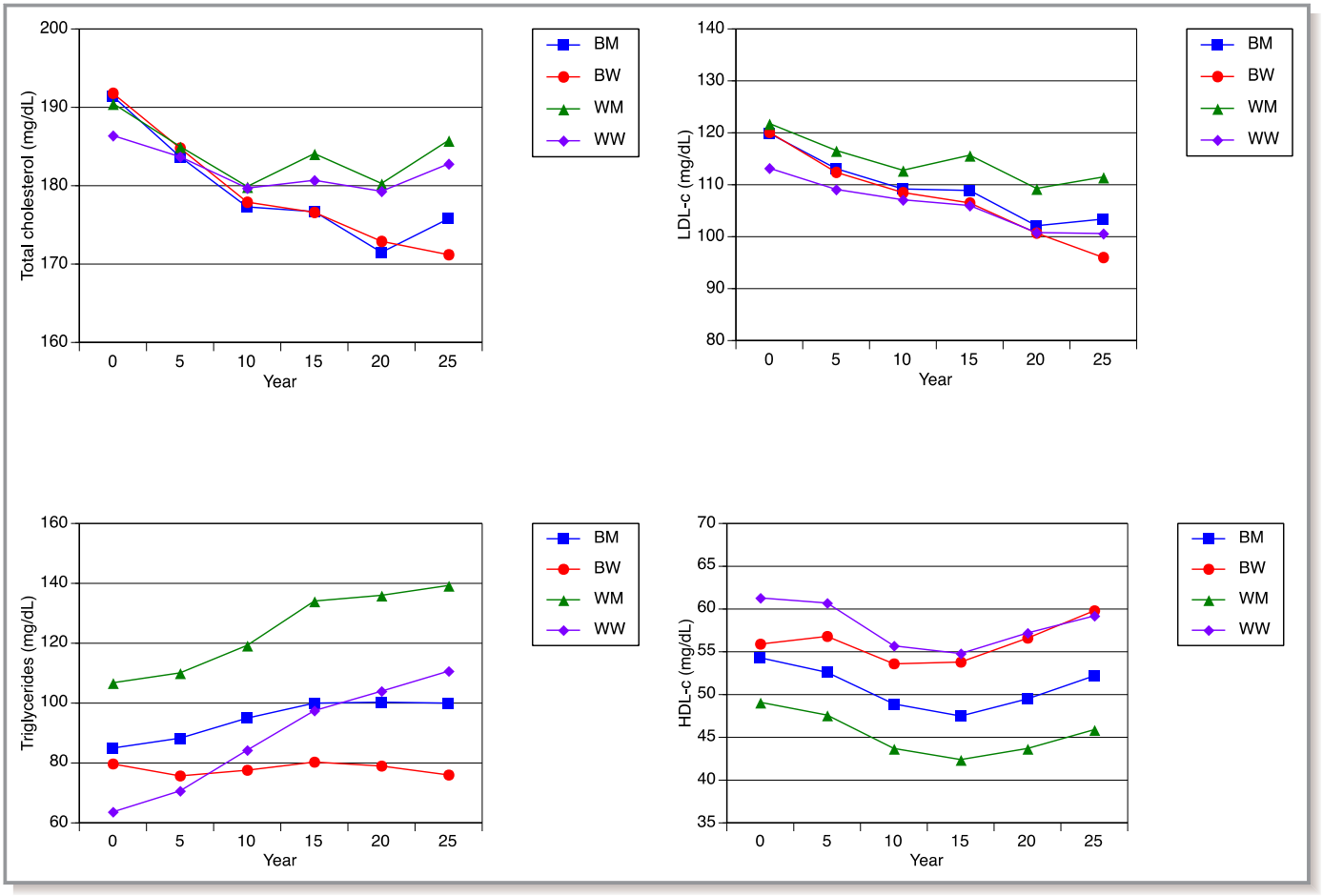

Figure 2. Secular trends in mean plasma lipid values by race and sex across 25 years of follow-up after adjusting for age (age+age^2): the CARDIA study, 1985–2011. BM indicates black men; BW, black women; CARDIA, Coronary Artery Risk Development in Young Adults; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; WM, white men; WW, white women.

with HDL-c levels was obesity, accounting for 5.5 and 4.6 mg/dL over 25 years in black men and white men, respectively. Despite these strong independent associations of obesity with HDL-c levels, the secular changes between examinations were minimally altered by modifiable lifestyle factors, as observed for total cholesterol and LDL-c. In addition, antihyperlipidemic medication use was not statistically significantly associated with HDL-c in men.

Unlike the other three lipids, triglycerides displayed essentially no secular trends in black men and white men before or after adding modifiable risk factors to the models. Obesity again was associated with the largest increases in triglycerides relative to nonobese participants, accounting for increases over 25 years of 29.3 mg/dL in black men and 45.8 mg/dL in white men. Physical activity, modeled as at or above the sex-specific 75th percentile compared with below the 75th percentile, was modestly and inversely associated with mean triglyceride levels over time, with a decrease of 5.2 mg/dL in black men and 9.1 mg/dL in white men. Current smoking status pooled over 25 years was associated with 6.2 and 12.1 mg/dL higher triglycerides compared to never smokers in black and white men, respectively.

Table 3 repeats the analyses presented in Table 2 for women. As with men, the interactions of time×race were statistically significant for all lipids. The largest mean LDL-c decreases were observed in black women, and obesity was strongly associated with LDL-c trends for both race groups (a 7.24 mg/dL increase among black women and a 9.61 mg/dL increase among white women). Total cholesterol trends were similar to LDL-c trends.

Consistent with men, HDL-c trends for women in both race groups were nonlinear, increasing in the later years of follow-up to 2.97 and 2.39 mg/dL in black women and white women, respectively, between years 20 and 25. Physical activity was associated with modest, but statistically significantly higher, HDL-c as was observed in men; however, current cigarette smoking was associated with lower HDL-c levels in women only. Once again, obesity accounted for large declines in HDL-c: 6.8 and 8.4 mg/dL decreases over 25 years in black women and white women, respectively.

Table 2. Changes in Plasma Lipid Levels (in mg/dL) Among Men in 5-Year Intervals Over 25 Years of Follow-up, Adjusted for Age, Education, and Clinic Site (Model 1) Plus Modifiable Lifestyle Factors (Model 2), by Race Group: the CARDIA Study, 1985–2011

	Black Men/Model 1	Black Men/Model 2	White Men/Model 1	White Men/Model 2
LDL-c				
CARDIA exams				
Year 5 to Year 0	−6.54 (−9.34, −3.73)*	−7.30 (−10.09, −4.51)*	−5.53 (−8.23, −2.83)*	−5.44 (−8.16, −2.71)*
Year 10 to Year 5	−3.23 (−0.25, −6.21)*	−4.13 (−7.06, −1.20)*	−3.95 (−6.82, −1.09)*	−4.68 (−7.49, −1.88)*
Year 15 to Year 10	0.14 (−2.95, 3.22)	−1.22 (−4.25, 1.80)	2.60 (−0.30, 5.51)	2.63 (−0.22, 5.47)
Year 20 to Year 15	−6.35 (−3.12, −9.57)*	−6.08 (−9.25, −2.90)*	−6.58 (−9.56, −3.59)*	−4.83 (−7.75, −1.91)*
Year 25 to Year 20	1.71 (−1.63, 5.05)	1.49 (−1.77, 4.76)	2.12 (−1.00, 5.25)	0.67 (−2.35, 3.69)
BMI (≥30 vs <30 kg/m^2)		7.74 (5.67, 9.81)*		2.41 (0.37, 4.46)*
Physical activity (≥75th percentile vs <75th percentile)†		−0.73 (−2.32, 0.86)		−1.48 (−2.98, 0.020)
Current vs never smokers		−7.64 (−10.08, −5.19)*		2.62 (−0.11, 5.36)
Former vs never smokers		−2.84 (−5.63, −0.048)*		0.44 (−2.03, 2.91)
Alcohol (yes/no)		−1.74 (−3.36, −0.11)*		0.026 (−1.56, 1.61)
Antihyperlipidemic medications (yes/no)		−31.0 (−34.6, −27.4)*		−44.2 (−47.0, −41.5)*
HDL-c				
CARDIA exams				
Year 5 to Year 0	−1.84 (−3.06, −0.62)*	−1.15 (−0.025, 2.32)	−1.38 (−2.40, −0.37)*	−1.03 (−2.01, −0.045)*
Year 10 to Year 5	−3.93 (−5.18, −2.67)*	−3.33 (−4.55, −2.11)*	−3.82 (−4.85, −2.78)*	−3.59 (−4.59, −2.60)*
Year 15 to Year 10	−1.48 (−2.78, −0.18)*	−0.89 (−2.15, 0.37)	−1.09 (−2.13, −0.043)*	−0.81 (−1.82, 0.19)
Year 20 to Year 15	1.94 (0.57, 3.30)*	2.20 (0.87, 3.52)*	1.51 (0.45, 2.58)*	1.70 (0.67, 2.73)*
Year 25 to Year 20	2.72 (1.31, 4.13)*	2.89 (1.52, 4.26)*	2.45 (1.35, 3.54)*	2.71 (1.65, 3.77)*
BMI (≥30 vs <30 kg/m^2)		−5.53 (−6.42, −4.65)*		−4.64 (−5.33, −3.95)*
Physical activity (≥75th percentile vs <75th percentile)†		1.00 (0.30, 1.69)*		1.42 (0.92, 1.93)*
Current vs never smokers		0.23 (−0.81, 1.27)		−2.41 (−3.37, −1.46)*
Former vs never smokers		−0.91 (−2.12, 0.29)		−0.35 (−1.20, 0.50)
Alcohol (yes/no)		4.10 (3.39, 4.80)*		3.01 (2.48, 3.55)*
Antihyperlipidemic medications (yes/no)		−0.052 (−1.61, 1.51)		0.47 (−0.45, 1.38)
Total cholesterol				
CARDIA exams				
Year 5 to Year 0	−7.35 (−10.40, −4.31)*	−7.71 (−10.77, −4.65)*	−5.82 (−8.85, −2.80)*	−5.70 (−8.75, −2.66)*
Year 10 to Year 5	−6.07 (−9.29, −2.85)*	−6.57 (−9.76, −3.37)*	−5.32 (−8.55, −2.10)*	−5.95 (−9.11, −2.80)*
Year 15 to Year 10	−0.16 (−3.50, 3.17)	−1.23 (−4.53, 2.07)	4.07 (0.81, 7.32)*	4.09 (0.91, 7.28)*
Year 20 to Year 15	−4.89 (−8.38, −1.40)*	−4.49 (−7.96, −1.03)*	−3.84 (−7.19, −0.50)*	−2.08 (−5.35, 1.19)
Year 25 to Year 20	4.79 (1.17, 8.42)*	4.54 (0.97, 8.11)*	5.21 (1.72, 8.71)*	3.70 (0.31, 7.09)*
BMI (≥30 vs <30 kg/m^2)		7.65 (5.37, 9.92)*		4.98 (2.72, 7.25)*
Physical activity (≥75th percentile vs <75th percentile)†		−0.86 (−2.62, 0.91)		−1.56 (−3.24, 0.12)

Continued

Table 2. Continued

	Black Men/Model 1	Black Men/Model 2	White Men/Model 1	White Men/Model 2
Current vs never smokers		−6.34 (−9.03, −3.66)*		2.76 (−0.30, 5.81)
Former vs never smokers		−2.62 (−5.70, 0.47)		1.95 (−0.80, 4.69)
Alcohol (yes/no)		2.48 (0.68, 4.28)*		3.29 (1.52, 5.06)*
Antihyperlipidemic medications (yes/no)		−32.8 (−36.8, −28.8)*		−46.2 (−49.2, −43.1)*
Triglycerides				
CARDIA exams				
Year 5 to Year 0	3.57 (−1.97, 9.11)	2.07 (−3.47, 7.61)	2.40 (−7.00, 11.76)	0.46 (−9.68, 8.75)
Year 10 to Year 5	6.84 (0.83, 12.84)*	6.21 (0.27, 12.15)*	7.77 (−2.33, 17.88)	6.71 (−3.28, 16.69)
Year 15 to Year 10	5.09 (−1.16, 11.33)	3.51 (−2.65, 9.67)	13.7 (3.46, 23.9)*	11.3 (1.23, 21.4)*
Year 20 to Year 15	−0.03 (−6.69, 6.63)	−0.45 (−7.06, 6.16)	0.70 (−9.79, 11.19)	−0.62 (−11.04, 9.79)
Year 25 to Year 20	0.49 (−6.53, 7.50)	−0.29 (−7.25, 6.66)	1.43 (−9.61, 12.47)	−1.39 (−12.37, 9.60)
BMI (≥30 vs <30 kg/m^2)		29.3 (24.7, 34.0)*		45.8 (38.2, 53.5)*
Physical activity (≥75th percentile vs <75th percentile)[†]		−5.21 (−9.01, −1.41)*		−9.09 (−14.81, −3.37)*
Current vs never smokers		6.16 (1.05, 11.27)*		12.1 (2.43, 21.86)*
Former vs never smokers		4.09 (−2.20, 10.37)		10.6 (1.76, 19.42)*
Alcohol (yes/no)		2.25 (−1.55, 6.05)		1.58 (−4.42, 7.57)
Antihyperlipidemic medications (yes/no)		−5.10 (−14.00, 3.81)		−18.2 (−29.1, −7.44)*

Model 1: adjusted for age, age^2, center, and education. Model 2: model 1 plus the other variables listed. BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.
*Statistically significant at $P<0.05$.
[†]75th percentile of exercise is 620 exercise units in men.

Triglyceride levels differed the most between sexes. As observed in men, there were essentially flat trends in black women before or after adding modifiable risk factors to the models; in white women, after year 5 (ages 23–35 years), small, but statistically significant, increases in triglycerides relative to each previous time window were observed. This trend in white women existed despite their lower mean BMI relative to the other groups at every time point (ranging from 23.1 to 28.1 kg/m^2 across time). Obesity again was associated with the largest increases in triglycerides relative to nonobese participants, accounting for 12.8- and 39.8-mg/dL increases over 25 years in black women and white women, respectively, after accounting for the time and aging trends. Physical activity was also not associated with triglyceride trends for white women, while statistically significant for black women.

Discussion

We have found that the initially favorable age-matched trends in total cholesterol and LDL-c values from 1985 to 2011 have slowed and show signs of leveling off or even worsening in a cohort of young healthy adults initially free of cardiovascular disease. These trends were largely unaffected by controlling for modifiable lifestyle factors. Secular trends were similar for blacks, whites, men, and women with the exception of black women, whose favorable lipid levels did not yet appear to be reversing. This is in contrast to results reported by Bild et al.[19] for the first 7 years of follow-up in CARDIA that showed more-pronounced favorable trends in the same cohort.

Secular trends in HDL-c generally improved in the cohort after a period of decline during early middle age, but triglycerides exhibited unfavorable upward secular trends in white women and relatively flat trends for blacks and white men between 1985 and 2011. Whereas modifiable lifestyle factors, such as alcohol consumption, cigarette smoking, and physical activity, were modestly associated with overall lipid trends, increases in obesity prevalence adversely affected lipid levels in all race-sex groups. The lack of confounding of the age-matched time associations with lipids suggests that other factors, such as physical activity and moderate alcohol

Table 3. Changes in Plasma Lipid Levels (in mg/dL) Among Women in 5-Year Intervals Over 25 Years of Follow-up, Adjusted for Age, Education, and Clinic Site (Model 1) Plus Modifiable Lifestyle Factors (Model 2), by Race Group: the CARDIA Study, 1985–2011

	Black Women/Model 1	Black Women/Model 2	White Women/Model 1	White Women/Model 2
LDL-c				
CARDIA exams				
Year 5 to Year 0	−7.66 (−9.93, −5.40)*	−7.87 (−10.15, −5.59)*	−4.29 (−6.72, −1.85)*	−4.83 (−7.25, −2.41)*
Year 10 to Year 5	−3.69 (−6.06, −1.32)*	−4.18 (−6.53, −1.83)*	−2.46 (−4.94, 0.017)	−3.10 (−5.53, −0.67)*
Year 15 to Year 10	−1.80 (−4.24, 0.63)	−2.32 (−4.74, 0.099)	−1.56 (−4.07, 0.94)	−2.70 (−5.16, −0.24)*
Year 20 to Year 15	−5.89 (−8.36, −3.42)*	−5.25 (−7.71, −2.80)*	−5.62 (−8.20, −3.05)*	−4.73 (−7.25, −2.21)*
Year 25 to Year 20	−4.53 (−7.08, −1.97)*	−3.18 (−5.73, −0.64)*	−0.39 (−3.08, 2.31)	−0.18 (−2.82, −2.45)
BMI (≥30 vs <30 kg/m^2)		7.24 (5.72, 8.76)*		9.61 (7.79, 11.44)*
Physical activity (≥75th percentile vs <75th percentile)†		−1.24 (−2.64, 0.17)		−1.22 (−2.45, 0.0044)
Current vs never smokers		−0.46 (−2.64, 1.72)		4.94 (2.63, 7.25)*
Former vs never smokers		−0.10 (−2.44, 2.25)		1.28 (−0.69, 3.25)
Alcohol (yes/no)		−3.10 (−4.39, −1.81)*		−2.58 (−3.88, −1.28)*
Antihyperlipidemic medications (yes/no)		−28.5 (−31.4, −25.4)*		−37.2 (−40.5, −33.8)*
HDL-c				
CARDIA exams				
Year 5 to Year 0	0.87 (−0.17, 1.92)	1.34 (0.33, 2.35)*	−0.65 (−1.86, 0.55)	0.39 (−0.75, 1.54)
Year 10 to Year 5	−3.26 (−4.29, −2.17)*	−3.17 (−4.19, −2.14)*	−4.95 (−6.17, −3.73)*	−4.41 (−5.57, −3.26)*
Year 15 to Year 10	0.39 (−0.69, 1.48)	0.31 (−0.74, 1.36)	−0.83 (−2.06, 0.40)	−0.51 (−1.68, 0.66)
Year 20 to Year 15	2.75 (1.65, 3.85)*	2.57 (1.50, 3.64)*	2.57 (1.30, 3.83)*	2.65 (1.46, 3.85)*
Year 25 to Year 20	3.27 (2.12, 4.41)*	2.97 (1.86, 4.09)*	2.12 (0.80, 3.43)*	2.39 (1.14, 3.64)*
BMI (≥30 vs <30 kg/m^2)		−6.83 (−7.52, −6.14)*		−8.44 (−9.32, −7.56)*
Physical activity (≥75th percentile vs <75th percentile)†		1.13 (0.48, 1.77)*		1.55 (0.96, 2.14)*
Current vs never smokers		−2.78 (−3.75, −1.81)*		−2.95 (−4.06, −1.85)*
Former vs never smokers		−0.59 (−1.64, 0.46)		−0.26 (−1.20, 0.68)
Alcohol (yes/no)		3.25 (2.66, 3.84)*		3.44 (2.82, 4.06)*
Antihyperlipidemic medications (yes/no)		−0.35 (−1.65, 0.95)		−1.06 (−2.64, 0.52)
Total cholesterol				
CARDIA exams				
Year 5 to Year 0	−6.91 (−9.36, −4.46)*	−6.64 (−9.13, −4.15)*	−3.01 (−5.67, −0.36)*	−2.77 (−5.43, −0.11)*
Year 10 to Year 5	−6.62 (−9.19, −4.04)*	−6.93 (−9.52, −4.35)*	−4.46 (−7.17, −1.75)*	−5.03 (−7.71, −2.36)*
Year 15 to Year 10	−0.96 (−3.60, 1.69)	−1.51 (−4.17, 1.15)	0.44 (−2.30, 3.19)	−0.94 (−3.66, 1.77)
Year 20 to Year 15	−3.74 (−6.42, −1.05)*	−3.26 (−5.95, −0.56)*	−1.84 (−4.67, 0.98)	−0.87 (−3.66, 1.92)
Year 25 to Year 20	−1.66 (−4.44, 1.12)	−0.51 (−3.31, 2.30)	3.19 (0.23, 6.16)*	3.18 (0.26, 6.10)*
BMI (≥30 vs <30 kg/m^2)		2.84 (1.15, 4.52)*		8.43 (6.36, 10.50)*

Continued

Table 3. Continued

	Black Women/Model 1	Black Women/Model 2	White Women/Model 1	White Women/Model 2
Physical activity (≥75th percentile vs <75th percentile)†		−0.91 (−2.48, 0.65)		0.52 (−0.88, 1.92)
Current vs never smokers		−1.11 (−3.51, 1.29)		4.06 (1.48, 6.64)*
Former vs never smokers		0.11 (−2.47, 2.70)		1.13 (−1.07, 3.33)
Alcohol (yes/no)		0.53 (−0.91, 1.96)		0.73 (−0.75, 2.20)
Antihyperlipidemic medications (yes/no)		−28.2 (−31.5, −25.0)*		−36.6 (−40.4, −32.9)*
Triglycerides				
CARDIA exams				
Year 5 to Year 0	−3.17 (−6.78, 0.45)	−2.79 (−6.38, 0.79)	6.30 (1.43, 11.16)*	4.79 (0.081, 9.49)*
Year 10 to Year 5	1.55 (−2.66, 5.77)	2.49 (−1.72, 6.69)	12.5 (7.57, 17.5)*	10.1 (5.36, 14.8)*
Year 15 to Year 10	2.88 (−1.46, 7.23)	3.49 (−0.86, 7.84)	12.1 (7.04, 17.1)*	9.42 (4.63, 14.20)*
Year 20 to Year 15	−0.52 (−4.97, 3.93)	−0.16 (−4.63, 4.31)	5.19 (0.0071, 10.36)*	5.24 (0.29, 10.20)*
Year 25 to Year 20	−2.69 (−7.35, 1.96)	−2.18 (−6.90, 2.54)	5.62 (0.15, 11.09)*	3.17 (−2.08, 8.43)
BMI (≥30 vs <30 kg/m^2)		12.8 (9.92, 15.6)*		39.8 (35.9, 43.7)*
Physical activity (≥75th percentile vs <75th percentile)†		−5.43 (−8.06, −2.81)*		0.88 (−1.84, 3.60)
Current vs never smokers		12.4 (8.61, 16.1)*		12.3 (7.69, 17.0)*
Former vs never smokers		5.62 (1.34, 9.90)*		1.27 (−2.72, 5.25)
Alcohol (yes/no)		3.32 (0.90, 5.73)*		−1.58 (−4.41, 1.25)
Antihyperlipidemic medications (yes/no)		3.45 (−2.80, 9.71)		5.94 (−1.42, 13.30)

Model 1: adjusted for age, age^2, center, and education. Model 2: model 1 plus the other variables listed. BMI indicates body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol.
*Statistically significant at $P<0.05$.
†75th percentile of exercise is 416 exercise units in women.

consumption, may counterbalance adverse associations with obesity.

Much of the information available for population trends in lipids comes from studies comprised of serial cross-sectional data. In particular, NHANES has reported trends in serum lipids from 1960 through 2010 in different waves and in various age strata. The earliest evidence of a declining trend in total cholesterol was presented for 3 time windows (1960–1962, 1971–1974, and 1976–1980) among men and women ages 20 to 74 years, with declines in both men and women, and in whites, but not in blacks.[20] Carroll et al.[5] extended these data to 2 additional waves through 2002, and reported that the decline in total cholesterol continued and was comparable for LDL-c. They attributed the trends to the increasing prevalence of individuals using lipid-lowering medications among the older age group, but suggested that the increases in mean serum triglycerides observed were related to increases in the prevalence of obesity. Carroll et al.[6] also examined the 2007–2010 age-adjusted NHANES data among adults not using lipid-lowering medications, and reported that the improved secular trends in lipids they observed earlier persisted through 2010. Reasons for the discrepancies between NHANES and CARDIA may include the CARDIA cohort's longitudinal data rather than serial cross-sectional data in NHANES and CARDIA's ability to adjust for multiple demographic and modifiable risk factors.

Winkleby et al.[21] found that trends for non-HDL-c and BMI in women surveyed between 1988 and 1994 were less favorable in those of lower educational attainment, and that these trends tracked with physical inactivity and cigarette smoking in Mexican-American and black women. The decline in the proportion of high total cholesterol (≥240 mg/dL) among those surveyed in NHANES was observed in all BMI groups from 1976 to 2000.[22] Taken together, these results mirror our results of a decline in total and LDL-c through the late 1990s with an increase in HDL-c, and that education, race, smoking, and physical inactivity were important independent contributors.

Other US surveys, such as the Minnesota Heart Survey (MHS), showed similar declines in total cholesterol levels and increases in BMI as NHANES despite lower mean values of these risk factors, but unlike NHANES and our data in CARDIA, HDL-c remained constant between 1980 and 2002.[9,23] The authors attributed these differences to the lower proportion of people in MHS with elevated risk factors, such as smoking, hypertension, and obesity, in agreement with our findings that these risk factors are associated with lipid values. The Pawtucket Heart Health Program observed a similar decline in HDL-c as in NHANES and our data through year 15, suggesting that the declines may be linked to a specific period of time.[24]

Surveys in adults from different countries, such as Spain, France, Finland, and Australia, all showed similar downward secular trends in total cholesterol and/or LDL-c,[25–28] although these serial cross-sectional surveys also reported declines in HDL-c and increases in triglycerides during the same time periods as our study. In contrast, surveys in countries such as Japan[7] and India[8] showed age-adjusted increases in secular trends for both mean total cholesterol and triglycerides in the same time period despite increases in lipid-lowering medication use, with increasing trends in total cholesterol and decreasing trends in HDL-c also observed in a Japanese longitudinal cohort study.[29] These data may point to populations that are at different stages of risk factor transition.

Limitations of the present study include the lack of dietary data at some time points. However, when we controlled for caloric intake and saturated fat using data from the year 0 exam, we observed no impact on the secular trends. Data from NHANES suggest that US diets have shown increases in mean energy intake, larger portion sizes, increased consumption of sweetened beverages, and more late-night snacking during the time period of our data collection. Though the percentage of energy from fat decreased, this was driven by increases in carbohydrates ad calories rather than an absolute reduction in fat intake.[30,31] For the sake of analytic simplicity, we chose to examine lipid trends in equal 5-year intervals rather than all time points. Though the age ranges across all 25 years do not completely overlap, sensitivity analyses showed little difference when limited to subsamples with overlapping age ranges longitudinally. In addition, because of the relatively narrow age range of the CARDIA participants, the birth cohort effect is likely to be minimal.[18]

The findings of our study are unique in capturing secular trends in a large biracial cohort of individuals followed longitudinally over time using standardized data collection and assays. The data also were collected in an age range when antihyperlipidemic medication use was relatively low, ranging from 0% at baseline to 15% to 20% by year 25, and may indicate that the improvements we observed in atherogenic lipids have diminished as the obesity epidemic continues and physical inactivity becomes more common, but that greater medication use could lead to the more-favorable trends previously observed.

Ford et al.[32] showed that in US adults 25 to 84 years observed from 1980 to 2000, deaths from coronary heart disease fell from 542.9 to 266.8 cases per 100 000 in men and from 263.3 to 134.4 per 100 000 in women. They estimated that half of this decline was linked to evidence-based medical therapies, such as medications and procedures, and the other half was linked to improvements in modifiable risk factors.

In conclusion, initially favorable secular trends in total cholesterol and LDL-c have leveled off and may be reversing, and were not markedly changed after controlling for modifiable lifestyle factors. Though we were not able to identify the cause of unfavorable secular trends in these observational data, factors such as dietary changes over 25 years and perhaps poor adherence to medications are candidates for additional investigation.

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Disclosures

None.

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