Changes in Fitness and Fatness on the Development of Cardiovascular Disease Risk Factors

Hypertension, Metabolic Syndrome, and Hypercholesterolemia

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Objectives   This study sought examine the independent and combined associations of changes in fitness and fatness with the subsequent incidence of the cardiovascular disease (CVD) risk factors of hypertension, metabolic syndrome, and hypercholesterolemia.

Background   The relative and combined contributions of fitness and fatness to health are controversial, and few studies are available on the associations of changes in fitness and fatness with the development of CVD risk factors.

Methods   We followed up 3,148 healthy adults who received at least 3 medical examinations. Fitness was determined by using a maximal treadmill test. Fatness was expressed by percent body fat and body mass index. Changes in fitness and fatness between the first and second examinations were categorized into loss, stable, or gain groups.

Results   During the 6-year follow-up after the second examination, 752, 426, and 597 adults developed hypertension, metabolic syndrome, and hypercholesterolemia, respectively. Maintaining or improving fitness was associated with lower risk of developing each outcome, whereas increasing fatness was associated with higher risk of developing each outcome, after adjusting for possible confounders and fatness or fitness for each other (all p for trend <0.05). In the joint analyses, the increased risks associated with fat gain appeared to be attenuated, although not completely eliminated, when fitness was maintained or improved. In addition, the increased risks associated with fitness loss were also somewhat attenuated when fatness was reduced.

Conclusions   Both maintaining or improving fitness and preventing fat gain are important to reduce the risk of developing CVD risk factors in healthy adults.   (J Am Coll Cardiol 2012;59:665–72) © 2012 by the American College of Cardiology Foundation

Cardiovascular disease (CVD) accounts for one-third of U.S. mortality, and the high prevalence of hypertension, metabolic syndrome, and hypercholesterolemia is a major factor (1). Cardiorespiratory fitness (hereafter fitness) and body fatness are strong predictors for CVD risk factors (2–4) as well as CVD morbidity and mortality (5–8).

Given the diverse combinations of both fitness and fatness in adult populations (9), the relative and combined contributions of fitness and fatness to health are controversial (3,4,8,10,11). Some studies indicate that fitness can eliminate the harmful effect of fatness (12,13), suggesting fat but fit persons do not have excess health problems. Others report that higher levels of fitness or physical activity are beneficial and attenuate, but do not completely eliminate, the negative effect of fatness (10,14). One possible reason for the discrepancy among these studies is the inaccurate measurement of fitness and fatness (11). Many population studies used self-reported physical activity rather than objectively measured fitness, and fatness was measured by body mass index (BMI), a crude estimate of body fatness (15). In addition, previous studies were conducted mostly on mortality outcomes, but little is known about the combined associations of fitness and fatness with the development of CVD risk factors.

Fitness and fatness change over time, and the patterns of change vary among individuals (16). However, most previ-

**Abbreviations
and Acronyms**

BMI = body mass index

CVD = cardiovascular
disease

HDL = high-density
lipoprotein

MET = metabolic
equivalent

ous studies were based on a single baseline assessment of either fitness or fatness with health outcomes. Combined associations of simultaneous changes in fitness and fatness with subsequent incident CVD risk factors remain uncertain. The purpose of this study was to examine the independent and combined associations of changes in fitness and fatness with the development of CVD risk factors, focusing on hypertension, metabolic syndrome, and hypercholesterolemia, in healthy adults using objectively measured fitness and fatness.

Methods

Study population. The ACLS (Aerobics Center Longitudinal Study) is a prospective observational study of individuals who received extensive preventive medical examinations at the Cooper Clinic in Dallas, Texas. More than 95% of participants are non-Hispanic whites from middle-to-upper socioeconomic strata (17). Participants are self-referred or are referred by their employers or physicians. Our current analyses included men and women age ≥18 years at baseline who received at least 3 medical examinations from 1979 to 2006. We used the first (baseline) and second examinations to assess changes in fitness and fatness, and followed up participants for incident CVD risk factors from the second through their final examinations. All participants achieved at least 85% of their age-predicted maximal heart rate (220 minus age in years) on the maximal exercise test at the first and second examinations (17,18).

We excluded participants with CVD, cancer, diabetes, or abnormal resting or exercise electrocardiogram at the first and/or second examinations (n = 1,525). For the analyses of incident hypertension, metabolic syndrome, and hypercholesterolemia as study outcomes, we also excluded participants with any of these conditions at either examination (n = 4,197). In addition, we excluded participants who answered "Yes" to the question about "unexplained weight loss or gain" at the second examination (n = 24). These exclusion criteria eliminated many participants. However, this conservative approach was important to minimize potential bias due to underlying or pre-existing disease on changes in fitness, body weight, and subsequent health risk (19,20). There were no women who were pregnant at the baseline or second examination. Our final sample included 3,148 healthy adults (2,622 men and 526 women). This study was reviewed and approved annually by the Cooper Institute Institutional Review Board. All participants provided written informed consent for the examinations and follow-up study.

Clinical examination. All participants completed comprehensive clinical examinations by a physician. Blood chem-

istries were analyzed after at least a 12-h overnight fast with automated bioassays in the Cooper Clinic laboratory. Resting blood pressure was measured by using standard auscultatory methods after at least 5 min of seated rest (21). Waist circumference was measured at the umbilicus level. Smoking status, alcohol consumption, leisure-time physical activity, and physician-diagnosed CVD, cancer, hypertension, diabetes, and hypercholesterolemia were obtained from a standardized medical history questionnaire.

Cardiorespiratory fitness, percent body fat, and BMI. Maximal treadmill testing using a modified Balke protocol was used to assess fitness in maximal metabolic equivalents (METs), as previously described (17,22). Participants were encouraged to give maximal effort, and the test was terminated on volitional exhaustion or medical reasons determined by the physician. Maximal METs were estimated based on the final treadmill speed and grade using the following formula from the American College of Sports Medicine: $[3.5 + (0.1 \times \text{speed}) + (1.8 \times \text{speed} \times \text{grade})]/3.5$ (23). Percent body fat was determined using 7-site skinfold measurements (chest, axilla, triceps, subscapular, abdomen, suprailiac, and thigh) with a skinfold fat caliper. Body fatness was estimated using a generalized body density equation that is highly correlated ($r > 0.90$) with percent body fat from hydrodensitometry (underwater weighing) (24). Detailed procedures for this percent body fat assessment have been reported previously (12,24). BMI was calculated as measured weight in kilograms divided by the square of measured height in meters.

Changes in fitness and fatness as continuous variables were calculated as the differences in maximal METs, percent body fat, and BMI between the first and second examinations, divided by number of years between examinations. Because the intervals between examinations vary among individuals in this cohort, we used changes in fitness and fatness per year. Approximately half of the participants showed increases in maximal METs (54%), percent body fat (52%), and BMI (53%), and others showed a decrease (or no change). On the basis of these approximately equal distributions, changes in fitness and fatness were categorized into thirds for simplifying the complicated combined associations of changes in fitness and fatness with 3 incident CVD risk factors. The lower thirds of changes in maximal METs, percent body fat, and BMI showing annual mean (range) decreases of −0.58 (−3.56 to −0.03) METs, −2.76% (−16.91% to −0.70%), and −0.84 (−9.93 to −0.18) kg/m², respectively, were categorized as "loss"; the middle thirds showing small changes of 0.16 (−0.03 to 0.46) METs, 0.05% (−0.70% to 0.72%), and 0.03 (−0.18 to 0.21) kg/m² were categorized as "stable"; and the upper thirds showing increases of 1.22 (0.46 to 5.64) METs, 2.11% (0.72% to 13.09%), and 0.64 (0.21 to 7.40) kg/m² were categorized as "gain." For the joint analyses, we created 9 combinations from each of the 3 fitness and percent body fat change categories.

CVD risk factors. Hypertension was defined as resting systolic or diastolic blood pressure at least 140/90 mm Hg or physician-diagnosed hypertension. Metabolic syndrome was defined as the presence of ≥3 of the following criteria: waist circumference >102 cm in men and 88 cm in women, triglycerides at least 150 mg/dl, high-density lipoprotein (HDL) cholesterol <40 mg/dl in men and 50 mg/dl in women, blood pressure at least 130/85 mm Hg or physician-diagnosed hypertension, and fasting glucose at least 100 mg/dl or physician-diagnosed diabetes according to the National Cholesterol Education Program–Adult Treatment Panel III (25). Hypercholesterolemia was defined as total cholesterol at least 240 mg/dl or physician-diagnosed hypercholesterolemia. Type 2 diabetes was not included in this analysis due to the small number of events (n = 43). Follow-up was calculated from the second examination to the first event of each CVD risk factor or the last examination through 2006.

Statistical analysis. We used Cox proportional hazards regression to estimate the hazard ratios and 95% confidence intervals of developing each CVD risk factor across changes in fitness and fatness. Linear trends across changes in fitness and fatness were tested using general linear models in Table 1 and Cox regression models in Table 2 using the exposure categories as linear variables. Because changes in lifestyle may distort the true relation between changes in fitness or fatness and incident CVD risk factors, analyses were adjusted for dummy variables for changes in each lifestyle characteristic (smoking status, alcohol intake, and physical activity). Each lifestyle change was categorized into 4 categories: remained nonsmokers, became nonsmokers, became smokers, or remained smokers; remained nonheavy drinkers, became nonheavy drinkers, became heavy drinkers (>14 drinks/week for men and >7 drinks/week for women), or remained heavy drinkers; and remained active, became active, became inactive, or remained inactive. We next explored how and to what extent changes in fitness or fatness were associated with simultaneous changes in each component of CVD risk factors, such as blood pressure and lipids, between the first and second examinations using Pearson partial correlation coefficients after adjusting for age, sex, and change in fatness or fitness for each other. To test effect modification according to sex on the associations between changes in fitness or fatness and incident CVD risk factors, we checked interaction terms in the Cox regressions and compared risk estimates in the sex-stratified analyses. We found similar trends in the development of CVD risk factors between men and women, and no significant interactions were observed; thus, we presented the results of pooled analyses. There were also no significant interactions between change in fitness and change in fatness on developing CVD risk factors, using interaction terms in the Cox regression. The proportional hazards assumptions were met by comparing the log–log survival plots. We used SAS software (version 9.2) for all statistical analyses, and 2-sided p values <0.05 were deemed statistically significant.

Results

Among 3,148 healthy participants, 752, 426, and 597 adults developed hypertension, metabolic syndrome, and hypercholesterolemia during the mean (interquartile range) follow-up of 6.1 (2.1 to 8.7), 6.6 (2.1 to 9.4), and 6.3 (2.1 to 9.0) years, respectively. The corresponding incidence rates were 39.2, 20.5, and 30.1 per 1,000 person-years. The mean (interquartile range) interval between the first and second examinations was 2.1 (1.0 to 2.2) years with a minimum of 5 months. In general, participants were middle-aged (mean age 42.3 years), relatively fit, normal weight, and healthy at baseline (Table 1).

Participants who maintained or improved fitness had 26% and 28% lower risk of incident hypertension, 42% and 52% lower risk of metabolic syndrome, and 26% and 30% lower risk of hypercholesterolemia, respectively, compared with those who lost fitness (Table 2) after adjusting for possible confounders and baseline fitness levels (model 1). However, those who gained percent body fat had 27%, 71%, and 48% higher risk of incident hypertension, metabolic syndrome, and hypercholesterolemia, respectively, compared with those who lost percent body fat. Similar results were observed in BMI change. When we additionally adjusted for fatness (baseline and change in percent body fat) for fitness change, or fitness (baseline and change in maximal METs) for fatness change (model 2), the observed associations were slightly attenuated but remained significant for all 3 CVD risk factors (all p for trend <0.05). Every 1-MET improvement in fitness between the baseline and second examinations was associated with 7%, 22%, and 12% lower risk of subsequent incidence of hypertension, metabolic syndrome, and hypercholesterolemia, respectively. Every unit increase in percent body fat or BMI was associated with 4%, 10%, and 5%, and 16%, 37%, and 18%, respectively, higher risk of developing corresponding CVD risk factors, after adjusting for confounders and baseline levels of each exposure (model 1). Additional adjustment for fatness or fitness for each other (model 2) did not alter the associations, except for the association between each 1-MET increase and hypertension, which did not reach statistical significance.

Because waist circumference is correlated with fatness, we additionally excluded waist circumference from the metabolic syndrome criteria. However, the associations between fatness change and incident metabolic syndrome were similar (data not shown). Thus, we decided to retain waist circumference as a metabolic syndrome component because waist circumference, a marker of abdominal obesity, has independent effects on CVD. In additional analyses, we examined how change in abdominal fatness (waist circumference) related to incident CVD risk factors. The associations between change in abdominal fatness and incident CVD risk factors were very similar to the associations between change in total body fatness (percent body fat) and incident CVD risk factors (data not shown).

Table 1 Baseline Characteristics According to Changes in Fitness and Fatness

| | Fitness Change | | | | Fatness Change | | | | | | | |
| | | | | | % Body Fat Change | | | | Body Mass Index Change | | | |
Characteristics	Loss (n = 785)	Stable (n = 1,333)	Gain (n = 1,030)	p Value*	Loss (n = 1,051)	Stable (n = 1,048)	Gain (n = 1,049)	p Value*	Loss (n = 1,049)	Stable (n = 1,050)	Gain (n = 1,049)	p Value*
Age (yrs)	42.3 ± 9.0	43.0 ± 8.8	41.4 ± 8.2	<0.001	43.5 ± 8.7	41.0 ± 8.7	42.4 ± 8.5	0.009	43.3 ± 8.8	41.8 ± 8.8	41.8 ± 8.3	0.009
Maximal METs	13.5 ± 2.5	12.7 ± 2.3	12.3 ± 2.3	<0.001	12.4 ± 2.3	13.0 ± 2.4	12.8 ± 2.4	<0.001	12.4 ± 2.4	13.0 ± 2.4	12.9 ± 2.4	<0.001
Unfit†	1.0	2.6	5.4	<0.001	4.4	2.1	2.9	<0.001	4.1	2.1	3.2	<0.001
Body mass index (kg/m²)	24.0 ± 2.7	24.0 ± 2.7	24.4 ± 2.9	<0.001	24.6 ± 2.9	23.9 ± 2.7	23.9 ± 2.6	<0.001	25.0 ± 2.8	23.7 ± 2.6	23.8 ± 2.6	<0.001
18.5–24.9	66.4	65.9	61.7	0.06	57.4	68.3	68.3	0.03	53.5	69.5	71.0	0.03
25.0–29.9	31.7	32.2	33.8	0.60	38.0	29.4	30.4	0.34	41.5	29.4	26.9	0.34
≥30	1.9	1.9	4.5	<0.001	4.6	2.3	1.3	<0.001	5.0	1.1	2.1	<0.001
Body fat (%)	19.0 ± 5.6	19.6 ± 5.5	19.7 ± 5.6	0.007	21.5 ± 5.4	18.8 ± 5.5	18.2 ± 5.2	0.004	21.0 ± 5.4	18.8 ± 5.4	18.7 ± 5.6	0.004
Waist circumference (cm)	84.2 ± 10.5	84.9 ± 10.4	86.2 ± 10.9	<0.001	86.8 ± 10.7	84.3 ± 10.5	84.3 ± 10.5	<0.001	87.6 ± 10.2	83.6 ± 10.7	84.3 ± 10.5	<0.001
SBP (mm Hg)	112 ± 10	113 ± 10	113 ± 10	0.03	113 ± (10)	113 ± 10	112 ± 10	0.008	114 ± 10	112 ± 10	112 ± 9	0.008
DBP (mm Hg)	75 ± 7	75 ± 7	75 ± 7	0.42	75 ± 7	75 ± 7	75 ± 7	0.19	76 ± 7	75 ± 7	75 ± 7	0.19
Fasting glucose (mg/dl)	94.2 ± 7.9	95.2 ± 8.6	94.6 ± 8.5	0.03	95.2 ± 8.6	94.8 ± 8.5	94.4 ± 8.1	0.37	95.4 ± 8.8	94.4 ± 8.2	94.4 ± 8.2	0.38
Total cholesterol (mg/dl)	186.3 ± 26.2	187.2 ± 26.5	188.8 ± 26.3	0.11	190.9 ± 26.8	185.2 ± 26.4	186.4 ± 25.6	0.04	190.7 ± 26.7	187.0 ± 25.6	184.8 ± 26.4	0.04
Triglycerides (mg/dl)	83.5 ± 43.4	85.5 ± 39.5	90.9 ± 42.7	<0.001	89.4 ± 41.0	84.2 ± 39.4	86.8 ± 44.3	<0.001	92.3 ± 46.1	84.1 ± 38.8	83.9 ± 39.2	<0.001
HDL cholesterol (mg/dl)	52.3 ± 13.0	51.7 ± 13.0	49.9 ± 12.4	<0.001	51.0 ± 12.9	50.7 ± 12.7	52.1 ± 12.8	<0.001	50.4 ± 13.1	51.5 ± 12.4	51.9 ± 12.9	<0.001
Current smoker	13.3	14.6	12.3	0.28	13.3	12.4	14.8	0.49	12.3	13.8	14.4	0.49
Heavy drinker‡	16.7	16.0	15.9	0.89	17.6	15.4	15.4	0.68	15.9	17.3	15.2	0.68
Physically inactive§	12.7	13.7	15.0	0.39	15.4	14.3	11.8	0.17	15.6	13.8	12.1	0.17

Values are mean ± SD or %. *p value for linear trend. †Defined as the lower 20% in each age- and sex-specific distribution of maximal treadmill exercise test duration from the entire Aerobics Center Longitudinal Study population. ‡Defined as alcohol drinks >14 per week for men and >7 alcohol drinks per week for women. §Defined as no leisure-time physical activity in the 3 months before the examination.

DBP = diastolic blood pressure; HDL = high-density lipoprotein; MET = metabolic equivalent; SBP = systolic blood pressure.

| Table 2 | Hazard Ratios of Incident Cardiovascular Disease Risk Factors by Changes in Fitness and Fatness | | | | | |

	Hypertension		Metabolic Syndrome		Hypercholesterolemia	
Variable	Model 1*	Model 2†	Model 1*	Model 2†	Model 1*	Model 2†
Fitness change						
Loss	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Stable	0.74 (0.62–0.89)	0.76 (0.63–0.91)	0.58 (0.45–0.75)	0.62 (0.48–0.79)	0.74 (0.60–0.91)	0.75 (0.61–0.93)
Gain	0.72 (0.59–0.88)	0.77 (0.62–0.95)	0.48 (0.37–0.63)	0.59 (0.44–0.78)	0.70 (0.56–0.88)	0.74 (0.59–0.94)
p value for linear trend	0.003	0.02	<0.001	<0.001	0.003	0.02
Per 1-MET increase	0.93 (0.87–0.99)	0.96 (0.89–1.03)	0.78 (0.71–0.85)	0.84 (0.75–0.93)	0.88 (0.81–0.95)	0.89 (0.82–0.97)
Fatness change						
% body fat change						
Loss	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Stable	1.20 (1.00–1.44)	1.18 (0.98–1.43)	1.26 (0.99–1.62)	1.16 (0.90–1.50)	1.37 (1.11–1.69)	1.33 (1.07–1.65)
Gain	1.27 (1.05–1.53)	1.24 (1.02–1.51)	1.71 (1.34–2.19)	1.52 (1.17–1.97)	1.48 (1.20–1.83)	1.41 (1.13–1.76)
p value for linear trend	0.01	0.03	<0.001	0.002	<0.001	0.003
Per 1% increase	1.04 (1.01–1.06)	1.03 (1.01–1.06)	1.10 (1.06–1.13)	1.08 (1.05–1.12)	1.05 (1.02–1.08)	1.04 (1.01–1.07)
BMI change						
Loss	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
Stable	1.28 (1.07–1.53)	1.28 (1.06–1.53)	1.19 (0.93–1.53)	1.12 (0.86–1.44)	1.17 (0.96–1.44)	1.16 (0.94–1.43)
Gain	1.28 (1.07–1.54)	1.27 (1.05–1.54)	1.90 (1.50–2.42)	1.74 (1.35–2.24)	1.51 (1.23–1.85)	1.46 (1.18–1.81)
p value for linear trend	0.002	0.006	<0.001	<0.001	<0.001	<0.001
Per 1-kg/m² increase	1.16 (1.08–1.24)	1.15 (1.08–1.24)	1.37 (1.26–1.48)	1.34 (1.23–1.47)	1.18 (1.10–1.27)	1.17 (1.09–1.26)

Values are hazard ratio (95% confidence interval). *Model 1 was adjusted for age, sex, examination year at baseline, and baseline systolic blood pressure for hypertension, baseline metabolic syndrome components (systolic blood pressure, fasting glucose, triglyceride, high-density lipoprotein cholesterol, and waist circumference) for metabolic syndrome, or baseline total cholesterol for hypercholesterolemia, and baseline maximal METs for fitness change, baseline percent body fat for percent body fat change, or baseline BMI for BMI change, and lifestyle changes (smoking status, alcohol intake, and physical activity) between the baseline and second examinations. †Model 2 was adjusted as for model 1 plus baseline percent body fat and percent body fat change for fitness change or baseline maximal METs and maximal MET change for fatness change.

BMI = body mass index; CI = confidence interval; MET = metabolic equivalent.

In the joint analyses (Fig. 1), fitness loss, combined with stable or increased fatness, was associated with a higher risk of developing hypertension and hypercholesterolemia, compared with the reference, fitness gain, and fatness loss groups. However, both losing fitness regardless of fatness change, and gaining fatness regardless of fitness change, were associated with a higher risk of developing metabolic syndrome. In the development of each CVD risk factor, the increased risks associated with fat gain appeared to be attenuated when fitness was maintained or improved. Similarly, the increased risks associated with fitness loss also appeared to be attenuated when fatness was reduced, particularly in hypertension and hypercholesterolemia. We observed similar results in the combined associations of changes in fitness and BMI with incident CVD risk factors (data not shown).

Fitness change was negatively associated with blood pressure, waist circumference, triglycerides, and total cholesterol and positively associated with HDL cholesterol (Table 3). Fatness change was positively associated with blood pressure, waist circumference, fasting glucose, triglycerides, and total cholesterol and negatively associated with HDL cholesterol. These significant correlations (all p values <0.05) were adjusted for baseline age, sex, and change in fatness or fitness for each other. In general, the correlations for change in fitness with components of CVD risk factors were as strong as the change in fatness. Changes in both fitness and fatness had relatively higher correlations with change in waist circumference. The correlation coefficient

between the change in fitness and the change in fatness (percent body fat) was −0.37 (p < 0.001).

Discussion

Changes in both fitness and fatness were significantly associated with the development of hypertension, metabolic syndrome, and hypercholesterolemia in these healthy adults. These associations were found after accounting for possible baseline confounders, changes in lifestyle, and simultaneous change in fatness or fitness for each other. Significant correlations between changes in fitness or fatness and each component of CVD risk factors, such as blood pressure, lipids, and fasting glucose, supported these results. In the joint analyses, maintaining or improving fitness appeared to attenuate, although not completely eliminate, some of the negative effects of fat gain. In addition, reducing body fat was likely to counteract some of the increased risk of developing CVD risk factors associated with fitness loss.

The CARDIA (Coronary Artery Risk Development in Young Adults) study found that improving fitness was associated with reduced risk for developing type 2 diabetes and metabolic syndrome but was not associated with hypertension or hypercholesterolemia (2). However, after further adjustment for baseline BMI and weight change, the hazard ratios were no longer significant for any CVD risk factors. The inconsistency between the CARDIA study and the current study may be due to the younger population in the
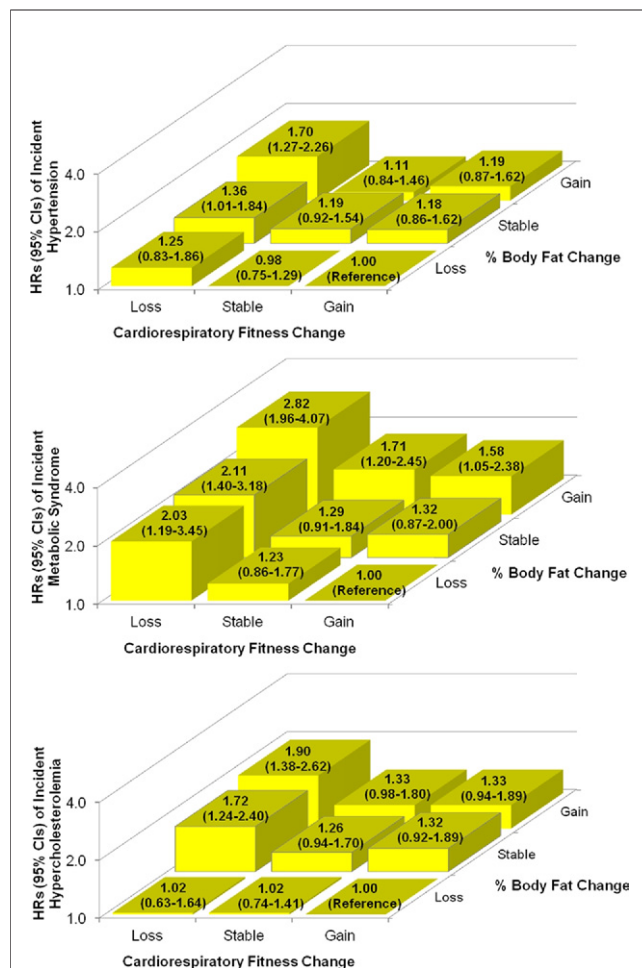
| Figure 1 | **HRs (95% CIs) of Incident Cardiovascular Disease Risk Factors According to Combined Categories of Changes in Cardiorespiratory Fitness and Percent Body Fat** |

Adjusted for age, sex, examination year, maximal metabolic equivalents, percent body fat at baseline, and baseline systolic blood pressure for hypertension, baseline metabolic syndrome components (systolic blood pressure, fasting glucose, triglyceride, high-density lipoprotein cholesterol, and waist circumference) for metabolic syndrome, or baseline total cholesterol for hypercholesterolemia, and lifestyle changes (smoking status, alcohol intake, and physical activity) between the baseline and second examinations. The number of participants in the fitness loss, stable, and gain groups were 130, 401, and 520 in the percent body fat loss group; 305, 488, and 255 in the stable percent body fat group; and 350, 444, and 255 in the percent body fat gain group, respectively. HR = hazard ratio; CI = confidence interval.

CARDIA study (mean age 25 years), resulting in lower incident rates for CVD risk factors. In addition, the CARDIA study excluded participants with only a given CVD risk factor at baseline from the incident analysis of that CVD risk factor, and fitness change over the 7 years was the first half of the 15 years of follow-up period for incident CVD risk factors.

There is convincing evidence from clinical trials and epidemiologic studies that improving physical activity or, especially, fitness is beneficial (2,26,27), whereas gaining weight or fatness is detrimental (7,28–30) for developing hypertension, metabolic syndrome, and hypercholesterolemia. Also, improving physical activity or fitness is correlated with favorable changes in components of CVD risk factors such as blood pressure, lipid profiles, and waist circumference (31–34) and gaining weight or fatness is correlated with unfavorable changes in such components (29,33,35). However, most previous studies have examined the associations between changes in either fitness or fatness and simultaneous changes in such CVD risk factors during the same time interval. Thus, the causal relationships among changes in fitness, fatness, and CVD risk factors are uncertain because CVD risk factors may also affect changes in fitness and fatness. Many studies on changes in fitness or fatness also have not mutually adjusted for each other, although both are strong independent risk factors on developing CVD risk factors.

Whether physical activity or fitness can compensate for the health hazards of overweight or obesity, comprising two-thirds of the U.S. adult population (36), and understanding the relative contributions among these factors has clinical and public health significance. Several prospective studies found that both physical activity or fitness and obesity are independent predictors for the development of CVD risk factors (18,37,38). Although study results vary depending on study population, health status, assessment of physical activity or fitness, and study outcome (11), objectively measured fitness results in stronger associations with health outcomes than does self-reported physical activity (39). Most previous studies examined the combined associations of fitness and fatness at one time point with subsequent incidence of outcomes. Our results support that not only baseline fitness and fatness but also changes in fitness and fatness are significantly associated with incident CVD risk factors.

It is postulated that improving fitness or physical activity by exercise training may reduce blood pressure through reductions in catecholamines and total peripheral resistance, as well as alterations in vasodilators and vasoconstrictors (40). Exercise-induced changes in metabolic factors, such as improvements in glucose metabolism, insulin sensitivity, lipoprotein subfraction profiles (32), and reductions in inflammation markers and visceral and liver fat, even in the absence of weight loss (31), may serve as links between improving fitness and the lower risk for metabolic syndrome and hypercholesterolemia independent of fatness change. For mechanisms between fatness and CVD risk factors, increases in sympathetic nervous system activity, renal sodium retention, and systemic vascular resistance have been considered to play a role in obesity-induced hypertension (41). Several proposed mechanisms linking obesity (particularly visceral fat) to metabolic syndrome and hyperlipidemias include insulin resistance, atherogenic dyslipidemia, oxidative stress, elevated fatty acids, inflammation, and ectopic fat deposition (42,43).

Study limitations. Limitations of our study include a population that consists primarily of well-educated, non-

| Table 3 | Correlations Between Changes in Fitness or Fatness and Changes in Components of Cardiovascular Disease Risk Factors Between Baseline and Second Examinations |

| | Fitness Change | | Fatness Change | | | |
| | | | % Body Fat Change | | BMI Change | |
CVD Risk Factor Components	r*	p Value	r*	p Value	r*	p Value
Unadjusted						
Systolic blood pressure change	–0.08	<0.001	0.10	<0.001	0.14	<0.001
Diastolic blood pressure change	–0.05	0.003	0.06	0.002	0.09	<0.001
Waist circumference change	–0.21	<0.001	0.35	<0.001	0.38	<0.001
Fasting glucose change	0.01	0.43	0.05	0.006	0.10	<0.001
Triglycerides change	–0.15	<0.001	0.16	<0.001	0.23	<0.001
HDL cholesterol change	0.11	<0.001	–0.12	<0.001	–0.11	<0.001
Total cholesterol change	–0.12	<0.001	0.21	<0.001	0.22	<0.001
Adjusted for age, sex, and % body fat change for fitness change or maximal MET change for fatness change						
Systolic blood pressure change	–0.05	0.006	0.07	<0.001	0.12	<0.001
Diastolic blood pressure change	–0.04	0.045	0.04	0.04	0.07	<0.001
Waist circumference change	–0.14	<0.001	0.37	<0.001	0.42	<0.001
Fasting glucose change	0.03	0.08	0.06	0.002	0.10	<0.001
Triglycerides change	–0.10	<0.001	0.12	<0.001	0.19	<0.001
HDL cholesterol change	0.08	<0.001	–0.09	<0.001	–0.08	<0.001
Total cholesterol change	–0.05	0.008	0.17	<0.001	0.18	<0.001

*Values are Pearson correlation coefficients in the unadjusted model and Pearson partial correlation coefficients in the adjusted model.
CVD = cardiovascular disease; HDL = high-density lipoprotein; other abbreviations as in Table 2.

Hispanic white subjects from middle-to-upper socioeconomic strata; thus, it is possible that the results may be different in other populations. However, fitness and other physiological characteristics in this cohort are similar to representative North American populations (17), and the socioeconomic homogeneity can reduce potential confounding of education, income, and ethnicity. We do not have information on whether changes in fitness and fatness were intentional, and cautious interpretation of these results is therefore necessary. However, to minimize potential confounding by unintentional changes in fitness and fatness due to disease, we excluded individuals with various chronic diseases and subclinical conditions before the outcome follow-up. In fact, we observed positive correlations between changes in fitness and physical activity (r = 0.22; p < 0.001), and negative correlations between changes in fatness and physical activity (r = −0.14; p < 0.001). The lack of data on medications and diet information may have biased the results through the misclassification of hypertension, metabolic syndrome, and hypercholesterolemia and potential effects on changes in fatness and the development of CVD risk factors.

This prospective study expands knowledge about the effects of fitness and fatness on CVD morbidity and mortality by exploring the independent and combined associations of changes in these exposures with the development of CVD risk factors over a wide age range of healthy adults, using objective measures for fitness and fatness. Given the concern over the strong confounding effect of ill health on these associations (19), extensive exclusion of pre-existing and subclinical conditions strengthens our results.

Conclusions

We found that changes in both fitness and fatness, even after controlling for each other, were significantly associated with the development of CVD risk factors of hypertension, metabolic syndrome, and hypercholesterolemia in this healthy adult population. In addition, maintaining or improving fitness is likely to counteract, although not completely eliminate, some of the adverse effects of fat gain. Similarly, reducing body fat seems to compensate for some of the increased risk of developing CVD risk factors associated with fitness loss.

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