Adverse Cardiovascular Response to Aerobic Exercise Training: Is This a Concern?

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ABSTRACT

LEIFER, E. S., C. R. MIKUS, L. KARAVIRTA, B. D. RESNICK, W. E. KRAUS, K. HÄKKINEN, C. P. EARNEST, and J. L. FLEG. Adverse Cardiovascular Response to Aerobic Exercise Training: Is This a Concern? *Med. Sci. Sports Exerc.*, Vol. 48, No. 1, pp. 20–25, 2016. **Purpose**: Aerobic exercise training in sedentary individuals improves physical fitness and various cardiovascular (CV) biomarkers. Nevertheless, there has been controversy as to whether exercise training may adversely affect some biomarkers in a small segment of the population. The purpose of this study was to investigate whether clinically significant worsening of CV biomarkers was more prevalent among individuals randomized to a supervised endurance training program as compared with those randomized to a control condition. **Methods**: Baseline and end of study measurements of fasting insulin (FI), triglycerides (TG), resting systolic blood pressure (SBP), and HDL cholesterol (HDL-C) were obtained on 1188 healthy sedentary subjects from 4 clinical studies. Each study randomized subjects to 4- to 6-month supervised aerobic exercise programs or to a control group of no supervised exercise training. For each of the 4 CV biomarkers, we calculated the respective proportions of control and exercise group subjects whose baseline–to–follow-up changes were greater than or equal to previously reported adverse change (AC) thresholds. Those thresholds were increases of 24 pmol·L^{-1} or greater for FI, 0.42 mmol·L^{-1} or greater for TG, 10 mm Hg or greater for SBP, and a decrease of 0.12 mmol·L^{-1} or greater for HDL-C. **Results**: The respective proportions of subjects meeting the AC threshold in the control and exercise groups were 15.2% versus 9.6% ($P = 0.02$) for FI, 14.9% versus 13.1% ($P = 0.37$) for TG, 16.9% versus 15.8% ($P = 0.52$) for SBP, and 28.6% versus 22.5% ($P = 0.03$) for HDL-C. All were nonsignificant at the 0.0125 Bonferroni threshold adjusting for multiple comparisons. **Conclusions**: These findings do not support the concept that aerobic exercise training increases the risk of adverse changes in the CV biomarkers we studied. **Key Words:** PHYSICAL ACTIVITY, BIOMARKER, INDIVIDUAL, RANDOMIZED TRIAL

Current public health recommendations are for adults to be physically active at a moderate intensity for 150 min or greater per week at a vigorous intensity for 75 min or greater per week or a combination thereof (20). These recommendations are based on studies showing that exercise training improves various cardiovascular, metabolic, and psychological measures (6,7). However, because of individual heterogeneity, there is the possibility that physical activity can adversely affect one or more of these measures in some individuals (4). If so, it would be important to accurately identify and quantify such responses as this has become a controversial area in the field of lifestyle medicine.

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In 6 pooled studies of sedentary subjects undergoing 4 to 6 months of aerobic exercise training, Bouchard et al. reported 8% to 13% adverse change (AC, defined precisely in the Methods below) rates from baseline to follow-up in fasting insulin (FI), triglycerides (TG), resting systolic blood pressure (SBP), and HDL cholesterol (HDL-C) (4). Bouchard et al. used data from the Dose Response to Exercise in Women (DREW) study; the Inflammation and Exercise (INFLAME) study; the University of Jyväskylä study; Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE); the Health, Risk Factors, Exercise Training And Genetics Family study (HERITAGE); and the University of Maryland Gene Exercise Research study (2,5,7,8,11,12,13,19,21). The first 4 studies included a group of control subjects who did not receive the exercise intervention, whereas the latter 2 studies did not.

Bouchard et al. restricted their analyses to the subjects who received the exercise intervention and did not make comparisons to subjects who did not receive the intervention. This strategy can be problematic because in the absence of a control group who did not receive the intervention, it is difficult to discern the extent to which observed changes in the

exercise group were due to factors independent of the exercise intervention, including day-to-day biological variation, technical variation associated with laboratory testing, and physiological change (3) unrelated to exercise (e.g., stress, illness, or changes in diet). To address this issue, we compared the AC rates between the control and exercise groups for the 4 studies that included a control group, restricting our analysis to the DREW, INFLAME, University of Jyväskylä, and STRRIDE cohorts.

METHODS

Data were obtained from 1188 healthy sedentary subjects enrolled in one of the following 4 studies: DREW, INFLAME, University of Jyväskylä, and STRRIDE that are briefly described below. Each study was approved by the institutional review board or ethics committee at the corresponding center, and subjects provided written informed consent.

Dose Response to Exercise in Women (DREW) study. The DREW trial enrolled 464 sedentary, postmenopausal overweight or obese women with normal-to-high systolic blood pressure and randomized them to either a nonexercise control group (n = 102) or one of 3 endurance exercise groups (n = 362), which expended 4, 8, or 12 kcal·kg^{-1}·wk^{-1}, respectively (7,13). Exercising women participated in 3 or 4 supervised training sessions each week for 6 months with target training intensity at the heart rate associated with 50% of each woman's peak relative oxygen consumption ($\dot{V}O_{2peak}$).

Inflammation and Exercise (INFLAME) study. The INFLAME study randomized 162 sedentary men and women with elevated C-reactive protein (≥2.0 mg·L^{-1} but <10.0 mg·L^{-1}) to a nonexercise control group (n = 82) or an endurance exercise group (n = 80) that trained for 4 months (8,19). The exercise group trained in a supervised exercise laboratory and had a target exercise dose of 16 kcal·kg^{-1}·wk^{-1}, which roughly corresponds to 150 to 210 min of 60% to 80% $\dot{V}O_{2peak}$ activity. The supervised exercise was divided into 3 to 5 sessions per week.

University of Jyväskylä study. The University of Jyväskylä study randomized 175 previously untrained volunteers to a nonexercise control group (n = 35) or a 21-wk supervised period of either strength training (S) twice a week (n = 31), endurance training (E) twice a week (n = 51), or their combination (ES, n = 54) 4 times per week (11). Endurance training included 30 to 90 min of indoor cycling per session of moderate to vigorous intensity. Because our analysis focuses on aerobic exercise, we only include in our exercise group the 105 subjects who were in the E or ES groups.

Studies of a Targeted Risk Reduction Intervention through Defined Exercise (STRRIDE). STRRIDE included 2 studies: the original STRRIDE study and STRRIDE aerobic training versus resistance training (AT/RT). STRRIDE was composed of 40 to 65-yr-old, sedentary dyslipidemic men and women with BMI 25–35 kg·m^{-2} (12). Subjects were randomized to either a nonexercise control group (n = 28) or one of 3 aerobic exercise groups (n = 166), which exercised for 8 months. STRRIDE also included n = 33 crossover subjects who had a nonexercise control period followed by an aerobic exercise period. In our analysis, the crossover subjects were included in our control group, and we only used their control period data. Thus, STRRIDE contributed (n = 28 + 33) 61 subjects to our control group and n = 166 subjects to our exercise group. STRRIDE-AT/RT enrolled subjects that were similar to those in STRRIDE. However, all STRRIDE-AT/RT subjects had a nonexercise control period, followed by an exercise period of aerobic and/or resistance training (2). We included in our control group the control period data from the n = 65 STRRIDE-AT/RT subjects who underwent resistance but no aerobic training. We included in our exercise group the exercise period data from the n = 130 STRRIDE-AT/RT who underwent aerobic training with or without resistance training.

Adverse change threshold. Fasting insulin, TG, SBP, and HDL-C measurements were measured at baseline and at the end of the study. For each of the respective 4 cardiovascular biomarkers, we analyzed all subjects who had baseline and end-of-study data by the intention-to-treat principle using their randomized group. We used the same AC thresholds that were defined by Bouchard et al. for FI, TG, SBP, and HDL-C (4). Those AC thresholds were baseline to end-of-study increases of 24 pmol·L^{-1} or greater for FI, 0.42 mmol·L^{-1} or greater for TG, 10 mm Hg or greater for SBP, and a decrease of 0.12 mmol·L^{-1} or greater for HDL-C. The purpose of the AC thresholds was to account for within-subject measurement variability for each of the 4 biomarkers. Such measurement variability arises from day-to-day biological variation, technical variation associated with laboratory testing, and physiological change (3) unrelated to exercise (e.g., stress, illness, or changes in diet). Bouchard et al. obtained these thresholds by measuring each biomarker 3 times (except twice for FI) in 60 HERITAGE subjects before exercise training over a period of 3 wk. The AC threshold corresponded to twice the within-subject standard deviation. For FI, other HERITAGE data and observations from the literature were also used to obtain the within-subject standard deviation.

Our 4 primary comparisons tested whether the AC rates for FI, TG, SBP, and HDL-C differed between the control and exercise subjects. These analyses were performed stratifying by study. A permutation version of the Mantel–Haenszel statistic was used to account for small sample sizes for some of the strata. The Mantel–Haenszel statistic is similar to the Fisher exact test statistic in that it tests whether the AC rates are the same in the control and exercise groups. However, unlike Fisher test, the Mantel–Haenszel statistic allows for stratifying by study. We also tested whether the control and exercise groups differed in the number of biomarkers that showed an adverse change per subject, using a permutation version of the Wilcoxon rank sum test stratified by study. We also examined whether the baseline characteristics age, sex, race/ethnicity, BMI, and $\dot{V}O_{2peak}$ (mL·min^{-1}·kg^{-1}) affected the probability of an AC differed between the control and exercise groups.

TABLE 1. Baseline characteristics of subjects.

	Overall $n = 1188$	Drew $n = 464$	Inflame $n = 162$	Jyväskylä $n = 140$	STRRIDE $n = 422$
Female (%)	73	100	73	49	48
Age	54 (41–64)	56 (50–66)	50 (35–64)	52 (43–64)	51 (39–62)
Ethnicity/race (%)					
White	74	64	65	100	80
African American	21	29	23	0	18
Hispanic or other	5	7	12	0	2
BMI ($kg \cdot m^{-2}$)	30 (25–36)	32 (27–37)	32 (27–37)	25 (21–29)	30 (26–34)
$\dot{V}O_{2peak}$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	19.6 (12.9–33.5)	15.1 (11.5–19.2)	17.7 (12.5–27.3)	30.1 (21.9–37.7)	27.2 (20.2–36.0)
Insulin ($pmol \cdot L^{-1}$)	58 (26–125)	63 (31–127)	77 (42–158)	28 (15–49)	53 (26–112)
Triglycerides ($mmol \cdot L^{-1}$)	1.32 (0.70–2.41)	1.37 (0.70–2.41)	1.25 (0.63–2.01)	1.00 (0.56–1.87)	1.45 (0.84–2.66)
SBP (mm Hg)	133 (112–153)	140 (123–156)	131 (107–156)	131 (113–149)	118 (104–136)
HDL-C ($mmol \cdot L^{-1}$)	1.29 (0.91–1.86)	1.42 (1.07–1.97)	1.35 (1.01–1.91)	1.27 (0.85–1.84)	1.11 (0.83–1.68)

Continuous variables are reported as: median (10^{th} percentile, 90^{th} percentile).

These analyses were performed using logistic regression where the log odds of an AC was modeled as a linear function of the randomization assignment, study, baseline characteristic, and randomization assignment-by-baseline characteristic interaction. Significance was determined using the Wald statistic for the randomization assignment-by-baseline characteristic interaction.

To examine the robustness of our results with respect to the choice of the AC threshold, we also compared the control and exercise groups using the control group's fifth percentile for baseline-to-follow-up change as the AC threshold. Those AC thresholds corresponded to baseline-to-follow-up increases of 39 $pmol \cdot L^{-1}$ or greater for FI, 0.95 $mmol \cdot L^{-1}$ or greater for TG, and 21 mm Hg or greater for SBP and a baseline-to-follow-up decrease of 0.36 $mmol \cdot L^{-1}$ or greater for HDL-C. Because the control group was used for setting the AC threshold, the *P* value computation was based on the negative hypergeometric distribution (10,15,16).

Finally, we tested whether the mean changes for each of the 4 CV biomarkers differed between the control and exercise groups, using an analysis of covariance with study as an adjustment factor. We used the Levene test adjusted for study to assess whether the standard deviation of the changes for each of the 4 CV biomarkers differed between the control and exercise groups.

We tested each of the 4 primary comparisons at the Bonferroni corrected 0.0125 = 0.05/4 two-sided significance level. Because the remaining analyses were exploratory, we used a 0.05 two-sided nominal significance level. Analyses were performed using R version 3.1.1 including the "rms" and "coin" packages (17) and SAS software version 9.3 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Table 1 gives the baseline characteristics for each study in our analysis and the overall sample. Table 2 reports the respective AC thresholds for each of the 4 biomarkers and the proportions of subjects in the control and exercise groups meeting those thresholds. There was no significant difference at the Bonferroni 0.0125 level between the control and exercise groups for any of the 4 biomarkers, although the observed control AC rate was larger than the observed exercise AC rate for all 4 biomarkers. This is reflected in Table 3, which reports the number of ACs per subject among the 651 subjects (55%) who had baseline and follow-up data for all 4 biomarkers. Among those subjects captured in Table 3, there were significantly more ACs per subject among controls than exercise subjects ($P = 0.02$). For the respective baseline characteristics age, BMI, $\dot{V}O_{2peak}$, sex, and race/ethnicity, there were no randomization assignment-by-baseline characteristic interactions (analyses available from the first author upon request).

Table 4 shows the AC rates according to the control group's fifth percentile AC thresholds. There were no significant differences between the exercise and control group AC rates for any of the 4 biomarkers.

Finally, histograms of baseline-to-follow-up changes for each of the 4 biomarkers are displayed in Figure 1 according to randomized group. As can be seen for each biomarker, the control and exercise groups' histograms are quite similar. In particular, for each biomarker, the standard deviations were nearly the same for the control and exercise groups. For the control versus exercise comparisons, the standard deviations of the baseline to follow-up changes were 28 versus 29 $pmol \cdot L^{-1}$ for FI, 0.56 versus 0.56 $mmol \cdot L^{-1}$ for TG, 0.20 versus 0.19 $mmol \cdot L^{-1}$ for HDL-C, and 13.1 versus 12.8 mm Hg for SBP. The similarity of standard deviations is important because if there were an excess of adverse changes in the exercise group, we would have expected to see a larger standard deviation in that group and a larger histogram tail in the adverse direction (14). Nevertheless, exercise group subjects had significantly more favorable mean changes than control subjects in fasting FI (control vs exercise: 1.8 vs -6.5 $pmol \cdot L^{-1}$, $P = 0.02$), TG (-0.03 vs -0.11 $mmol \cdot L^{-1}$, $P = 0.02$), and HDL-C

TABLE 2. Adverse change thresholds for the baseline-to-follow-up differences for the 4 metabolic variables.

	AC Threshold	Controls Meeting AC Threshold	Exercisers Meeting AC Threshold	*P* Value[a]
Insulin	≥ 24 $pmol \cdot L^{-1}$	44/289 (15.2%)	65/676 (9.6%)	0.02
Triglycerides	≥ 0.42 $mmol \cdot L^{-1}$	47/315 (14.9%)	99/754 (13.1%)	0.37
SBP	≥ 10 mm Hg	41/243 (16.9%)	89/562 (15.8%)	0.52
HDL-C	≥ -0.12 $mmol \cdot L^{-1}$	90/315 (28.6%)	170/755 (22.5%)	0.03

[a]Two-tailed permuted Mantel-Haenszel test stratified on study.

TABLE 3. Number (and percent of total) of adverse changes per subject.[a]

	Number (%) of Adverse Changes				
	0	1	2	3	4
Control	78 (39.6)	90 (45.7)	20 (10.2)	9 (4.6)	0 (0)
Exercise	232 (51.1)	158 (34.8)	56 (12.3)	7 (1.5)	1 (0)

[a]Includes the 651 subjects (55%) who had baseline and follow-up data for all 4 cardiovascular variables. Two-tailed P value = 0.02 using a permuted Wilcoxon rank sum test stratified by study.

(-0.03 vs 0.00 mmol·L^{-1} $P = 0.02$) with no significant difference for SBP (-1.9 vs -2.0 mm Hg, $P = 0.36$).

DISCUSSION

Bouchard et al. defined AC thresholds for FI, TG, SBP, and HDL-C for subjects undergoing aerobic exercise training. The current analyses showed that for each of those 4 CV biomarkers in the 1188 subjects comprising 4 aerobic exercise training studies, there were no significant differences between the control and exercise groups' AC rates using a Bonferroni-corrected 0.0125 significance level. Nevertheless, for all 4 biomarkers, the observed AC rates for the exercise group were lower than those for the control group with a trend toward significance for FI ($P = 0.02$) and HDL-C ($P = 0.03$). The lower observed AC rates in the exercise group were reflected in the 651subjects who had complete baseline and follow-up data for all 4 biomarkers. Among those subjects, there were more ACs per subject among controls than exercise subjects ($P = 0.02$). Nevertheless, with respect to AC rates, there were no significant interactions between randomized group and the respective baseline characteristics of age, sex, race/ethnicity, BMI, and $\dot{V}O_{2peak}$ (mL·min^{-1}·kg^{-1}). Finally, the mean changes in FI, TG, and HDL-C reflected the expected benefit of exercise training. Thus, the current findings do not suggest that 4 to 6 months of aerobic exercise training is associated with a higher likelihood of adverse response in these biomarkers than in nonexercising individuals.

It is important to note that different AC thresholds could have been used than the ones defined by Bouchard et al. The AC thresholds from that analysis were based on the within-subject standard deviation from an ancillary study of HERITAGE in conjunction with observations from the literature. We used those AC thresholds to make our results directly comparable with theirs. A criticism of such an approach is that the within-subject standard deviation from a single study might not be applicable to a cohort of subjects from other studies. This suggests using the control subjects in the current cohort to set the AC threshold because it is this control group that is the direct comparator to this cohort's exercise group. For example, the AC threshold could be set at some percentile (e.g., 5th or 10th) of the control group's baseline-to-follow-up changes. The choice of percentile is subjective and should correspond to a reasonable amount of natural biological and technical variation in the control group.

To examine the robustness our results, we used the control group's fifth percentile for the AC threshold, which corresponded to baseline-to-follow-up increases of 39 pmol·L^{-1} or greater for FI, 0.95 mmol·L^{-1} or greater for TG, 21 mm Hg or greater for SBP and a baseline-to-follow-up decrease of 0.36 mmol·L^{-1} or greater for HDL-C. At first glance, these thresholds may seem extreme and are substantially larger than the primary analysis thresholds in Table 2. Nevertheless, as these are the control group's fifth percentiles, then by definition, approximately 5% of control subjects exceeded each threshold. Thus, in the control group, there was substantial natural biological variability over the 4- to 6-month follow-up period. By randomization, it is reasonable to assume such natural variability also existed in the exercise group. Using these more extreme AC thresholds, there were also no significant differences between the exercise and control group AC rates for any of the 4 biomarkers (Table 4).

In a recent review on interindividual differences in the physiological response to an intervention, Atkinson and Batterham emphasize the importance of having a control group to which the within-subject random variation of the intervention group can be compared (1). They present a useful example with simulated blood pressure data, which shows how individual differences in blood pressure response to an intervention that were simulated to be solely due to random variation could be mistaken for true differences if the control group data were ignored. In their discussion, they explain that "If the standard deviation of the changes in the intervention group is not substantially larger than that in the control arm, then it can be said that there is negligible interindividual variability response to the intervention." This is exactly what we

TABLE 4. Adverse change (AC) thresholds based on the control group's approximate 5th percentile.

	AC Threshold[a]	Controls Meeting AC Threshold	Exercisers Meeting AC Threshold	P Value[b]
Insulin	≥39 pmol·L^{-1}	12/289 (4.2%)	30/676 (4.4%)	0.40
Triglycerides	≥0.95 mmol·L^{-1}	15/315 (4.8%)	22/754 (2.9%)	0.16
SBP	≥21 mm Hg	12/243 (4.9%)	21/562 (3.7%)	0.46
HDL-C	≥-0.36 mmol·L^{-1}	13/315 (4.1%)	25/755 (3.3%)	0.56

[a]The AC thresholds correspond to the upper 5th percentile in the adverse direction of the control group's observed changes. The 5th percentile corresponds to approximately and not exactly 5% of the control subjects due to ties in the baseline–to–follow-up changes in the control group and the fact that the number of control subjects is not a multiple of 20 since 0.05 = 1/20.
[b]Negative hypergeometric distribution 2-sided P value.

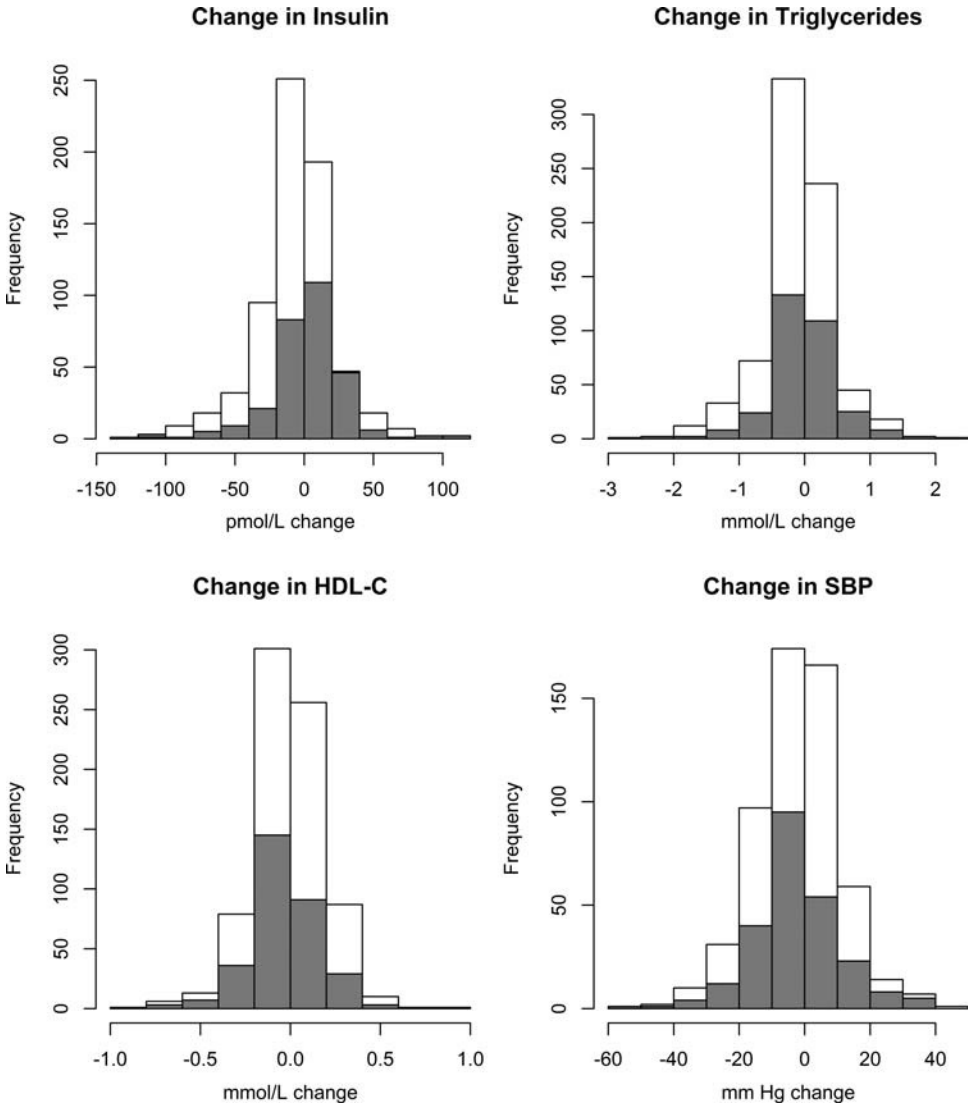

FIGURE 1—Histograms of the control (n = 345) and exercise group's (n = 843) baseline–to–follow-up changes for fasting insulin, triglycerides, SBP, and HDL-C. The control group corresponds to the shaded bars, and the exercise group corresponds to the unshaded bars.

observed in our data, where for the control versus exercise group, respectively, the standard deviations of the baseline–to–follow-up changes were 28 versus 29 pmol·L^{-1} for FI, 0.56 versus 0.56 mmol·L^{-1} for TG, 0.20 versus 0.19 mmol·L^{-1} for HDL-C, and 13.1 versus 12.8 mm Hg for SBP. Moreover, we obtained similarly shaped histograms of baseline–to–follow-up changes for the control and exercise groups. This is important because if adverse changes were more prevalent in the exercise group in conjunction with more favorable mean changes in that group, we would have expected to see a larger histogram tail in the adverse direction of the exercise group as compared with controls.

Our study has the following limitations: First, our analysis is limited to generally healthy middle-age subjects studied over 4 to 6 months of aerobic training. Thus, these findings cannot necessarily be extrapolated to older individuals or those with overt CV disease or to other forms of exercise training. Next, our findings apply only to the 4 CV biomarkers measured. In addition, it is possible, although unlikely, that some of the control group subjects exercised regularly. This would have increased the similarity between the control and exercise groups, making it more difficult to detect a difference in the AC rates. Perhaps most importantly, the parallel arm study design makes it virtually impossible to identify specific individuals as having an adverse response to exercise. Indeed, a subject would need to participate in a multiperiod crossover design to definitively determine whether he or she consistently responds adversely to exercise. Such a design would require several periods under the control and exercise conditions in random order (18). Our parallel arm design only allows us to set a reasonable threshold that is suggestive of an adverse change and to compare the respective proportions of control and exercise subjects who met that threshold. Nevertheless,

the exercise group was closely monitored for adherence to the intervention, and we did not observe an excess of exercise subjects as compared with controls who met the AC thresholds.

In conclusion, the current data do not support the concept that aerobic exercise training confers increased risk for an adverse response for the common CV biomarkers we studied as compared with nonexercising individuals. Thus, current guidelines to participate in moderate intensity exercise programs are reasonable for the general population without significant concerns of adverse responses in these biomarkers. Moreover, this study reaffirms the benefits of exercise on the basis of the larger mean positive changes in the exercise group. However, monitoring of individuals' responses remains important as for any given risk marker, including those for whom exercise therapy might be recommended because there is significant variability of response and the possibility of adverse change.

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