

Separate Effects of Intensity and Amount of Exercise on Interindividual Cardiorespiratory Fitness Response

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Abstract

Objective: To determine the separate effects of exercise intensity and amount on interindividual cardiorespiratory fitness (CRF) response.

Participants and Methods: Participants were 121 (75 females, 62%) sedentary, middle-aged (mean [SD] age, 53.2 [7.5] years), abdominally obese adults who completed at least 90% of 5 weekly exercise sessions prescribed over a 24-week intervention. Participants were randomly assigned to (1) low-amount, low-intensity exercise (LALI) (180 and 300 kcal per session for women and men, respectively, at 50% of CRF [$\dot{V}O_{2peak}$]; n=39), (2) high-amount, low-intensity exercise (HALI) (360 and 600 kcal per session for women and men, respectively, at 50% of CRF; n=51), or high-amount, high-intensity exercise (HAHI) (360 and 600 kcal per session for women and men, respectively, at 75% of CRF; n=31). Cardiorespiratory fitness was measured using a treadmill test at 4, 8, 16, and 24 weeks. The study duration was September 1, 2009, through May 31, 2013.

Results: Cardiorespiratory fitness increased within all 3 groups at 24 weeks ($P<.001$). At 24 weeks, 38.5% (15 of 39), 17.6% (9 of 51), and 0% (0 of 31) of the participants within the LALI, HALI, and HAHI groups, respectively, were CRF nonresponders. At a fixed exercise intensity, increasing exercise amount reduced the rate of nonresponse by 50% ($P=.02$). At a fixed amount of exercise, increasing the exercise intensity eliminated nonresponse ($P=.001$). Exposure to exercise decreased the number of CRF nonresponders between 4 and 8 weeks for LALI and by 16 weeks for HALI but plateaued thereafter. For HAHI, the number of CRF nonresponders decreased continually over the 24 weeks.

Conclusion: For a fixed amount of exercise, increasing exercise intensity consistent with consensus recommendations eliminated CRF nonresponse. Low-intensity exercise may not be sufficient to improve CRF for a substantial proportion of sedentary obese adults.

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Cardiorespiratory fitness (CRF) is an established independent predictor of cardiovascular disease (CVD) and all-cause mortality,¹⁻³ and the addition of CRF to established algorithms improves CVD risk classification.⁴ Although it is known that increasing physical activity is associated with improvements in CRF at the group level,⁵ there is a growing body of evidence confirming that the association between physical activity and CRF may not apply to each member of that group. Bouchard and Rankinen⁶ were the first to carefully document the enormous heterogeneity in CRF response with variability in improvement to a standardized dose of exercise ranging from 0 (nonresponse) to 1 L of oxygen, a finding later confirmed by others.^{7,8} Of importance is the observation that

in all studies, a substantive proportion of the participants were considered CRF nonresponders. Given that exercise-induced improvement in CRF is associated with corresponding reductions in CVD risk,^{9,10} CRF nonresponse to exercise is a clinically relevant concern.

The mechanistic underpinnings responsible for the heterogeneity in response to a standard dose of exercise are unclear. Sisson et al⁸ considered whether varying the amount of exercise performed influenced the rate of CRF nonresponse in postmenopausal women. The authors reported that the amount (energy expenditure) of exercise performed at a fixed intensity significantly influenced CRF response—participants exercising for approximately 120 min/wk were

55% more likely to improve CRF than those exercising for 60 min/wk.

We⁵ and others¹¹ have found that for a fixed amount of exercise, intensity is positively associated with greater improvements in CRF compared with lower-intensity exercise at the group level. To our knowledge, there are no randomized studies that have simultaneously investigated the separate and combined effects of exercise intensity and amount on interindividual CRF response. Thus, questions with important practical and clinical implications remain unanswered: For a fixed amount of exercise, does increasing intensity influence the rate of CRF nonresponse? Does the combination of higher amount and intensity of exercise influence the rate of CRF nonresponse more than increasing intensity or amount of exercise alone? Is exposure to exercise associated with CRF nonresponse independent of exercise amount or intensity? Answers to these questions are important and would help practitioners who seek to add precision to exercise-based strategies designed to improve CRF and consequently decrease CVD risk.

In this ancillary study, we sought to determine the separate and combined effects of exercise intensity and amount on the heterogeneity of CRF response during a 24-week, rigorously controlled exercise trial among abdominally obese adults. We measured CRF at multiple time points during the trial to examine the effect of exercise exposure on CRF. To help isolate the effects of exercise on CRF response, we accounted for physical activity performed outside the exercise prescribed through multiple objective measures of unstructured daily physical activity.

PARTICIPANTS AND METHODS

Study Setting and Participants

Details of the trial design and methods¹² and findings from the primary analysis⁵ have been published elsewhere. Briefly, we conducted a 24-week, single-center, randomized controlled trial with a parallel group design between September 1, 2009, and May 31, 2013. The primary objective of the original investigation was to determine the separate effects of exercise intensity and amount on waist circumference (WC) and glucose tolerance among 300 sedentary, abdominally obese adults. Potential participants were

excluded if they reported a history of heart disease, stroke, or any condition that would prevent them from engaging in exercise, if they were already engaging in 2 or more planned exercise sessions per week, and if they were diabetic. All participants provided informed consent before participation, and the study was originally approved by the Queen's University Health Sciences Research Ethics Board.

The purpose of the current analysis was to examine the separate effects of exercise intensity and amount on interindividual CRF response and nonresponse. Therefore, of the 300 participants originally randomized, participants were excluded from the final data set if they were in the nonexercise control group ($n=75$), did not complete the study and/or did not have follow-up CRF data ($n=74$), or had an exercise adherence (number of exercise sessions attended) of less than 90% ($n=30$). This resulted in a study sample of 121 participants (mean [SD] age, 53.2 [7.5] years; 75 females, 62%).

Exercise Intervention

Participants were randomly assigned to (1) low-amount, low-intensity exercise (LALI; $n=39$), (2) high-amount, low-intensity exercise (HALI; $n=51$), or (3) high-amount, high-intensity exercise (HAHI, $n=31$). All participants performed primarily walking exercise on a treadmill for the time required to achieve the desired energy expenditure (kcal per session) 5 times per week at the required intensity (relative to CRF [$\dot{V}O_{2peak}$]) for 24 weeks. Using the heart rate and oxygen consumption data obtained from the baseline exercise test, the heart rate associated with an oxygen consumption of approximately 50% (LALI and HALI) and approximately 75% (HAHI) were prescribed for each participant. At these exercise intensities, the energy expenditure targets (exercise amount) for women and men were 180 and 300 kcals, respectively, for LALI and 360 and 600 kcals for both HALI and HAHI. Heart rate was monitored continuously for all exercise participants at every session to help ensure adherence to the prescribed exercise intensity. All exercise sessions were performed under supervision by specially trained personnel with undergraduate degrees in kinesiology.

Accelerometry

Physical activity performed outside the supervised exercise sessions was monitored using

TABLE 1. Baseline Characteristics of the 121 Study Participants^{a,b}

Characteristic	LALI (N=39)	HALI (N=51)	HAHI (N=31)	P value
Age (y)	53.7 (6.9)	52.5 (8.0)	53.9 (7.2)	.64
BMI (kg/m ²)	33.2 (3.9)	33.1 (5.1)	32.9 (3.7)	.06
WC (cm)	104.4 (9.8)	104.1 (12.8)	104.4 (11.7)	.97
SED (min/d)	615.2 (72.3)	577.0 (72.1)	600.9 (94.5)	.33
TPA (min/d)	319.3 (77.3)	335.7 (60.3)	341.3 (77.0)	.51
Sex ratio, F:M (% F)	25:14 (64.1)	32:19 (62.7)	18:13 (58.1)	.64
Baseline CRF				
L/min	2.6 (0.7)	2.7 (0.7)	2.8 (0.7)	.88
mL/kg/min	28.1 (5.3)	29.0 (5.0)	28.6 (5.2)	.93

^aBMI = body mass index; CRF = cardiorespiratory fitness; F = female; HAHI = high-amount, high-intensity exercise; HALI = high-amount, low-intensity exercise; LALI = low-amount, low-intensity exercise; M = male; SED = sedentary time; TPA = total unstructured physical activity; WC = waist circumference.

^bValues are presented as mean (SD) unless indicated otherwise.

ActiGraph GT3X accelerometers for a 1-week period at baseline and at 16 and 25 weeks. Participants wore the accelerometer for at least 4 days each period. Established accelerometer cut points were used to estimate the duration and intensity of physical activity and sedentary behavior.¹³

Dietary Regimen

During a 1-week baseline period, participants were instructed to maintain baseline body weight through maintenance of calorie intake while recording their daily consumption of self-selected foods. During the intervention, participants were instructed to maintain the calorie intake targets determined during baseline. All participants were prescribed a balanced diet and were asked to submit daily diet intake records for the duration of the intervention. As previously reported,⁵ no differences were observed among the exercise groups for total caloric intake or dietary fat intake.

Cardiorespiratory Fitness

Cardiorespiratory fitness was assessed using standard open-circuit spirometry techniques (SensorMedics) during a graded exercise test in which participants walked on a treadmill at a self-selected speed at zero elevation for 3 minutes, after which the incline was increased by 5% for 2 minutes, then by 2% every subsequent 2 minutes until volitional fatigue.¹²

Statistical Analyses

Cardiorespiratory fitness nonresponse was identified using a technical error (TE) measure

based on the methods outlined by Bouchard et al¹⁴ and as originally used in the National Health and Nutrition Examination Survey.¹⁵

Technical error is a conservative measure of assessor error and day-to-day variation in conducting a CRF test. Briefly, TE is calculated by taking the square root of the sum of squared differences of repeated measures divided by the total number of paired samples multiplied by 2. Any value less than $1 \times TE$ was considered a nonresponse. Nonresponse was calculated to be 0.204 L/min. Percent nonresponse was calculated on the basis of the number of individuals who met the less than $1 \times TE$ calculation per exercise group. A Mann-Whitney test was performed to compare body mass index (BMI; calculated as the weight in kilograms divided by the height in meters squared), WC, age, baseline absolute and relative CRF, sedentary time, and daily unstructured physical activity (eg, activities of daily living) between responders and nonresponders at baseline in each exercise group. Furthermore, a Pearson χ^2 test was performed to compare the sex distribution between responders and nonresponders in each exercise group at baseline. A 1-way analysis of variance was performed to compare BMI, WC, sex ratio, age, baseline absolute and relative CRF, nonresponse, sedentary time, and daily (unstructured) physical activity between exercise groups at baseline. A 1-way analysis of variance was also performed to compare change in absolute CRF after 24 weeks between exercise groups. Least significant difference post hoc tests were performed to further identify significance when necessary. A paired Student *t* test was performed to compare change in absolute CRF from baseline to 24 weeks within exercise groups. McNemar tests were performed to compare the rates of nonresponse between time points 4, 8, 16, and 24 weeks for each group. Statistical significance was set at $P < .05$. All statistical analyses were performed using SPSS software, version 22.0 (SPSS Inc).

RESULTS

The baseline characteristics of the study participants are summarized in Table 1, and Table 2 presents these characteristics stratified by CRF response. There were no significant differences for age ($P = .64$), BMI ($P = .06$),

TABLE 2. Baseline Characteristics of the 121 Study Participants, Stratified by CRF Response^{a,b}

Characteristic	LALI (N=39)		HALI (N=51)		HAHI (N=31)		P-value
	Nonresponder (n=15)	Responder (n=24)	Nonresponder (n=9)	Responder (n=42)	Nonresponder (N=0)	Responder (N=31)	
Age (y)	52.9 (5.0)	54.2 (7.8)	53.1 (7.2)	52.3 (8.1)	NA	53.9 (7.2)	.60
BMI, kg/m ²	34.7 (4.0)	32.3 (3.5)	34.5 (5.4)	32.9 (5.0)	NA	32.9 (3.7)	.11
WC (cm)	105.8 (9.0)	103.5 (10.1)	108.2 (16.8)	103.3 (11.6)	NA	104.4 (11.7)	.77
SED (min/d)	587.8 (72.4)	628.9 (68.3)	604.0 (90.2)	572.0 (67.1)	NA	600.9 (94.5)	.29
TPA (min/d)	351.6 (76.9)	294.5 (67.8)	302.6 (67.3)	343.3 (55.9)	NA	341.3 (77.0)	.54
Sex ratio, F:M (% F)	12:3 (80.0)	13:11 (54.2)	5:4 (55.6)	27:15 (64.3)	NA	18:13 (58.1)	.32
Baseline CRF							
L/min	2.6 (0.6)	2.6 (0.7)	2.9 (0.6)	2.7 (0.7)	NA	2.8 (0.7)	.93
mL/kg/min	28.4 (5.2)	28.0 (5.3)	29.0 (3.9)	29.0 (5.2)	NA	28.6 (5.2)	.97

^aBMI = body mass index; CRF = cardiorespiratory fitness; F = female; HAHI = high-amount, high-intensity exercise; HALI = high-amount, low-intensity exercise; LALI = low-amount, low-intensity exercise; M = male; NA = not applicable; SED = sedentary time; TPA = total unstructured physical activity; WC = waist circumference.

^bValues are presented as mean (SD) unless indicated otherwise.

WC ($P=.97$), sedentary time ($P=.33$), daily (unsupervised) physical activity (light or moderate physical activity, $P=.51$), sex ratio ($P=.64$), and baseline absolute or relative CRF ($P=.88$ and $P=.93$, respectively) between groups or between responders and nonresponders ($P=.60$, $P=.11$, $P=.77$, $P=.29$, $P=.54$, $P=.32$, $P=.93$, $P=.97$, respectively). All participants adhered to at least 90% (108 of 120) of the prescribed exercise sessions. The mean (SD) exercise times were 31.2 (4.0), 57.9 (7.6), and 39.7 (6.4) minutes per session for the LALI, HALI, and HAHI groups, respectively (Supplemental Table 1).

Table 3 shows the effects of exercise intensity and amount on change in CRF. Mean (SD) CRF (L/min) increased within the LALI (0.26 [0.25]), HALI (0.41 [0.31]), and HAHI (0.63 [0.29]) groups at 24 weeks ($P<.001$). Improvements in CRF were significantly greater for HAHI than both HALI ($P=.001$) and LALI ($P<.001$) and greater for HALI than LALI ($P=.02$). For the LALI group, change in CRF ranged from -0.19 to 0.87 L/min (-8.0% to 29.8%); for HALI, change in CRF ranged from -0.33 to 1.37 L/min (-10.0% to 42.6%); for the HAHI group, change in CRF ranged from 0.25 to 1.34 L/min (7.4% to 117.9%). The mean (SD) improvement in CRF for responders was 0.41 (0.19) L/min, 0.49 (0.27) L/min, and 0.63 (0.29) L/min for the LALI, HALI, and HAHI groups, respectively. The mean (SD) improvement in CRF for nonresponders was 0.03 (0.11) L/min and 0.03 (0.16)

L/min for the LALI and HALI groups, respectively.

Figure 1 illustrates the individual variability in CRF response for all 3 groups at 4, 8, 16, and 24 weeks. At 24 weeks, 38.5% (15 of 39), 17.6% (9 of 51), and 0.0% (0 of 31) of the participants in the LALI, HALI, and HAHI groups, respectively, were CRF nonresponders, meaning that 61.5% (24 of 39), 82.4% (42 of 51), and 100% (31 of 31), respectively, improved CRF beyond the measurement error for CRF.

At a fixed intensity of exercise (50% CRF), the rate of nonresponse was reduced by about 50% (from 38.5% to 17.6%) when exercise amount was doubled (LALI [~ 30 minutes] vs HALI [~ 60 minutes]; $P=.02$). At a fixed amount of exercise (300 and 600 kcals per session for women and men, respectively), nonresponse was abolished when exercise intensity was increased from 50% to 75% of CRF (HALI vs HAHI; $P=.001$).

As illustrated in Figure 1, there was a significant reduction in the number of nonresponders within both the LALI ($P=.04$) and HALI ($P=.008$) groups between 4 and 8 weeks. A significant reduction in nonresponders was also observed between 4 and 16 weeks of exercise for all groups ($P<.05$). Although the number of nonresponders continued to decrease within the HAHI group from 16 to 24 weeks, it did not reach statistical significance ($P=.25$). No further statistically significant reduction in the number of nonresponders was observed for the LALI ($P>.99$) or HALI ($P=.75$) groups after 16 weeks.

In this study, exercise adherence was set to 90% to help ensure that the effects of exercise amount and intensity on CRF were not biased by poor adherence at any time point throughout the intervention (Figure 2). However, we observed very little difference in the rate of response when adherence was reduced to 80% and even 70% (Supplemental Table 2). When the adherence levels of the participants within each group decreased from 90% to 70%, the relative number of nonresponders for the LALI and HALI groups was within 4 percentage points from that observed with 90% adherence. Nonresponse was observed for 5 of 41 participants (12.2%) in the HALI group at 70% adherence. This indicates that 87.8% (36 of 41) of the participants in the HALI group increased CRF beyond the TE despite participating in only 84 of the 120 exercise sessions.

DISCUSSION

The novel finding of this study is that for those who adhered to at least 90% of the exercise sessions prescribed at fixed amounts of exercise, increasing exercise intensity within a range consistent with current guidelines completely eliminated CRF nonresponse over 24 weeks. That this observation was obtained in response to about 40 minutes of brisk walking across 4 to 5 days each week is promising and suggests that reduction in CVD risk through improvements in CRF can be achieved for most, if not all, abdominally obese, previously sedentary adults in a pragmatic manner. However, our finding that low-intensity exercise performed for about 150 min/wk may not be sufficient to improve CRF for a substantive proportion of adults is reason for concern.

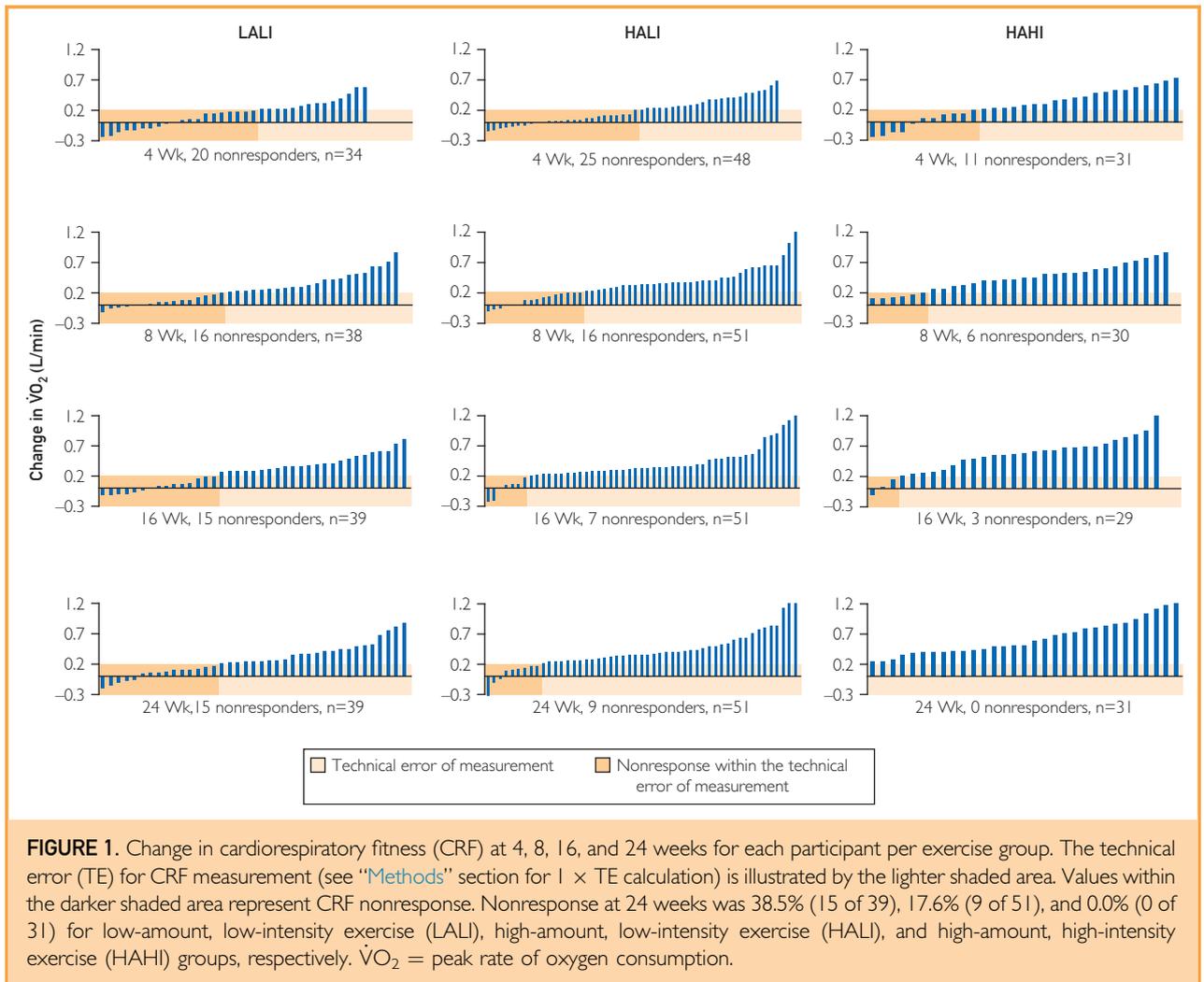
To our knowledge this is the first study to report that for a given amount of exercise, increasing exercise intensity abolished CRF nonresponse in previously sedentary adults. The mechanism underlying this observation remains unclear. Evidence derived from short-term studies suggests that increases in CRF at the group level in younger men are intensity dependent and that improvements in CRF are positively associated with corresponding improvements in stroke volume.¹⁶ Others suggest that peripheral adaptations within skeletal muscle including increased mitochondrial mass and peripheral vascular structure and function are responsible for the beneficial

TABLE 3. Cardiorespiratory Fitness Response at 24 Weeks^{a,b}

Variable	LALI			HALI			HALI		
	Total (N=39)	Responder (n=24)	Nonresponder (n=15)	Total (N=51)	Responder (n=42)	Nonresponder (n=9)	Total cohort (N=31)	Responder (n=31)	Nonresponder (n=0)
ΔCRF (L/min)	0.26 (0.25)	0.41 (0.19)	0.03 (0.11)	0.41 (0.31)	0.49 (0.27)	0.03 (0.16)	0.63 (0.29)	0.63 (0.29)	NA
Range in ΔCRF (L/min)	-0.19 to 0.87	0.21 to 0.87	-0.19 to 0.16	-0.33 to 1.37	0.22 to 1.37	-0.33 to 0.17	0.25 to 1.34	0.25 to 1.34	NA
Range in ΔCRF (%)	-8.0 to 29.8	11.0 to 29.8	-8.0 to 7.9	-10.0 to 42.6	9.9 to 42.6	-10.0 to 4.9	7.4 to 117.9	7.4 to 117.9	NA

^aΔCRF = change in cardiorespiratory fitness; HALI = high-amount, high-intensity exercise; HALI = high-amount, low-intensity exercise; LALI = low-amount, low-intensity exercise; NA = not applicable.

^bValues are presented as mean (SD) unless indicated otherwise. All participants included in the analysis completed a minimum of 90% of the exercise sessions (108 out of 120).

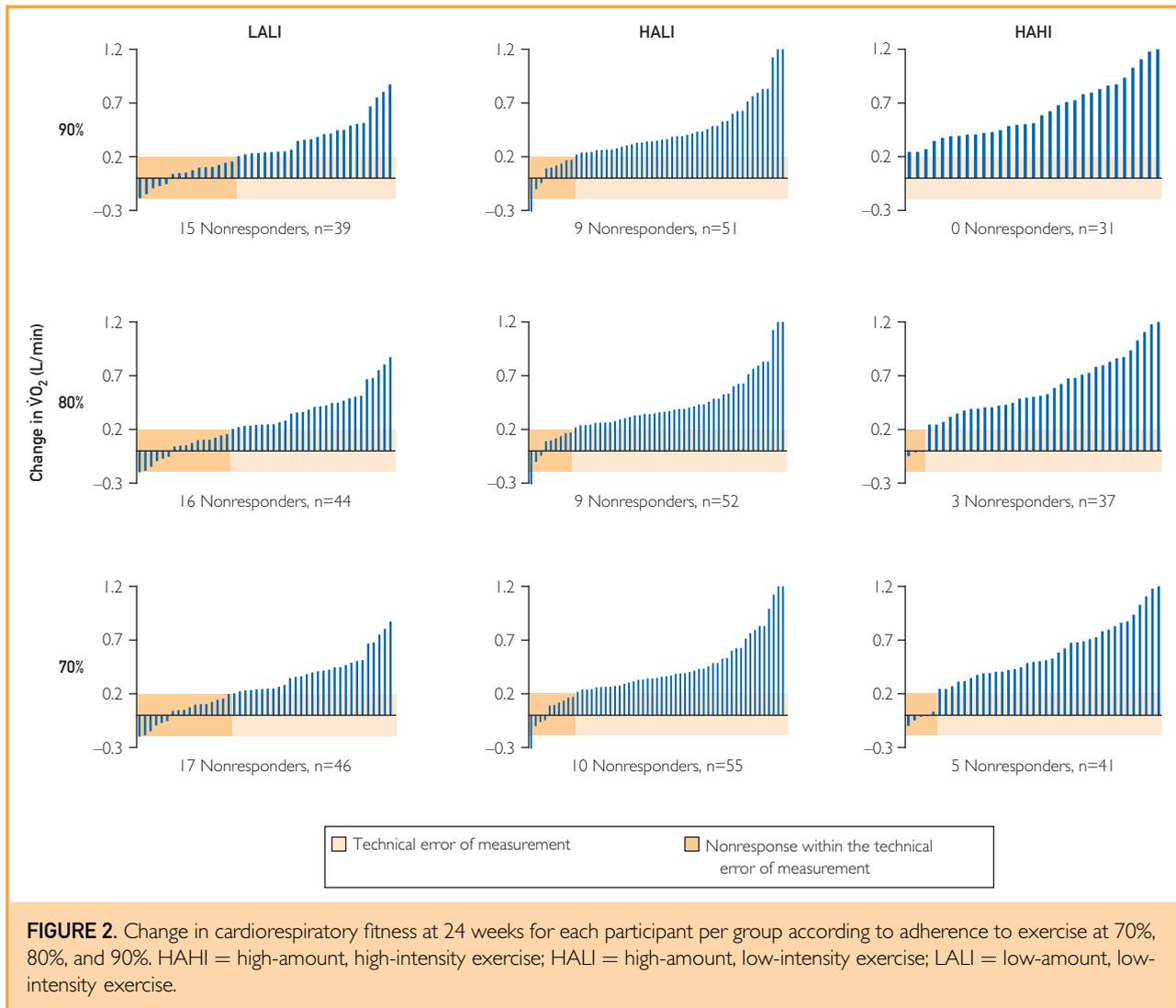


effects of higher-intensity exercise.¹⁷ Although further studies are needed to characterize the underlying mechanisms, it is readily apparent that increasing exercise intensity is a very strong determinant of CRF across individuals.

Our finding that increasing the amount of exercise at fixed intensities reduces the number of CRF nonresponders by about half extends the work of Sisson et al,⁸ who observed a dose-response relationship between exercise amount and CRF nonresponse in postmenopausal women. In that study, CRF did not change in 20% of the women who exercised for 200 min/wk for 6 months at 50% of CRF, values that are similar to those observed in our group that exercised for about 300 min/wk at the same intensity for 6 months. Direct comparison between studies is not straightforward, however, because

CRF nonresponse in our study was defined as any change within the TE, whereas in the study by Sisson et al it was defined as any change less than or equal to zero. Nevertheless, it is clear that increasing exercise amount from the low end to the high end of the current guidelines (eg, 150 to 300 min/wk) will increase the likelihood of a positive change in CRF. However, it is also clear that further benefit is associated with increasing exercise intensity.

A troubling observation in our study was that CRF for about 40% of the participants—those who exercised for 150 min/wk at 50% of CRF or about 60% of predicted maximal heart rate—did not improve. This level of nonresponse is consistent with findings from other investigators⁸ and suggests that exercise that meets the low end of the consensus recommendation with respect



to intensity may be insufficient for improving CRF for a substantial proportion of the adult population. Although our findings suggest that the nonresponders in this group would benefit from increasing exercise amount and/or intensity, this is speculation that requires trial evidence to prove.

We are unaware of any prior trial that has considered whether exercise exposure is a determinant of interindividual CRF response. Indeed, it may be argued that CRF improvement in response to lower-intensity exercise may simply take more time compared with higher-intensity exercise. To the contrary, the relative number of responders within our LALI group plateaued at 8 weeks with no change from 8 to 24 weeks.

When exercise amount was doubled (LALI [30 minutes] to HALI [60 minutes]), the number of CRF responders plateaued at 16 weeks. In contrast, the relative number of responders within the higher-intensity group increased continuously over time. Thus, it appears that at lower-intensity exercise consistent with consensus recommendations (150 min/wk at ~50% of maximum CRF), if CRF has not improved for a given individual after about 8 weeks of regular exercise, it is unlikely that it will.

It is important to note that nonresponse in CRF following regular exercise does not necessarily suggest nonresponse for other cardio-metabolic risk factors. Although it has been

established that improvement in CRF is associated with decreases in risk of CVD,⁹ the lack of association between changes in CRF and exercise-induced changes in other cardio-metabolic risk factors is well documented,^{6,9} reinforcing the notion that physical activity is associated with benefit across a wide range of health outcomes regardless of whether a change in CRF is observed.

Several features of our experimental approach strengthen our findings. We accounted for the TE of measurement, thereby helping to ensure that a response in CRF was a reflection of a biological adaptation and not TE. We also accounted for variation in daily physical activity (eg, activities of daily living), which we have previously reported is positively related to CRF,¹⁸ thereby helping to isolate the effects of exercise on CRF. Our study sample was primarily white and obese, which may limit generalizability of our findings. Whether amount and intensity of exercise influenced submaximal fitness levels and/or exercise tolerance independent of change in CRF as measured by $\dot{V}O_{2peak}$ is unknown. Whether increasing exercise intensity at fixed but lower amounts of exercise reduces nonresponse is also unknown. Finally, our findings are restricted to those who adhered to at least 90% of the exercise program prescribed.

CONCLUSION

Our finding that increasing either the intensity or the amount of exercise substantially decreases the rate of nonresponse for CRF provides treatment options for practitioners who counsel sedentary adults seeking to improve CRF and hence decrease CVD risk. Further, our findings add to an emerging body of evidence suggesting the need for greater precision when prescribing exercise for health benefit. Although it is doubtless true that 150 minutes of exercise per week at low intensity is associated with benefit for many adults, at least for CRF, this may not be true for a substantial portion of the population. These observations highlight the need to measure CRF in clinical practice not only to characterize health risk but also to determine treatment efficacy.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: <http://www.mayoclinicproceedings.org>. Supplemental material attached to journal articles

has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: BMI = body mass index; CRF = cardiorespiratory fitness; CVD = cardiovascular disease; LALI = low-amount, low-intensity exercise; HAHl = high-amount, high-intensity exercise; HALI = high-amount, low-intensity exercise; TE = technical error; WC = waist circumference

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