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**Exaggerated Health Benefits of Physical Fitness and Activity due to
Self-selection.**

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Abbreviations: BMI: body mass index; km kilometer;

Short title: **Self-selection and the Benefits of Fitness**

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Background: The predicted health benefits of becoming physically active or fit will be exaggerated if health outcomes cause fitness and activity rather than the converse in prospective and cross-sectional epidemiological studies.

Objective: Assess whether the relationships of adiposity to fitness and activity are explained by adiposity prior to exercising.

Design: Cross-sectional study of physical fitness (running velocity during 10km foot race) and physical activity (weekly running distance) to current BMI ($BMI_{current}$) and BMI at the start of running ($BMI_{starting}$) in 44,370 male and 25,252 female participants of the National Runners' Health Study.

Results: $BMI_{starting}$ explained all of the association between fitness and $BMI_{current}$ in both sexes, but less than a third of the association between physical activity and $BMI_{current}$ in men. In women, $BMI_{starting}$ accounted for 58% of the association between $BMI_{current}$ and activity levels. The 95th percentile of $BMI_{current}$ showed substantially greater declines with fitness and activity levels than the 5th percentile of $BMI_{current}$ in men (i.e., the negative slope for 95th percentile was 2.6-fold greater than the 5th percentile for fitness and 3-fold greater for activity) and women (6-fold and 3.4-fold greater, respectively). At all percentiles, the regression slopes relating $BMI_{starting}$ to fitness were comparable or greater (more negative) than the slopes relating $BMI_{current}$ to fitness, whereas the converse was true for activity.

Conclusion: Self-selection bias accounts for all of the association between fitness and adiposity and probably a portion of other health outcomes, but has less affect on associations involving physical activity.

Keywords: Cardiorespiratory fitness, exercise, prevention, genetics, bias.

Sedentary lifestyle is purported to cause as large an increase in the risk of premature deaths as smoking, obesity, high cholesterol, or hypertension{1}, and accounts for 12% of deaths in the United States {2,3}. The Surgeon General and other government and nongovernment organizations recommend thirty minutes of moderate-intensity physical activity on most days of the week {4-6}. These recommendations are largely inferred from cross-sectional and prospective epidemiological studies suggesting lower morbidity and mortality in men and women who are more physically active or fit. However such study designs cannot distinguish between cardiorespiratory fitness causing health vis-a-vis leanness and cardiovascular health that predispose individuals to be more physically active and fit.

Studies of cardiorespiratory fitness have been particularly influential in the formulation of exercise recommendations {7,8}. Fitness may be calculated from respiratory gases as maximum aerobic capacity or estimated from treadmill test duration until exhaustion, heart rate during submaximal exercise, and running speed {9}. Accomplished runners can run 10 km race velocities requiring between 79% and 98% of maximum oxygen uptake {10-13}. Fitness varies among individuals due to age, genetic constitution, and health, independent of physical activity{14-17}. Physical activity may also be affected by health and genetic constitution {17}. Separating the causal effects of exercise from the confound effects of other variables is critical to projecting the health benefits of physical activity promotion.

This report uses recollection of weight when starting to exercise to assess whether the inverse association of runners' weights and their physical activity and fitness can be attributed to self selection. Problems of statistical adjustment to correct for self-selection are also considered. The self-selection effects demonstrated in this paper are unlikely to be limited to body weight, suggesting that current estimates of the attributable risk due to sedentary lifestyle may be substantially overstated.

Methods

The design and methods of the National Runners' Health Study are described elsewhere {18-21}. Briefly, a two-page questionnaire, distributed nationally at races and to subscribers of the nation's largest running magazine (Runners' World, Emmaus PA), solicited information on demographics, running history, weight history, smoking, prior history of heart attacks and cancer, and medications for blood pressure, thyroid, cholesterol and diabetes. For this report cardiorespiratory fitness is defined as velocity during the participant's best 10km race during the previous five years. Running was the predominant physical activity of the runners. In the analyses to follow, fitness and physical activity are compared to current BMI ($BMI_{current}$) and BMI when participants first began running 12 or more miles per week ($BMI_{starting}$), and to current and starting waist, hip and chest circumferences, and bra cup sizes.

Statistics are expressed as mean $\pm$ SE or slopes $\pm$ SE except where noted. Multiple linear regression was used to age adjust adiposity, physical activity, and fitness using both age and age² as covariates. The effects of self-selection were estimated as follows: 1) we divided the sample into deciles of fitness or physical activity, 2) we calculated the decrease in $BMI_{current}$ at each decile relative to the lowest decile of fitness or activity, and 3) we compared these decreases to the corresponding differences in starting BMI (specifically their recollection of adiposity when they first began running 12 or more miles per week). Self-selection was calculated as proportion of the mean reduction in $BMI_{current}$ represented by the mean decrease in starting BMI. We also compared the slopes for $BMI_{current}$ versus fitness, and $BMI_{current}$ versus physical activity, to the slopes for the differences between current and starting BMI ($BMI_{current} - BMI_{starting}$) versus fitness or activity, after adjustment for age.

We previously demonstrated that the relationships of women's BMI and body circumferences to running distance were nonlinear (convex) [8], and in the course of the current analyses found the relationships of

running velocity to adiposity measures were convex as well. We therefore used standard polynomial regression with adiposity measures as the dependent variable and running distance (km/wk) and running distance squared (km/wk²) as the independent variables. From these equations, the change in adiposity corresponding to a one km/wk or m/s increment in running distance or speed (i.e., from X to $X+1$ m/s) was calculated as the tangent to the regression curve, which is given by first derivative of the polynomial regression equation evaluated at velocity X (Figure 1). The percentages attributable to self-selection were computed from the ratio of the slopes for BMI_{starting} and BMI_{current} evaluated at selected distances and speeds, and the weighted average of these ratios based on the distribution of distance and velocity in the sample, where we specified a maximum of 100 if the ratio exceeded one and a minimum of 0 percent when the ratio was less than zero.

In addition to being convex, we have also previously demonstrated that the regression slopes relating adiposity to running distance depend upon the sample percentile of the BMI or body dimension {20-23}. Following the procedure previously developed for relating percentiles of adiposity to women's walking distances, nearest neighbors were used to determine the percentiles of the dependent variable corresponding to each X_i , $i=1..N$. Specifically, the bivariate observations (X_i, Y_i) were ordered from smallest to largest X to yield the ordered set of observations $(X_{[i]}, Y_i)$. We then sorted values of the dependent variable from the one hundred nearest walking distances to $X_{[i]}$ from smallest to largest. These sorted values were used as the 1st ($Y_{i[1]}$), 2nd ($Y_{i[2]}$), 3rd ($Y_{i[3]}$), ...100th ($Y_{i[100]}$) percentile of adiposity corresponding to the walking distance $X_{[i]}$. Quadratic polynomial regression was applied to $(X_i, Y_{i[k]})$ to estimate the relationship of weekly walking distance to the k^{th} percentile of BMI. The tangent slopes were calculated at selected velocities and plotted as functions of percentiles as done elsewhere [8-12]. We also computed the average ratio of the slopes for starting and current weight over all percentiles and across all distances or velocities using weights based on sample distribution of distances or speeds.

Results

Of the 48,969 men and 29,420 women who provided complete information on age, weekly running distance, 10km race performance, and weight when they began running 12 or more miles per week, 627 men and 1309 women were excluded for thyroid medication use, 220 men and 60 women for using medications for diabetes, 1,446 men and 680 women for smoking, and 2,306 men and 2,199 women for following strict vegetarian diets. The remaining 44,370 men and 25,252 women were generally middle-aged (means $\pm$ SD, men: 44.47 $\pm$ 10.58, women: 38.51 $\pm$ 9.61 years), lean (BMI men: 23.96 $\pm$ 2.68; women: 21.37 $\pm$ 2.42 kg/m²), ran an average of 39.79 $\pm$ 22.20 and 37.64 $\pm$ 20.70 km/wk, and had ran a 10km race at an average speed of 3.91 $\pm$ 0.56 and 3.42 $\pm$ 0.54 m/s, respectively. In addition, 37,850 men and 19,959 women reported their current and past waist circumferences, 16,413 men and 19,077 women reported current and past hip circumferences, 30,171 men and 20,035 women reported current and past chest circumferences, and 21,181 women reported their bra cup sizes.

Figure 1 presents the histogram of the mean difference in BMI_{current} and current waist circumference between the least-fit men (1st decile) and men of the 2nd through 9th decile of fitness. The differences in BMI_{current} between the lowest and higher fitness categories increased with progressively greater differences in fitness. However, the differences in average BMI_{starting} between the least fit and higher fitness categories also increased progressively with fitness and accounted for over 97% of the differences in adiposity between the least fit and fitter men. Differences in BMI_{current} also increased with physical activity, however little of these differences were accounted for by BMI_{starting}. Similar results were obtained for waist circumference (a measure of intra-abdominal fat).

The corresponding analyses for women (Figure 2) shows that BMI_{current}, current hip circumference, and bra cup size also declined progressively with fitness but that these declines were all accounted

for by differences in starting adiposity. Women who ran greater weekly distances were also leaner than less active women. Less than a third of the increases in leanness with physical activity can be ascribed to starting differences in adiposity, except for BMI_{current} in the seventh through tenth deciles, and current hip circumference in the ninth and tenth deciles.

Table 1 presents the quadratic regression equations relating BMI_{current} and BMI_{starting} to fitness. For completeness, we also reported the regression coefficients for the difference between BMI_{current} and BMI_{starting}. The table includes the formulas for the tangent slopes, which are used to estimate the expected effect per m/s change in running velocity on adiposity at 2.9 m/s (column 4), 3.9 m/s (column 5), and 4.9 m/s (column 6). Cardiorespiratory fitness exhibits primarily a linear relationship to current adiposity (i.e., weak significance of the quadratic term and similar tangent slopes at all velocities), a concave relationship to starting adiposity (i.e., significant negative quadratic coefficients and increasingly negative tangent slopes with increasing velocity), and convex relationship to the difference between current and starting adiposity (significant positive quadratic coefficients and the increasingly less negative tangent slopes with velocity). Below the tangent slopes are the percents of the relationships attributable to self-selection, which are calculated from the ratio of the slopes for BMI_{starting} to BMI_{current} {i.e., $100 * (\text{slope for BMI}_{\text{starting}} / \text{slope for BMI}_{\text{current}})$ }. Comparing the tangent for current and starting adiposity suggests all of the association of BMI and circumferences of the waist, hip and chest are due to self selection above 3.71, 3.67, 3.68 and 3.51, respectively. The weighted averaged for the proportion due to self-selection based on the sample distribution of velocities were 93%, 95.0% 92.7% and 94.1%, respectively for BMI, and waist, hip, and chest circumferences.

Table 2 presents the corresponding analyses for women. The relationships of current and starting adiposity to fitness were all significantly nonlinear and convex. All of the association of current adiposity to women's race velocity was attributed to self-selection

above __ m/s, respectively, for BMI, and waist, hip, and chest circumferences, and over the total sample of women the proportions attributable to self-selections were 99.2% for BMI, 97.9% for waist circumference, 99.99% for hip circumference, 97.8% for chest circumference, and 95.7% for bra cup size. The declines in women's adiposity with fitness are all rendered nonsignificant by the removal of starting level.

Figure 3 displays relationships of the 5th, 25th 50th, 75th, and 95th percentiles of BMI_{current} to fitness. The slopes for BMI_{current} versus fitness becomes progressively greater (more negative) at higher BMI percentiles in both men and women. Specifically, compared to the decline at the 5th percentile the decline at the 95th percentile of men's BMI_{current} was over three-fold larger at 3.2 m/s, 2.5-fold larger at 4 m/s, and two-fold larger at 4.8 m/s. In women, compared to the decline at the 5th percentile the decline at the 95th percentile of BMI_{current} was nine-fold larger at 2.4 m/s and over four-fold larger at 3.8 m/s. The corresponding graphs for BMI_{starting}, presented below.

The slopes for BMI_{starting} versus fitness are comparable (above the median) or greater (below the median) than the slopes for BMI_{current}, and would appear to account for all the fitness-BMI relationship. The relationships of women's BMI starting to fitness appears to account for essentially all of the relationship between fitness and BMI_{current}. When average The slopes for BMI_{current} versus physical activity were also significantly steeper at the higher than lower percentiles, however, the slopes for BMI_{starting} are significantly smaller (less negative) than the slopes for BMI_{current}, and do not appear to explain the association between activity and BMI_{current}. The slopes for BMI_{starting} versus physical activity are negative in value, but unlike the slopes for fitness, they do not become progressively greater (more negative) at higher percentiles.

Discussion

We have shown self-selection, the tendency for leaner men and women to become fitter runners, accounts for the association between cardiorespiratory fitness and current leanness in a large cross-sectional sample of runners. This was demonstrated in both men and women respect to a variety of adiposity measures, which include fat depositions that are characteristically masculine and feminine. Although recollections of starting weight may be biased by current weight, this would not explain the very different results for fitness and physical activity.

Self-selection and cardiorespiratory fitness The expected health benefits from promoting physical activity rely strongly on studies of cardiorespiratory fitness{1,7,8}. Yet analyses presented in this paper suggest there is greater self-selection bias when adiposity is compared to cardiorespiratory fitness than activity. It has been argued that fitness is a better, less subjective measure of physical activity than activity measures themselves {4}, but this is not our belief . Meta-analyses of prospective epidemiological studies show that fitness and physical activity have different relationships to cardiovascular disease {24}. It has also been argued that changes in cardiovascular fitness predict changes in cardiovascular disease risk {8}, but the results can be explained by statistical artifact {25,26}. The effects of self-selection are unlikely to be limited to weight. Cardiac output and stroke volume affect maximum oxygen uptake and predict cardiovascular disease risk. This association could link fitness to less cardiovascular disease without necessarily invoking physical activity.

Genes contribute to differences in cardiorespiratory fitness independent of physical activity. Rats selectively bred for treadmill endurance achieve a 58% improvement in mean distance run until exhaustion after one generation {16} and a 70% improvement after three generations {15}. Data from twins suggest as much as 93% of maximum aerobic power in unconditioned individuals may be genetically determined {14}, and data from young adults suggest genetics account for approximately 70% of total work performed during a 90 minute

maximal ergocycle {27} (see references {28,29} for lower estimates). Cardiac output and stroke volume, factors that contribute to maximum aerobic capacity, also exhibit significant inheritance in sedentary individuals and changes in responses to endurance training {30}. The HERITAGE study reported maximal heritability estimate of 47% for increases in maximum aerobic consumption in family members after twenty weeks of training {31}.

Self-selection and physical activity The current analyses show that starting weight also affect the quantity of physical activity performed weekly, and that between 30% (men) and 50% (women) of the association between physical activity and current weight may be due to initially leaner men and women running longer distances. These results are consistent with the observations by others that body weight is a barrier to being physically active {32} and that body weight predicts inactivity in prospective epidemiological studies {33,34}. Weight differences between active and sedentary older women have been shown to trace back to their weights during young adulthood {35}. Self-selection would explain why the relationship between adiposity and physical activity is more easily documented in cross-sectional observational studies than training studies. Specifically, self-selection augments cross-sectional associations but not longitudinal associations of change.

Self-selection for running has also been associated with plasma high-density lipoprotein (HDL) cholesterol concentrations. Men who have elevated HDL-cholesterol may select to run because they find it easier and do better at it than those with low HDL-cholesterol. We reported and subsequently confirmed that sedentary men who have higher HDL-cholesterol at baseline will run longer weekly distances at the end of a training program compared to men who start out with low HDL {36,37}. In addition, we have reported high HDL-cholesterol concentrations (averaged 51 mg/dl) in sedentary men whose association with exercise was limited to having an identical twin who ran an average of 56 ± 18 km/wk {38}. This level of HDL-cholesterol falls within the top tertile of adult men {39}, suggesting that just a genetic predilection to run

(as represented by their more active brother) confers high HDL-cholesterol. High HDL may identify individuals genetically endowed with a high proportion of slow-twitch red muscle fibers. These fibers are more adaptive to endurance exercise and are relatively enriched with lipoprotein lipase, an enzyme that promotes higher HDL {47}.

This propensity for individuals with high HDL to run may explain why there is a greater calculated increase in HDL-cholesterol with running distance in cross-sectional samples of men (0.136 mg/dL per km {18}) and women (0.133 mg/dL per km run {19}) than measured in training studies or calculated from discordant monozygotic twins (0.10 mg/dL per km for both). These numbers suggest that self selection accounts for approximately a quarter of the cross-sectional relationship between HDL-cholesterol and running distance among runners. An even larger proportion of the HDL-cholesterol differences will be due to self-selection when runners are compared to sedentary men (we estimate 50%) because HDL-cholesterol is lower in sedentary men than low-mileage runners.

Statistical adjustment for adiposity Compared to the slope for the 5th percentile of BMI_{current} versus fitness, the slope for 95th percentile was 2.5-fold larger in men and 6-fold larger in women (Figures 3 and 4). Plotting the slopes for the percentiles of BMI_{current} show that the corresponding slopes for BMI_{starting} are at least as great if not greater. In contrast, the slopes for BMI_{starting} vs physical activity show no correspondence with the slopes for BMI_{current} versus physical activity. Although BMI_{starting} is inversely related to distance run, its effect is constant or weakened among relatively heavier individuals, whereas the slopes for BMI_{current} versus physical activity are greater for heavier men and women.

Although most prospective epidemiological studies of physical activity or fitness adjust for BMI {40}, this may be inadequate for two reasons. First, classical adjustment for covariates requires that the same relationship applies at all percentiles of BMI, whereas figures 3 and 4 show there is a two to six-fold difference from lowest to

highest BMI percentiles. Thus, classical methods will over-adjust the lower percentiles of BMI and under-adjust the higher percentiles. Second, classical statistical adjustment also assumes that the covariate is determined without measurement error, and will under-adjust the data if measured imprecisely because the coefficient for the covariate will be biased toward zero {41}. This can be demonstrated in our own data. If BMI_{starting} is included in the regression model as a covariate, then the slope relating BMI_{current} to fitness adjusted for BMI_{starting} is -1.047 ± 0.019 kg/m² per m/s in men and -0.414 ± 0.021 in women. Their differences from the unadjusted slopes (Table 1, column 2) would lead to the conclusion that self-selection accounted for 53% of the BMI-fitness relationship in men and 70% in women. The analyses of Table 1 do not use BMI_{starting} as a covariate but rather subtract BMI_{starting} directly from BMI_{current}. Errors in recalling BMI_{starting} (i.e., measurement error) contribute to the residual errors do not bias the estimate of the regression slope, and although this increases the SE for the regression slope this is inconsequential given our sample size. The analyses of Table 1, which is possible because both BMI_{starting} and BMI_{current} are measured on the same metric, shows all of the association between BMI_{current} and fitness is attributable to starting BMI, i.e., self-selection, and that classical adjustment substantially underestimates its effect.

In summary, we have demonstrated that self-selection accounts for all of the association between fitness and weight and a nontrivial portion of the association between physical activity and weight in men and women who engage in at least some vigorous activity. More importantly, we have demonstrated in principle that self-selection may seriously distort estimates of the health benefits of physical activity, particularly those based on fitness. The bias is unlikely to be restricted to weight. Current estimates of the attributable risk of inactivity deduced from fitness, that are deemed comparable to obesity, smoking, high cholesterol or hypertension, are likely to be overstated because cardiovascular risk factors may predispose individuals to sedentariness. There remains strong compelling arguments for most Americans to increase their physical activity,

however, the impact on disease risk may be significantly less than currently projected.

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Table 1. Relationship of fitness and physical activity to current and historic adiposity				
	Regression coefficient±SE			% of effect attributable to starting adiposity (self-selection)
	Starting adiposity	Current adposity	Difference	
Males				
Cardiorespiratory fitness (10km performance, m/s)				
BMI	-2.013±0.023¶	-2.197±0.031¶	0.184±0.025¶	>100
Waist circumference	-4.462±0.054¶	-4.879±0.078¶	0.417±0.069¶	>100
Hip circumference	-3.644±0.114¶	-4.030±0.137¶	0.374±0.091¶	>100
Chest circumference	-3.897±0.081¶	-4.365±0.100¶	0.468±0.069¶	>100
Physical activity (running distance, km/wk)				
BMI	-0.033±0.001¶	-0.010±0.001¶	-0.023±0.001¶	31
Waist circumference	-0.079±0.001¶	-0.015±0.002¶	-0.063±0.002¶	20
Hip circumference	-0.067±0.003¶	-0.027±0.003¶	-0.041±0.002¶	39
Chest circumference	-0.060±0.002¶	-0.022±0.002¶	-0.038±0.002¶	37
Females				
Cardiorespiratory fitness (10km performance, m/s)				
BMI	-1.290±0.028¶	-1.447±0.033¶	0.158±0.024¶	>100
Waist circumference	-2.545±0.085¶	-2.997±0.100¶	0.452±0.078¶	>100
Hip circumference	-3.796±0.103¶	-3.682±0.104¶	0.429±0.077¶	>100
Chest circumference	-1.363±0.066¶	-1.857±0.075¶	0.465±0.059¶	>100
Bra cup size	-0.285±0.011¶	-0.297±0.011¶	0.156±0.026¶	>100
Physical activity (running distance, km/wk)				
BMI	-0.026±0.001¶	-0.015±0.001¶	-0.011±0.000¶	58
Waist circumference	-0.069±0.002¶	-0.036±0.003¶	-0.033±0.002¶	52
Hip circumference	-0.077±0.002¶	-0.045±0.003¶	-0.032±0.002¶	58
Chest circumference	-0.042±0.002¶	-0.021±0.002¶	-0.021±0.001¶	50
Bra cup size	-0.005±0.000¶	-0.002±0.000¶	-0.011±0.00¶	<0%
Significance levels for regression coefficients adjusted for age are coded * P<0.05; † P<0.01; § P<0.001; and ¶ P<0.0001. The percent attributable to self-selection was calculated as the proportion of the slopes for BMI _{current} versus fitness, and BMI _{current} versus physical activity, to the slopes for the differences between current and starting BMI (BMI _{current} - BMI _{starting}) versus fitness or activity, after adjustment for age.				

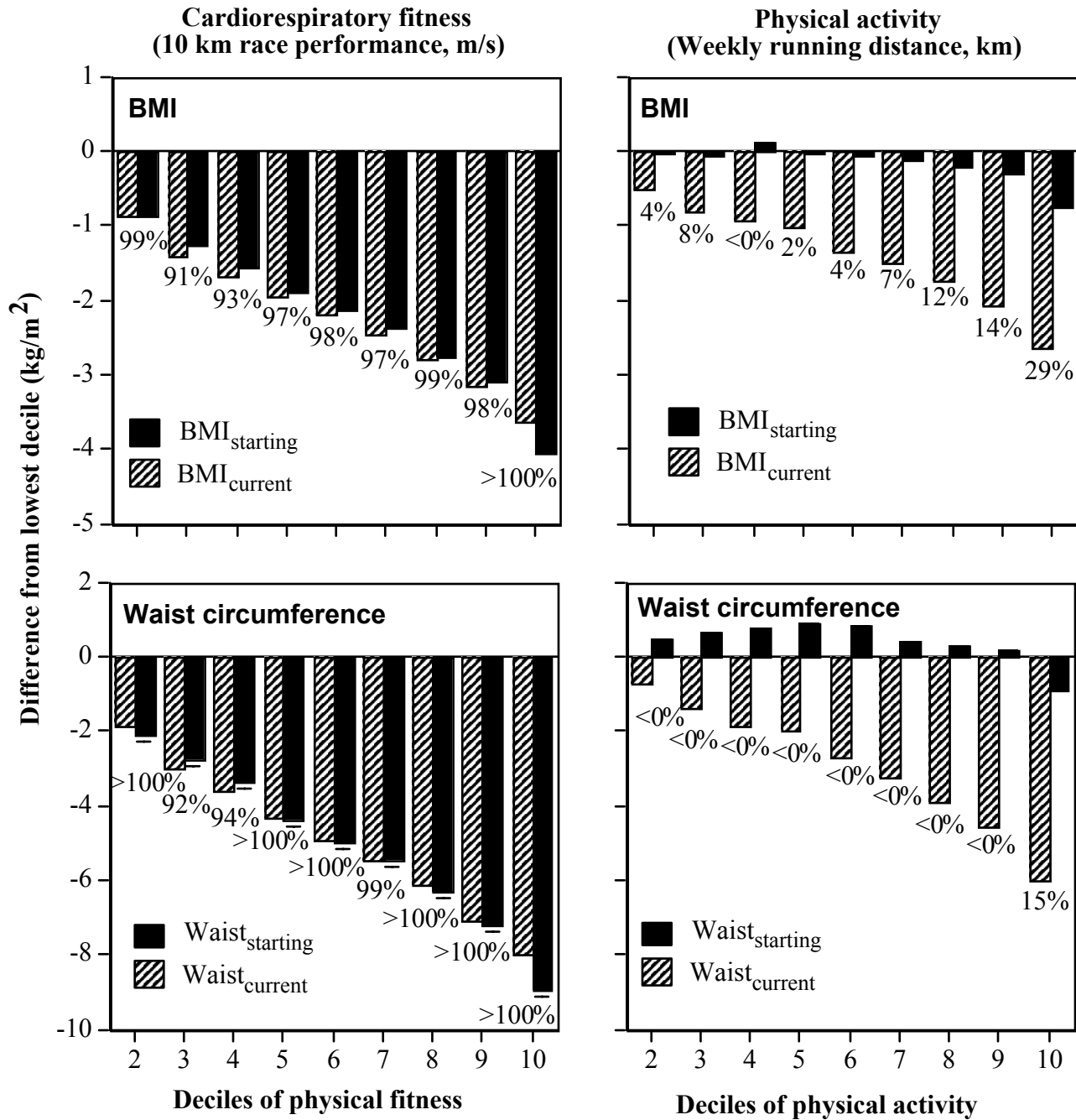
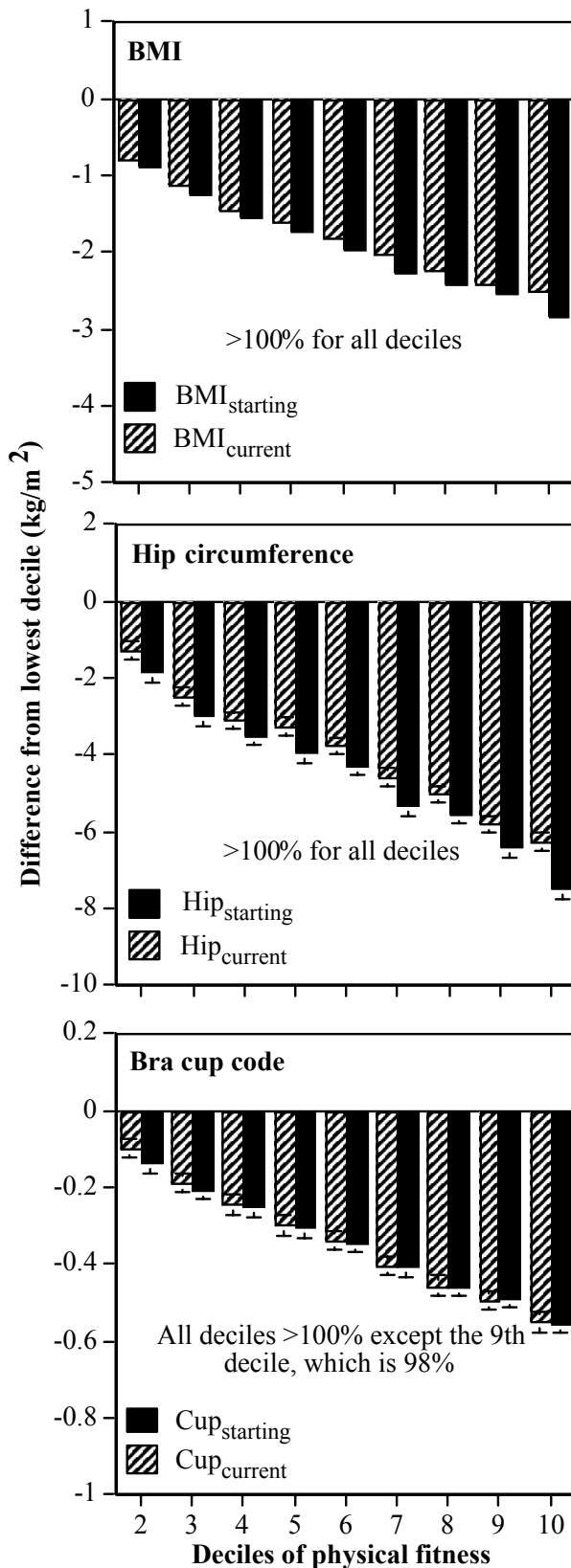


Figure 1 Self-selection in men. Values above bars represent the proportions accounted for by self-selection, which were estimated as follows: 1) we divided the sample into deciles of fitness or physical activity, 2) we calculated the decrease in BMI_{current} at each decile relative to the lowest decile of fitness or activity, and 3) we compared these decreases to the corresponding differences in starting

BMI (specifically their recollection of adiposity when they first began running 12 or more miles per week). Self-selection was calculated as proportion of the mean reduction in BMI_{current} represented by the mean decrease in starting BMI Values. Negative heights mean fitter men were leaner. All variables age-adjusted.

Cardiorespiratory fitness
(10 km race performance, m/s)



Physical activity
(Weekly running distance, km)

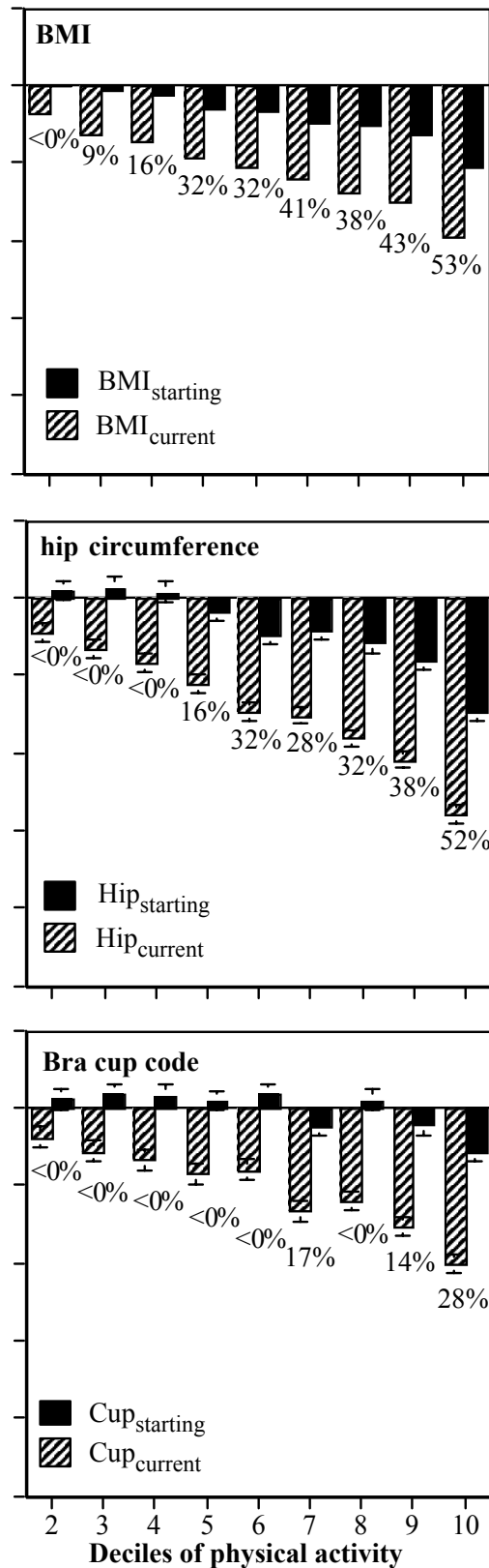


Figure 2. Self-selection in women. Histogram of the mean difference in current BMI, hip circumference, and bra-cup size between the least-fit women (1st decile) and women of the 2nd through 9th decile of fitness (left) and between the active women (1st decile) and men of the 2nd through 9th decile of physical activity (right). Negative heights means fitter men were leaner. Adiposity, physical fitness and activity are all age-adjusted.

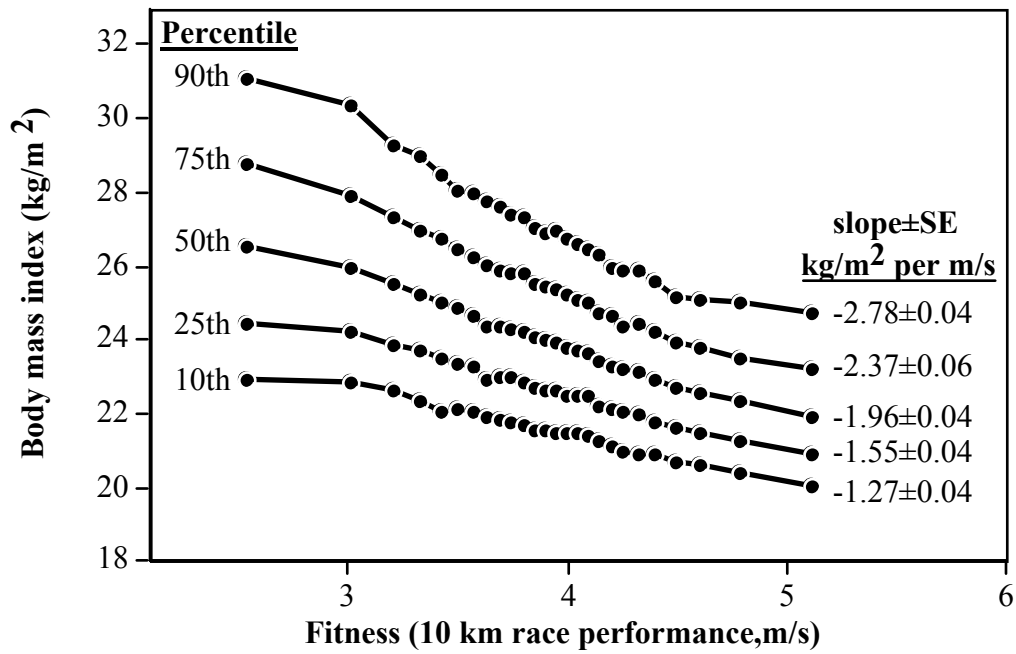


Figure 3. Plot of percentiles of age-adjusted BMI versus age-adjusted fitness in men. All slopes significant at $P < 0.0001$ and there is a significant linear trend for the slopes to be steeper at higher percentiles.

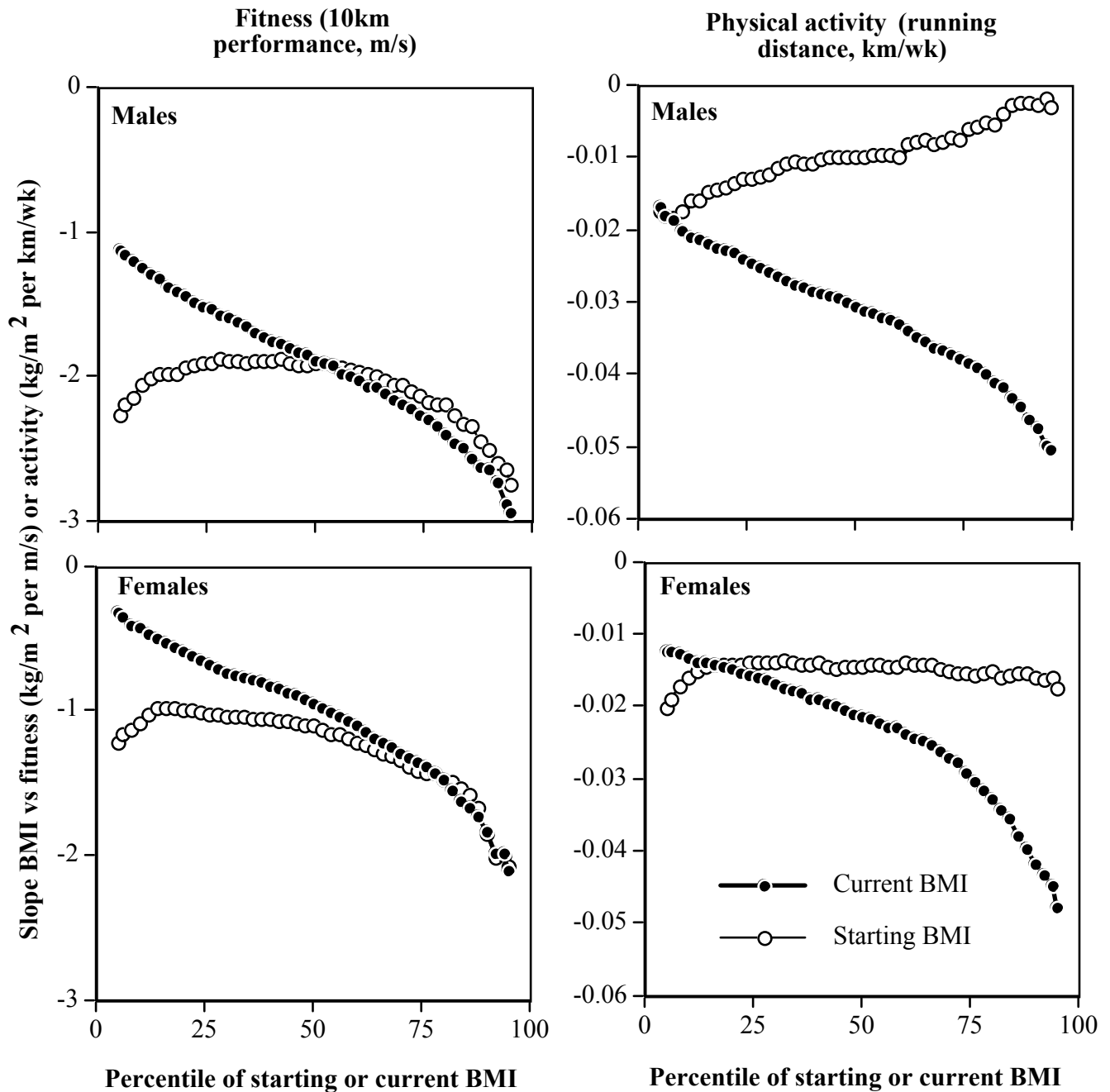


Figure 4. Relationships of the slopes (plotted along Y-axis) of current and starting BMI versus fitness (running velocity) and physical activity (km run per week) by percentile of BMI (plotted along X-axis). All slopes statistically significant using bootstrap resampling. All variables age-adjusted. Starting BMI accounts for

slopes for current BMI versus fitness but not current BMI versus physical activity.