

# Longitudinal impact of physical activity on lipid profiles in middle-aged adults: the Atherosclerosis Risk in Communities Study<sup>S</sup>

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**Abstract** Evidence exists that increased levels of physical activity decrease the population burden of cardiovascular disease (CVD). Although risk factors for CVD, including plasma lipids and lipoproteins, have been associated with physical activity, studies including a sizeable number of minority participants are lacking. Our purpose was to interrogate the longitudinal effect of physical activity on plasma lipids and lipoproteins in the African American and white participants of the Atherosclerosis Risk in Communities (ARIC) Study. Nine years of follow-up data on 8,764 individuals aged 45–64 years at baseline were used in linear mixed-effects models to estimate the association between increases in baseline physical activity on mean change in HDL, LDL, total cholesterol, and triglyceride levels. Increases in the level of activity were associated with increases in HDL in all strata and decreases in triglycerides among white participants. Physical activity was associated with LDL in all women, while the association with total cholesterol was limited to African American women. This study is one of the few to investigate the effect of physical activity on lipids and lipoproteins in a race- and sex-specific manner. Overall our results highlight the importance of physical activity on plasma lipid profiles and provide evidence for novel differential associations.—Monda, K. L., C. M. Ballantyne, and K. E. North. **Longitudinal impact of physical activity on lipid profiles in middle-aged adults: the Atherosclerosis Risk in Communities Study.** *J. Lipid. Res.* 2009. 50: 1685–1691.

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It has been well established that higher levels of physical activity decrease the incidence of and mortality from cardiovascular disease (1–3). This decrease in risk has been

shown in some instances to be independent of weight or body fat loss (4–6). A National Institutes of Health Consensus Development Panel (7) declared physical inactivity to be a major risk factor for cardiovascular disease (CVD), citing the noted improvement to HDL levels that has been associated with physical activity. There have been a number of both observational and experimental studies examining the relationship between physical activity and plasma lipids and lipoproteins. However, few of these studies have included a sizeable number of nonwhite participants, and data on racial and ethnic differences in the response of lipids to activity are sparse.

The purpose of this investigation was to assess the longitudinal effect of physical activity on plasma lipids and lipoproteins by race and gender. The Atherosclerosis Risk in Communities (ARIC) Study, a longitudinal, community-based cohort study designed to investigate the etiology of and risk factors for cardiovascular disease, is particularly well suited for our purpose. Not only does this large observational study have measures of cardiovascular risk factors over time and detailed measures of physical activity, but it also includes sufficient numbers of both African American and white men and women to perform subgroup analyses.

## METHODS

### Study population

The ARIC Study is a multi-center prospective investigation of atherosclerotic disease (8). White and African American men and women aged 45–64 years at baseline were recruited from four communities: Forsyth County, North Carolina; Jackson, Mis-

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Abbreviations: ARIC, Atherosclerosis Risk in Communities; BMI, body mass index; CVD, cardiovascular disease; HRT, hormone replacement therapy; MET, metabolic equivalent

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Mississippi; suburban areas of Minneapolis, Minnesota; and Washington County, Maryland. A total of 15,792 individuals participated in the baseline examination in 1987–1989, with three triennial follow-up examinations. This study was approved by the institutional review board at each field center, and the analysis was approved by the University of North Carolina at Chapel Hill School of Public Health institutional review board on research involving human subjects. Informed consent was received by all subjects or their representatives.

Of the 15,792 participants at baseline, we excluded those self-reporting race other than white or African American, and non-white persons from Minneapolis and Washington County ( $n = 103$ ). We further excluded individuals who reported taking cholesterol-lowering medication at any visit, as well as those who were diabetic at any visit. Prevalent type 2 diabetes was defined as the presence of any of the following: a fasting blood glucose level of  $\geq 126$  mg/dl (7.0 mmol/L); a nonfasting blood glucose level of  $\geq 200$  mg/dl (11.1 mmol/L); self-reported physician diagnosis of type 2 diabetes; or pharmacologic treatment of diabetes in the past two weeks. Finally, individuals with missing information on physical activity or model covariates were excluded. Final sample sizes were  $n = 3,456, 3,829, 626,$  and  $853$  for white men and women and African American men and women, respectively. For models analyzing LDL, final sample sizes were slightly smaller ( $n = 3,433, 3,821, 624,$  and  $851$ ).

## Measures

Blood samples were collected following a fast of at least 8 h and sent to the ARIC Central Lipid Laboratory for processing. Total plasma cholesterol and triglycerides were determined by enzymatic methods, HDL was measured after dextran-magnesium precipitation, and the Friedewald equation (9) was used to calculate LDL in those with triglyceride levels under 400 mg/dl. Detailed information on these procedures is available elsewhere (8, 10). Blood chemistries were performed at the Central Chemistry Laboratory of the University of Minnesota, and blood lipid analyses were performed at the University of Texas, Houston.

Physical activity at baseline was derived from a slightly modified Baecke Physical activity questionnaire (11) in which participants were asked to report in an open-ended format the four sports or exercises in which they most frequently participated. They were then asked the h per week ( $<1.0; \geq 1.0$  and  $<2.0; \geq 2.0$  and  $<3.0; \geq 3.0$  and  $<4.0; \geq 4.0$ ) and months per year ( $<1.0; \geq 1$  and  $<4; \geq 4$  and  $<7; \geq 7$  and  $<10; \geq 10$ ) spent in each activity. Each of the 150 reported sports and exercises was assigned a specific metabolic equivalent (MET) value according to the Compendium of Physical Activities (12), where 1.0 MET is considered a resting metabolic rate obtained during quiet sitting. MET values were then multiplied by the time and proportion of the year spent for a final value in units of MET-minutes per week. For comparison we also calculated the MET-minutes per week spent in moderate (3.0–6.0 METs) to vigorous ( $>6.0$  METs) activity, as well as in vigorous activity alone.

Baseline age was calculated as interview date minus birth date. Time between visits (in days) was calculated as visit 3 minus visit 1 date. Education was categorized as less than a high school education, high school graduate or some vocational education, and college educated or higher. Baseline smoking status was dichotomized as current versus former or never. Dietary variables were assessed using a semi-quantitative food frequency questionnaire (13). Weight was measured at all clinic visits to the nearest pound and height was measured without shoes to the nearest centimeter. Body mass index (BMI) was computed as weight (in kg) divided by height squared (in meters).

## Statistical analysis

We used longitudinal linear mixed-effects models to estimate the effect of an increase in MET-minutes per week of sport or exercise physical activity at baseline on HDL, LDL, total cholesterol and triglycerides from all four visits. This model form allows us to take advantage of the multiple measures of lipids available in the data, yet account for the clustering inherent within individuals. Model fitting diagnostics suggested we model visit as a random slope which allows the effect of physical activity on lipids to vary by individual across time. We specified an unstructured variance-covariance matrix in which all variances and covariances are distinctly estimated. Graphical techniques were used to confirm linearity between dependent and independent variables.

Likelihood ratio tests were used to examine statistical interactions between both race and sex with physical activity on lipids by comparing  $-2$  log likelihood  $\chi^2$  between nested models with and without the cross-product terms. Significant effect measure modification was found in a number of models, thus all analyses are stratified by race and sex. Covariates included age, education, and smoking status at baseline, field center, and an indicator variable denoting visit. We also tested baseline and change in intake of total calories, total fat, carbohydrate, dietary cholesterol, keys score, and alcohol as covariates. However because they did not confound the association based on a change of estimate criterion, they were not included in the final models. Finally, we ran additional models excluding women on hormone replacement therapy and individuals using anti-hypertensive medications. Differences were not noted (results not shown).

Beta coefficients derived from models were multiplied by 180 in order to estimate the mean effect of a 180 MET-minute/week increase in sport or exercise physical activity on lipids over each visit period of approximately three years. 180 MET-minutes represents the addition of one 3-MET activity (e.g., walking for pleasure, weight lifting, or bowling) for 60 min per week or one 6-MET activity (e.g., playing basketball, hiking, or modern dance) for 30 min per week. All analyses were conducted using Stata (StataCorp, College Station, TX).

## RESULTS

**Table 1** presents baseline characteristics of ARIC participants stratified by race and sex. We observe that women have higher HDL and total cholesterol, while men have higher LDL and triglycerides. Further, African American men and women have substantially lower triglyceride levels than white men and women. We also note that African American men and women have lower total and moderate-to-vigorous sport and exercise physical activity than white men and women. However, African American men have higher vigorous physical activity than their white counterparts. Overall, the proportion of total sport and exercise physical activity classified as vigorous is 17–36%; the majority of activity is of moderate intensity. This middle-aged population is overweight, with mean BMIs for all groups greater than  $25 \text{ kg/m}^2$  (14, 15); African American women are on average obese, with a mean BMI of just over  $30 \text{ kg/m}^2$ .

Age-adjusted mean between-visit changes in plasma lipids, BMI, and weight by race and sex are shown in **Table 2**. Mean time between visits was approximately 3 years ( $2.99 \pm 0.22$  for whites and  $2.95 \pm 0.38$  for African Americans). Over time, HDL and LDL showed statistically significant

TABLE 1. Baseline characteristics of study participants by race and sex

	Men		Women	
	White	African American	White	African American
Age (y)	54.6 ± 5.7	53.7 ± 6.0	53.7 ± 5.7	52.8 ± 5.7
Education level (%)				
Elementary	17.2	43.5	15.1	36.4
Intermediate	39.3	26.1	50.8	30.4
Advanced	43.5	30.4	34.1	33.2
Smokers (%)	25.2	39.6	25.2	26.0
BMI (kg/m <sup>2</sup> )	27.2 ± 3.9	27.1 ± 4.7	26.2 ± 5.2	30.2 ± 6.4
HDL (mg/dl)	43.3 ± 12.4	51.6 ± 17.1	58.6 ± 16.9	59.7 ± 17.7
LDL (mg/dl)	139.8 ± 35.2	137.0 ± 42.1	134.3 ± 39.1	135.5 ± 42.6
Total cholesterol (mg/dl)	210.5 ± 37.9	210.1 ± 43.9	216.7 ± 41.2	215.1 ± 44.3
Triglycerides (mg/dl)	140.7 ± 84.9	110.9 ± 82.6	119.7 ± 67.7	100.4 ± 55.3
Total sport PA (MET-min/wk)	95.2 ± 69.4	82.1 ± 70.7	75.6 ± 60.4	58.6 ± 51.9
Mod-vig sport PA (MET-min/wk)	92.0 ± 70.0	76.9 ± 70.1	74.4 ± 60.2	57.0 ± 52.2
Vig sport PA (MET-min/wk)	27.2 ± 54.8	29.5 ± 61.2	14.7 ± 40.8	9.7 ± 35.4

Continuous values are mean ± SD; Individuals with diabetes and/or on cholesterol-lowering medications excluded. BMI, body mass index; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; PA, physical activity; MET, metabolic equivalent; Mod-vig, moderate to vigorous; Vig, vigorous.

decreases per visit interval for all race-sex groups, total cholesterol statistically significantly decreased for all except white women, and triglycerides statistically significantly increased for all except African American men. This latter increase was most marked in white women. Weight, and therefore BMI, also showed statistically significant increases per visit interval for all race-sex groups, particularly in women. Statistically significant differences between race-sex groups were noted for all risk factors.

Results of regression models estimating the effect on plasma lipids of a 180 MET-minute/week increase in sports or exercise physical activity are shown in **Table 3**. Physical activity is associated with increased HDL (increases ranged 2.96–4.85 mg/dl), where estimates reach statistical significance in all four race-sex groups. Physical activity is associated with decreased LDL only in women, particularly African American women (–3.97 and –10.55 mg/dl for whites and African Americans, respectively). To further investigate this finding, we looked at hormone replacement therapy (HRT) and menopausal status as potential explanatory variables. We found no difference when ex-

cluding women on HRT, but we found a statistically significant interaction for menopausal status and physical activity in both white ( $P < 0.0001$ ) and African American ( $P < 0.001$ ) women. Results of stratified analysis show that the association of a 180 MET-minute/week increase in physical activity on LDL is greater in menopausal women [–5.91 (–10.47, –1.35) for whites; –14.68 (–23.82, –5.53) for African Americans] than in those who have not yet undergone menopause [–3.33 (–6.66, 0.01) for whites; –3.50 (–14.32, 7.33) for African Americans]. Stratified results for total cholesterol were similar and more extreme in African American than in white women. We observe an association of physical activity with decreased total cholesterol levels only in African American women (–7.41 mg/dl). Statistically significant decreases in triglycerides are observed in association with increased physical activity in whites (–12.93 and –8.95 mg/dl for men and women, respectively); however, although decreased triglycerides are observed also in African Americans, they do not reach statistical significance. Results from models estimating the association of lipids with increased moderate-to-vigorous

TABLE 2. Age-adjusted mean between-visit changes in CVD risk factors by race and sex

	White men			African American men			White women			African American women		
	N <sup>c</sup>	Mean	95% CI	N	Mean	95% CI	N	Mean	95% CI	N	Mean	95% CI
HDL (mg/dl) <sup>a</sup>	4,233	–0.61	–0.82, –0.40	999	–0.92	–1.37, –0.47	4,996	–1.06	–1.25, –0.88	1,642	–1.09	–1.44, –0.75
LDL (mg/dl) <sup>b</sup>	4,156	–3.68	–4.20, –3.16	994	–4.67	–5.79, –3.54	4,950	–1.32	–1.78, –0.85	1,635	–2.93	–3.80, –2.07
Total cholesterol (mg/dl) <sup>b</sup>	4,238	–3.53	–4.07, –2.99	1,001	–5.61	–6.78, –4.43	5,000	–0.22	–0.71, 0.27	1,643	–3.49	–4.39, –2.58
Triglycerides (mg/dl) <sup>b</sup>	4,238	3.91	2.77, 5.06	1,001	–0.50	–2.98, 1.98	4,999	11.44	10.41, 12.48	1,643	3.03	1.11, 4.94
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	4,240	0.37	0.33, 0.40	1,009	0.23	0.16, 0.30	5,004	0.57	0.55, 0.60	1,673	0.46	0.41, 0.51
Weight (lbs) <sup>b</sup>	4,240	1.97	1.77, 2.16	1,010	1.36	0.95, 1.77	5,004	2.70	2.53, 2.88	1,674	2.30	1.98, 2.62

Individuals with diabetes and those on cholesterol-lowering medications excluded. Values represent the mean change in risk factor per visit interval (approximately 3 years). CI, confidence interval; CVD, coronary vascular disease; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; BMI, body mass index.

<sup>a</sup>  $P < 0.01$ .

<sup>b</sup>  $P < 0.001$  for differences of 4 means between race-sex groups.

<sup>c</sup> Numbers vary due to differing missing data.



TABLE 3. Estimates from mixed regression models of the association of a 180 MET-minutes/week increase in baseline physical activity from sports/exercise with lipid parameters over each visit period of approximately three years

	Men		Women	
	White	African American	White	African American
HDL	2.96 (1.94, 3.99) <sup>a</sup>	4.41 (1.66, 7.82) <sup>a</sup>	4.85 (3.39, 6.30) <sup>a</sup>	3.49 (0.43, 6.54) <sup>a</sup>
LDL	-0.03 (-2.74, 2.67)	-1.46 (-8.78, 5.86)	-3.97 (-7.09, -0.85) <sup>a</sup>	-10.55 (-17.38, -3.72) <sup>a</sup>
Total cholesterol	0.22 (-2.72, 3.15)	1.54 (-6.07, 9.15)	-1.48 (-4.74, 1.78)	-7.41 (-14.57, -0.26) <sup>a</sup>
Triglyceride	-12.93 (-19.67, -6.18) <sup>a</sup>	-7.54 (-17.39, 2.30)	-8.95 (-15.05, -2.85) <sup>a</sup>	-4.63 (-14.55, 5.29)

β (95% confidence interval) × 180 MET-minutes/week shown. Models controlled for baseline age, education, smoking status, ARIC field center, and visit. HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol.

<sup>a</sup> *P* < 0.05.

physical activity were similar, while associations with only vigorous physical activity tended to be more pronounced (see supplementary Table I).

## DISCUSSION

In this study we examined the relationship between increases in baseline level of sport or exercise physical activity and mean change in level of triglycerides and total, HDL, and LDL cholesterol per visit interval (~3 years) over 12 years in a cohort of African American and white middle-aged men and women. Increases in the baseline level of activity were associated with increases in HDL in all participants and decreases in triglycerides in white participants. Physical activity was associated with LDL only in women and with total cholesterol only in African American women. We chose to look at the effect of an increase of 180 MET-minutes/week because this value is equal to an additional h per week of a 3-MET activity such as walking for pleasure, weight lifting, or bowling, or an additional 30 min per week of a 6-MET activity such as basketball, hiking, or modern dance. Our results mirror those found in prior longitudinal analyses of observational data in which associations are primarily limited to HDL and triglycerides. In the Amsterdam Growth and Health Study, Twisk et al. found that physical activity was positively related to HDL but not to total cholesterol (16). In the Cardiovascular Risk in Young Finns Study, change in physical activity over six years was inversely associated with change in serum triglycerides, but no association was found with HDL or total cholesterol (17). In CARDIA, Sternfeld et al. found an association between activity change and HDL (18), as did Young et al. in the Stanford Five-City Project (19). Similarly, in exercise training studies, increases of HDL and decreases in triglycerides are observed more frequently than decreases in either LDL or total cholesterol (20, 21). Meta-analyses of exercise-training studies found average increases in HDL of 1.2, 2.53, and 1.95 mg/dl and average decreases in triglycerides of 15.8 and 7.12 mg/dl (22–24).

Our finding of sex-specific associations of activity on LDL are for the most part novel. However, in the HERITAGE Study using principal components analysis, Katzmarzyk and colleagues found that loadings were stronger for LDL and total cholesterol in women, suggesting some sex differences in the response of lipids to exercise (25).

Some physiologic and metabolic factors that may influence an effect in women but not men include menopausal status and the use of HRT. While analyses excluding women on HRT did not show any differences, we did find that physical activity had a greater effect on LDL in women who were postmenopausal. In ARIC, 92% of whites and 96% of African Americans were postmenopausal by the fourth visit.

We found that, at baseline, African American men and women had higher HDL and lower triglyceride levels than white men and women. Similar racial differences have been cited in the NHANES sample (26) as well as others (27, 28). We also find that African Americans do not participate in as much sport and exercise physical activity as whites. Similarly, African American NHANES participants were significantly more likely to be physically inactive (from nonwork sources) than white participants (29, 30). Over the years of the survey, we found that while overall LDL and total cholesterol levels improved for all race/sex groups, triglycerides increased for all except African American men. These changes have been noted in other ARIC publications (31, 32) as well as in the populations from NHANES between 1960 and 2002 (33), the Minnesota Heart Survey (MHS) over 20 years (34), and the Framingham Heart Study (35). Presumably some of the decline is due to the increased use of lipid-lowering medications. However, some of the decline appears to be independent of drug use, as shown in our sample as well as analyses from the MHS (34).

Only limited data are available on ethnic differences in the response of lipids to activity. While the direction of effect was the same for whites and African Americans, the association between increased baseline activity and mean decrease in triglycerides per visit period was only statistically significant in whites. Although differences in statistical significance are largely due to lack of precision in our results (not only does ARIC have fewer African American participants, but whites have an average of 3.2 visits whereas African Americans have an average of 2.8 visits), we do observe an overall smaller effect size in African Americans. African American participants had lower triglyceride levels at all visits than white participants, and there is some, albeit limited, evidence that baseline lipid levels may influence the response to activity (20). Our results also suggest increased responsiveness of LDL to activity in African American versus white women, and decreases in total cholesterol with increasing activity only in African American

women; results that have not been duplicated in the few other studies where ethnic differences were evaluated. In the HERITAGE Family Study, Ardern et al. found no ethnic differences in lipid response (36); however, in subgroup analyses by HDL subfraction, Leon et al. found a significantly greater mean increase in HDL<sub>2</sub> in African American versus white participants (37), an analysis we were unable to replicate due to lack of data. In the CARDIA Study, correlations between change in activity and change in lipids were small and did not differ greatly between African American and white participants (18).

There is great heterogeneity in response of blood lipids to physical activity, and genetic variations likely contribute to these differences. Consequently, variability in our results may reflect differences among sub-populations as well as potential residual confounding from numerous life-style variables for which we were only partially able to control. Further, while participants were instructed to be in a fasting state, a single session of exercise has been shown to have an effect on plasma triglycerides for up to 24–48 h afterwards (38); thus, timing of blood sampling may also have played a role.

Controversy exists as to whether improvements in lipid profile from physical activity are independent of weight or body fat loss. In our analyses, we purposefully chose not to present results adjusted for BMI given BMI's role as an intermediate between physical activity and lipid parameters. Inappropriate control of intermediate variables is not a reliably valid technique for effect decomposition and can create spurious statistical associations resulting in incorrect and misleading inferences (39–43). In fact, in models in which we controlled for BMI, we found that estimates were biased through, toward, and away from the null (see supplementary Table II). Clearly, this bias is unpredictable in both magnitude and direction. While these effects are difficult to tease apart using observational data, sophisticated techniques have been developed that allow for a greater understanding of effect decomposition, including marginal structural modeling or path analysis (44–46). In this work, it was our intent to estimate the total effect and not to perform a mediation analysis. Results from experimental studies in which participants have undergone exercise training where body weight was held constant are mixed. Sopko et al. demonstrated independent and additive effects of weight loss and exercise on increased HDL (47), and Thompson et al. showed increased HDL levels in exercise-trained, weight-stable men over one year (48). However, in an exercise intervention conducted by Fonong et al., there was no change in HDL level when weight was kept constant (49). Changes in lipoproteins following a single bout of exercise are well reported and provide evidence for the hypothesis that activity independently influences the lipid profile (38).

This study has a number of limitations worth noting. First, physical activity was assessed via questionnaire, which is subject to recall and other biases, and cannot provide the same precision in measurement that one would achieve with an objective device. Nonetheless, for large epidemiologic surveys such as ARIC, the use of a questionnaire is

the most feasible way to measure physical activity (50). Further, the Baecke questionnaire performs well, with high reliability and accurate assessment (11, 51–53). Second, these results cannot be generalized to individuals with type 2 diabetes or those on cholesterol-lowering medications. It has been well documented that exercise training is beneficial for those with type 2 diabetes (54, 55), likely acting through one of a number of proposed mechanisms, including decreased systemic inflammation and decreased abdominal visceral fat accumulation (56). However, we excluded diabetic persons because of the effect diabetes can have on the lipoprotein profile and because drugs for the treatment of diabetes (e.g., thiazolidinediones and metformin) exert an effect on lipoproteins (57). Limitations in generalizability may also arise due to these data being drawn from four geographic communities, three for whites and two for African Americans.

Despite these limitations, the ARIC Study is a unique resource by which to evaluate the longitudinal association between physical activity and lipid measures. Not only is it a large biracial cohort that allows for estimation of race- and sex-specific effects with adequate precision, study investigators also utilized validated methods for the measurement of physical activity. These strengths, combined with careful attention to analytic methods, inform the literature examining differential effects of activity on lipid profiles.

In summary, in the ARIC Study, we confirm the benefits of physical activity on HDL and triglycerides seen in previous research. We also found an additional benefit of activity on reducing LDL in women, particularly African American women. Data from large prospective studies suggest that each 1 mg/dl increase in HDL is associated with significant reductions in risk of coronary heart disease of at least 2% and 3% in men and women, respectively (58), and there is substantial evidence that moderate levels of physical activity confer significant health benefits (7). Although there is considerable interindividual variability in the response to physical activity, and with the understanding that physical activity is not necessarily an easily modified behavior, these results and others provide further evidence for and highlight the importance of consistent activity on plasma lipid profiles. ■

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