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The Impact of Cardiorespiratory Fitness Levels on the Risk of Developing Atherogenic Dyslipidemia

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Abstract

Background—Low cardiorespiratory fitness has been established as a risk factor for cardiovascular-related morbidity. However, research regarding the impact of fitness on lipid abnormalities, including atherogenic dyslipidemia, has produced mixed results. The purpose of this investigation is to examine the influence of baseline fitness and changes in fitness on the development of atherogenic dyslipidemia.

Methods—All participants completed at least three comprehensive medical examinations performed by a physician that included a maximal treadmill test between 1976 and 2006 at the Cooper Clinic in Dallas, Texas. Atherogenic dyslipidemia was defined as a triad of lipid abnormalities: low HDL-C (<40 mg/dL), high TGs (≥200 mg/dL), and high LDL-C (≥160 mg/dL).

Results—A total of 193 participants developed atherogenic dyslipidemia during an average of 8.85 years of follow-up. High baseline fitness was protective against the development of atherogenic dyslipidemia in comparison to those with low fitness (OR: 0.57; 95% CI: 0.37–0.89); however, this relationship became non-significant after controlling for baseline HDL-C, LDL-C, and TG levels. Participants who maintained fitness over time had lower odds of developing

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CONFLICT OF INTEREST DISCLOSURES

None

atherogenic dyslipidemia than those with a reduction in fitness (OR: 0.56; 95% CI: 0.34–0.91) after adjusting for baseline confounders and changes in known risk factors.

Conclusions—High fitness at baseline and maintenance of fitness over time are protective against the development of atherogenic dyslipidemia.

Keywords

exercise capacity; cholesterol; dyslipidemia; epidemiology

Introduction

Epidemiological studies consistently demonstrate the independent effects of lipid abnormalities as risk factors for cardiovascular disease in populations worldwide.[1,2] In the United States, about half of the adult population has at least one lipid abnormality and about six percent have a triad of lipid abnormalities.[3] The lipid triad, also known as atherogenic dyslipidemia, consists of a combination of elevated low density lipoprotein cholesterol (LDL-C), reduced levels of high density lipoprotein cholesterol (HDL-C), and elevated triglycerides (TGs).[4,5] In addition to the independent effects, the presence of the lipid triad, as a whole, is considered a strong independent risk factor for cardiovascular disease.[6]

Between 1988 and 1994, there was a six-fold increase in U.S. adults aged 18 to 64 years who were prescribed cholesterol-lowering medication, and almost half (46.7%) of Americans over the age of 65 years reported taking cholesterol-lowering medication within the previous 30 days.[7] Pharmacotherapy in conjugation with lifestyle modification is strongly promoted and this multifactorial approach targets several lifestyle behaviors, including physical inactivity and/or poor dietary patterns, each with known impacts on lipid abnormalities.[8,9,10]

The literature indicates that regular exercise elicits significant improvements to TG, total cholesterol, and HDL-C levels,[10–12] whereas LDL-C is largely unaffected by regular exercise when body weight and diet remain unchanged.[10,11,13] In addition to exercise, cardiorespiratory fitness (hereafter referred to as fitness) – an objective indicator of habitual physical activity and a strong predictor for cardiovascular disease -related outcomes – is associated with lipid abnormalities.[14–18] There is evidence suggesting that higher levels of baseline fitness are positively associated with plasma levels of HDL-C as well as with a lower odds of developing incident hypercholesterolemia.[19–22]

In addition to baseline fitness levels, the impact of fitness changes over time on plasma lipid concentrations have also been examined, but the results are mixed. Some investigators have observed no associations between changes in fitness levels following an exercise intervention with changes in the individual components of the lipid triad.[23–27] While other studies have observed significant correlations between changes in fitness levels and changes in total cholesterol, HDL-C, and TG levels.[18,28,29,30] Additionally, maintaining or improving fitness levels over time is associated with a lower risk for elevated total cholesterol in adults.[18,31]

Although the findings are mixed, the overall trend demonstrates that the greatest improvements to plasma cholesterol levels are more likely to occur among individuals who have greater increases in fitness post-intervention. However, the literature has focused primarily on the individual components of the lipid triad. Therefore, the purpose of this present study was to examine the association between baseline fitness levels and changes in fitness levels on the odds of developing atherogenic dyslipidemia in adults using data from the Aerobics Center Longitudinal Study (ACLS).

Methods

Study Population

Participants were 9,651 patients (8,203 men and 1,448 women) who were at least 20 years of age at their initial examination and completed at least three medical examinations between 1976 and 2006 at the Cooper Clinic in Dallas, Texas. All participants were free of atherogenic dyslipidemia, cardiovascular disease, cancer, and diabetes at baseline, had normal resting and exercise ECGs, and were able to achieve at least 85% of their age-predicted maximal heart rate during their first and second treadmill tests. Most of the participants were non-Hispanic whites with a socioeconomic status of middle to upper class. Written informed consent was obtained from all participants and the ACLS study has been reviewed and approved annually by the Cooper Institute Institutional Review Board.

Clinical Examination

Following 12-hour overnight fasting, all participants completed at least three comprehensive medical examinations performed by a physician, which has been previously described.[33,34] Questionnaires were administered to all participants in order to obtain lifestyle habits regarding smoking (never or current smoker), alcohol intake (heavy drinker versus non-heavy drinker), and physical activity (active versus inactive). Heavy alcohol drinking was defined as consuming more than 14 drinks per week for males or more than 7 drinks per week for females. Physical inactivity was defined as not participating in any leisure-time physical activity within the previous three months prior to their medical examination.[35] Personal and family health histories were obtained through a standard medical health questionnaire that asked whether they had ever been diagnosed with cardiovascular disease, cancer, hypertension, diabetes, or hypercholesterolemia by a physician. A parental history of cardiovascular disease was defined as either parent having suffered from a heart attack, coronary heart disease, angioplasty, or stroke before the age of 50 years. Changes in lifestyle characteristics were categorized into four groups: remained active, became active, became inactive, or remained inactive; remained nonsmoker, became nonsmoker, became smoker, or remained smoker; and remained non-heavy drinker, became non-heavy drinker, became heavy drinker, or remained heavy drinker. Additionally, changes in hypertension status were divided into three groups: remained normotensive, became hypertensive, or remained hypertensive.

Body Mass Index (BMI) and Fitness

Height and weight were measured on all participants and BMI was calculated [weight (kg)/height $(m)^2$]. BMI was classified as follows: normal weight (18.5–24.9 kg/m^2) or

overweight/obese (≥25.0 kg/m^2).[36] Fitness was determined through a maximal effort treadmill test using a modified Balke protocol.[34,37] The test was terminated once the participant reached volitional fatigue or prematurely by a physician due to medical reasons. The final treadmill speed and grade was used to estimate fitness levels in metabolic equivalents (METs) using the following American College of Sports Medicine formula: [3.5 + (0.1 × speed) + (1.8 × speed × grade)]/3.5.[38] Age- and gender-specific tertiles for fitness were created for the current population using the maximal treadmill time in each age and sex group (20–39, 40–49, 50–59, and 60+ years).[39]

Changes in fitness levels per year were calculated and categorized following a similar procedure that was previously described.[40] Briefly, the difference in maximal METs between baseline and the second medical examination was divided by the number of years between the two examinations. This standardized the changes in fitness levels because of varying lengths of time between examinations among the participants. Since there are no commonly accepted categories for changes in fitness over time in the literature, changes in maximal METs were further categorized into three groups: “loss” (<0 METs/year), “stable” (0 METs/year), and “gain” (>0 METs/year). Changes in BMI between examinations were categorized into four groups: “remained normal weight”, “became normal weight”, “became overweight/obese”, and “remained overweight/obese”.

Ascertainment of Incident Atherogenic Dyslipidemia

Atherogenic dyslipidemia was defined as a triad of lipid abnormalities: low HDL-C (<40 mg/dL), high TGs (≥200 mg/dL), and high LDL-C (≥160 mg/dL),[4] and was assessed at both baseline and each follow-up visit. Follow-up was calculated two ways in order to address both research questions: 1) from baseline to either the first event of atherogenic dyslipidemia or the last examination through the end of 2006 for non-cases, or 2) from the second examination to either of the above end point criteria.

Statistical Analysis

SAS 9.3 (SAS Institute Inc., Cary, NC, USA) was used in this analysis. Tests of linear trends across baseline fitness groups were calculated with general linear models. Multiple logistic regression was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for atherogenic dyslipidemia across the baseline fitness groups (low, middle, and high) and changes in fitness groups (“loss”, “stable”, and “gain”) using two separate models. The first model estimating the odds of atherogenic dyslipidemia for each of the baseline fitness groups was adjusted for age, sex, baseline BMI, lifestyle characteristics (physical activity, smoking status, and alcohol intake), hypertension, and parental history of cardiovascular disease. A second model was adjusted for model 1 plus baseline HDL-C, LDL-C, and TG levels to account for the impact of initial values on subsequent risk. The first model pertaining to changes in fitness was adjusted for the following potential confounders: age, sex, baseline BMI, maximal METs at baseline, changes in lifestyle characteristics (physical activity, smoking status, and alcohol intake) and BMI between baseline and second examinations, changes in hypertension status, and parental history of cardiovascular disease. The second model adjusted for all of the variables included in model 1 in addition to baseline HDL-C, LDL-C, and TG levels. Interactions between sex and baseline fitness and

changes in fitness levels were tested and both of the interaction terms were non-significant; therefore, the results are presented as pooled analyses. Statistical significance was determined using a 2-sided p-value <0.05.

Results

Among the 9,651 participants, a total of 193 developed atherogenic dyslipidemia (2.0%) over an average of 8.85 (range: 0.59–27.67) years of follow-up. The mean duration between baseline and second examination was 2.15 (range: 0.03–22.05) years. Baseline sample characteristics are presented by fitness level in Table 1. Overall, the participants were middle-aged with a BMI of 25.2 kg/m^2. At baseline, participants with low fitness were more likely to be current smokers, physically inactive, hypertensive, and overweight. They were also more likely to have higher total cholesterol, LDL-C, and TG levels and lower HDL-C levels in comparison to participants categorized in the middle or high fitness groups.

After adjustment for covariates, participants with high baseline fitness levels had 43% lower odds of developing atherogenic dyslipidemia in comparison to those with low fitness at baseline (Table 2). This association became non-significant after further accounting for baseline HDL-C, LDL-C, and TG levels (OR: 1.03; 95% CI: 0.65–1.64). The odds ratios between those with fitness in the middle tertile at baseline and those in the lowest fitness tertile failed to reach significance in both models.

In comparison to those who saw a reduction in their fitness levels, participants who maintained their fitness had 43% lower odds of developing atherogenic dyslipidemia after adjusting for baseline confounders and changes in known risk factors between baseline and their second examination (Table 3). This association was strengthened slightly and remained statistically significant after additionally adjusting for baseline HDL-C, LDL-C, and TG levels (OR: 0.56; 95% CI: 0.34–0.91). The participants who gained fitness also saw a reduction in their odds of developing atherogenic dyslipidemia compared to those who lost fitness; however, the association was non-significant in both models. Furthermore, a one MET increase per year in fitness was not significantly associated with a reduction in the odds of developing atherogenic dyslipidemia.

Discussion

In this relatively healthy sample of adults, high baseline fitness as well as maintaining fitness levels over time were protective against the development of atherogenic dyslipidemia even after adjusting for potential confounders and risk factors. However, the association between baseline fitness and atherogenic dyslipidemia became non-significant after further adjusting for baseline HDL-C, LDL-C, and TG levels; whereas the significant association between the maintenance of fitness over time and atherogenic dyslipidemia persisted after accounting for each component of the lipid triad. To the best of our knowledge, this is the first study that linked both baseline fitness and changes in fitness during follow-up to the risk of developing atherogenic dyslipidemia.

Evidence from previous studies has been somewhat inconsistent in demonstrating the impact of fitness or changes in fitness in eliciting modifications in the lipid profile, even with

increases in maximal oxygen consumption (VO_{2max}).[25] A review paper of exercise training studies demonstrated baseline VO_{2max} to be negatively correlated with percent change in TGs post-training.[25] Similar results were observed in another subsample of the ACLS, in which fitness changes were inversely associated with changes in TGs as well as with changes in total cholesterol.[18] Another observational study conducted within the Coronary Artery Risk Development in Young Adults (CARDIA) cohort also observed a significant negative correlation in men and white women only, but this became non-significant after accounting for weight changes over a seven-year period.[41]

Additionally, within the ACLS population, fitness changes were positively associated with changes in HDL-C even after adjusting for covariates, which was similarly observed in the CARDIA cohort.[17,41] However, when weight change was accounted for in the CARDIA study, the correlation between changes in fitness and changes in HDL-C was attenuated to non-significance in all but two of the race/gender groups (black men and white women).[41] Other studies have observed significant increases in HDL-C following an exercise training intervention;[12,25,32] but, there are some that report significant negative or no associations between changes in VO_{2max} and changes in HDL-C depending on the study design and population characteristics.[28, 32,42]

In regard to LDL-C, the CARDIA study observed no partial correlations between changes in fitness and changes in LDL-C after adjusting for weight change.[41] Similarly, the significant inverse association between baseline fitness levels and 15-year incidence of elevated LDL-C (≥160 mg/dL) in another CARDIA subsample of middle–aged adults was attenuated to non-significance after adjusting for baseline BMI.[15] Additionally, improved fitness over a seven-year period was not significantly associated with the incidence of elevated LDL-C nor was a one minute increase in treadmill test duration.[15] This is consistent with the evidence from a review of aerobic exercise training interventions in that percent change in VO_{2max} was not correlated with percent change in LDL-C,[25] whereas another meta-analysis observed a significant inverse association.[32]

Furthermore, a recent report from the CARDIA study examined the impact of fitness on the individual components of the lipid triad.[43] The authors found the 25-year incidence of developing each of the individual components of the lipid triad to be inversely associated with baseline fitness levels after adjustment for several lifestyle characteristics and risk factors.[43] Also, individuals who developed low HDL-C (<40 mg/dL) or high LDL-C (≥160 mg/dL) between follow-up years 20 and 25 were more likely to have a greater loss in fitness levels over a 20 year period than those who remained normolipidemic; however these associations became non-significant after adjusting for covariates.[43]

These inconsistencies in the individual components of the lipid triad may be due to differences in baseline fitness levels, which one meta-analysis has identified as a potential factor that may moderate the effects of an exercise intervention in producing favorable changes in the lipid triad components.[32] This indicates that those with initially low fitness levels will more likely see greater improvements in their lipid profile following an exercise intervention in comparison to those who are more fit.[32] Additionally, change in body weight/fat distribution may potentially confound the relationship.[41]

In contrast to the majority of the literature, this study examined the impact of baseline fitness and changes in fitness on the odds of developing atherogenic dyslipidemia, a condition consisting of a triad of lipid abnormalities. The findings of this study further demonstrate the beneficial impact of high baseline fitness levels in reducing the odds of developing atherogenic dyslipidemia in comparison to those with low baseline fitness. However, this association appears to be dependent upon baseline levels of HDL-C, LDL-C, and TGs. Additionally, individuals who maintained their fitness over time had lower odds of developing atherogenic dyslipidemia compared to those with declining fitness levels. This association remained significant even after adjusting for changes in lifestyle factors, hypertension status, BMI, and each of the components of the lipid triad; thus, making our current study markedly different from other studies.

The results of this study are strengthened by the valid and objective measure of fitness in addition to the large sample size and ample follow-up time. However, there are several limitations that need to be considered, including the use of a homogeneous study sample which limits the generalizability of the results. Also, caution should be used when interpreting these results as there was not a way of distinguishing whether or not the changes in fitness were intentional or whether the benefits of fitness on lipids is causal. However, to minimize bias by unintentional changes in fitness, participants with pre-existing and subclinical conditions were excluded. The association between fitness and atherogenic dyslipidemia was adjusted for most risk factors with the exception of diet, changes in dietary habits, or the use of over-the-counter substances. Finally, self-reported leisure-time physical activity cannot avoid recall bias or social desirability.

Conclusions

The present study found that high fitness levels at baseline and maintenance of fitness with aging are protective against the development of atherogenic dyslipidemia. Furthermore, this study expands the knowledge about the influence of fitness as an important cardiovascular disease risk factor and lends additional support to incorporating enough physical activity to maintain or improve fitness with pharmacotherapy in order to have direct effects on lipid abnormalities. With more evidence showing that fitness levels decline[44,45] and lipid profiles worsen with aging,[46] clinicians should actively counsel their patients to avoid low levels of fitness and/or maintain fitness over time for primary prevention of atherogenic dyslipidemia and cardiovascular disease.

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List of Abbreviations

ACLS	Aerobics Center Longitudinal Study
BMI	body mass index
CARDIA	Coronary Artery Risk Development in Young Adults
HDL-C	high density lipoprotein cholesterol
LDL-C	low density lipoprotein cholesterol
MET	metabolic equivalent
TG(s)	triglyceride(s)

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- Baseline cardiorespiratory fitness is strongly associated with lower odds of developing atherogenic dyslipidemia that is a triad of lipid abnormalities.
- The maintenance of cardiorespiratory fitness over time is protective against the development of atherogenic dyslipidemia.
- Clinicians should actively counsel their patients to avoid low levels of cardiorespriatory fitness and/or maintain cardiorespiratory fitness with aging.

Table 1

Baseline Characteristics of Participants by Fitness Levels

Characteristics	Total (n=9,651)	Low (n=3,269)	Middle (n=3,208)	High (n=3,174)	P Value
Age, y	44.8 (9.1)	45.2 (9.2)	44.9 (9.0)	44.4 (9.1)	<0.001
Gender, male, %	85.0	85.1	85.2	84.6	0.59
Body weight, kg	79.4 (13.6)	83.4 (15.2)	79.3 (12.6)	75.3 (11.3)	<0.001
Body mass index, kg/m^2					<0.001
18.5–24.9, %	51.3	34.7	49.7	69.9	
≥25.0, %	48.7	65.3	50.3	30.1	
Fitness, maximal METs	12.0 (2.3)	9.9 (1.3)	11.9 (1.1)	14.4 (1.9)	<0.001
Systolic blood pressure, mm Hg	118 (12)	120 (12)	118 (12)	118 (12)	<0.001
Diastolic blood pressure, mm Hg	80 (8)	80 (10)	80 (8)	78 (8)	<0.001
Hypertension, %[a]	24.0	29.9	22.8	19.2	<0.001
Total cholesterol, mg/dL	205.2 (40.6)	209.5 (37.9)	205.7 (36.9)	200.4 (45.9)	<0.001
HDL-C, mg/dL	49.3 (13.7)	45.5 (12.7)	48.9 (13.4)	53.4 (14.1)	<0.001
LDL-C, mg/dL	132.6 (38.5)	135.8 (35.7)	133.5 (34.6)	128.5 (44.3)	<0.001
TGs, mg/dL	116.7 (78.9)	140.9 (91.5)	116.4 (78.8)	92.2 (53.0)	<0.001
Current smoker, %	12.4	18.0	11.7	7.2	<0.001
Heavy drinker, %[b]	7.2	6.7	6.8	8.2	0.02
Physically inactive, %[c]	18.1	35.9	13.4	4.6	<0.001
Parental history of cardiovascular disease, %	29.3	30.2	29.0	28.5	0.13

Values are mean ± SD unless otherwise stated.

HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; MET = metabolic equivalent; TGs = triglycerides.

[a]Defined as systolic or diastolic blood pressure ≥140/90 mm Hg or physician-diagnosis.

[b]Defined as alcohol drinks >14 per week for men and >7 alcohol drinks per week for women.

[c]Defined as no leisure-time physical activity in the 3 months before the examination.

Table 2

Odds Ratio of Atherogenic Dyslipidemia by Tertiles of Baseline Fitness Levels

Baseline Fitness	Number at risk	Number of cases	Model 1[a]	Model 2[b]
Low	3,269	85	1.00 (Reference)	1.00 (Reference)
Middle	3,208	75	1.07 (0.77–1.49)	1.35 (0.95–1.91)
High	3,174	33	0.57 (0.37–0.89)	1.03 (0.65–1.64)
P for linear trend			<0.001	<0.001

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; TGs = triglycerides.

[a]Adjusted for age, sex, baseline BMI, lifestyle characteristics (physical activity, smoking status, and alcohol intake), hypertension, and parental history of cardiovascular disease.

[b]Adjusted for Model 1 plus baseline HDL-C, LDL-C, and TG levels.

Table 3

Odds Ratio of Atherogenic Dyslipidemia by Changes in Fitness Levels during Follow-up

Fitness Change	Number at risk	Number of cases	Model 1[a]	Model 2[b]
Loss	2,475	53	1.00 (Reference)	1.00 (Reference)
Stable	2,025	28	0.57 (0.36–0.91)	0.56 (0.34–0.91)
Gain	5,151	112	0.81 (0.57–1.16)	0.81 (0.56–1.17)
P for linear trend			<0.001	<0.001
Per 1-Met increase			0.96 (0.81–1.13)	0.97 (0.83–1.14)

BMI = body mass index; HDL-C = high-density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; MET = metabolic equivalent; TGs = triglycerides.

[a]Adjusted for age, sex, baseline BMI, baseline maximal METs, change in lifestyle characteristics (physical activity, smoking status, and alcohol intake), change in hypertension status, change in BMI, and parental history of cardiovascular disease.

[b]Adjusted for Model 1 plus baseline HDL-C, LDL-C, and TG levels.