

# Health effects resulting from exercise versus those from body fat loss

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## ABSTRACT

WILLIAMS, P. T. Health effects resulting from exercise versus those from body fat loss. *Med. Sci. Sports Exerc.*, Vol. 33, No. 6, Suppl., 2001, pp. S611–S621. **Objective:** The purpose of this review was to assess whether body weight confounds the relationships between physical activity and its health benefits. **Methods:** The review includes 80 reports from population-based studies (Evidence Category C) of physical activity or fitness and cardiovascular disease (CVD) or coronary heart disease (CHD). **Results:** Eleven of 64 reports on activity found no relationship between physical activity and disease. Of the remaining 53 reports, 11 did not address the possible confounding effects of body weight, nine cited reasons that weight differences should not explain their observed associations, and 33 statistically adjusted for weight (as required). Only three of these changed their associations from significant to nonsignificant when adjusted. Ten of 16 reports on cardiorespiratory fitness and CHD or CVD used statistical adjustment, and none of these changed their findings to nonsignificant. Population studies show that vigorously active individuals also have higher high-density lipoprotein (HDL)-cholesterol concentration, a major risk factor for CHD and CVD, than sedentary individuals when statistically adjusted for weight. In contrast, intervention studies, which relate dynamic changes in weight and HDL, suggest that adjustment for weight loss largely eliminates the increase in HDL-cholesterol in sedentary men who begin exercising vigorously. Adjusting the cross-sectional HDL-cholesterol differences for the dynamic effects of weight loss eliminates most of the HDL-cholesterol difference between active and sedentary men. **Conclusion:** Population studies show that the lower incidence of CHD and CVD and higher HDL of fit, active individuals are not because of lean, healthy individuals choosing to be active (i.e., self-selection bias). Nevertheless, metabolic processes associated with weight loss may be primarily responsible for the HDL differences between active and sedentary men, and possibly also their differences in CHD and CVD. **Key Words:** CARDIORESPIRATORY FITNESS, PHYSICAL ACTIVITY, CHD RISK, CARDIOVASCULAR DISEASE, PUBLIC HEALTH RECOMMENDATIONS, DOSE-RESPONSE, EXERCISE, EPIDEMIOLOGY, RELATIVE RISK, HDL-CHOLESTEROL, TRIGLYCERIDES, LIPOPROTEINS

The effectiveness of physical activity to reduce obesity and improve dyslipoproteinemias, insulin action and glucose tolerance, hypertension, and thrombotic profiles has been recently reviewed (21,42,82,110). This article focuses on the statistical treatment of adiposity in population studies of physical activity and health outcomes.

Physical inactivity and obesity are associated with many of the same health outcomes, including higher total mortality (97,120), cardiovascular disease (CVD) and coronary heart disease (CHD) morbidity and mortality (79,120), stroke (120,122), colon cancer (79,120), type 2 diabetes and insulin resistance (79,120), hypertension (79,120), low plasma high-density lipoprotein (HDL)-cholesterol and elevated plasma triglyceride concentrations (79,120), and preponderance of small, dense low-density lipoprotein (LDL) particles (79,137). An inverse relationship between physical activity and adiposity is evident for vigorous leisure-time activity (43,120) and is frequently observed for total activity (57,84) or leisure-time activities of mixed intensities (the

association with occupational activity is less consistent) (34,86,89). Because physical activity has been proven to produce losses of both total weight and body fat (113,139,140), body fat potentially confounds the relationships between physical activity and its health outcomes.

Confounding effects (such as body weight) are traditionally eliminated by including the variable as a covariate in the statistical data analysis. In this review, it is shown that traditional statistical adjustment for body weight has little effect on the relationships of physical activity to CVD, CHD, or plasma lipoprotein levels in population studies. This is in contrast to intervention studies that suggest that the metabolic processes associated with adiposity are pivotal to the high HDL-cholesterol in runners. The discrepancy arises because the traditional approach assumes that the confounding effects of leanness are attributable to the static process of self-selection rather than the dynamic process of weight loss.

## POPULATION STUDIES OF CVD AND CHD

Tables 1 and 2 summarize the treatment of weight in population studies relating physical activity and cardiorespiratory fitness to CHD and CVD. They include articles cited in Tables 4.1 and 4.2 of the Surgeon General's report (120), 13 additional articles cited in a recent meta-analysis of the dose-response relationship between CVD and physical

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TABLE 1. Population-based studies of the association of physical activity with CVD or CHD.

Study	Adjustment for Adiposity
Canadian Health Survey 7-yr follow-up study in men and women (2)	No dose-response relationship between CVD and leisure-time physical activity. Relative risks adjusted for BMI, sex, age, and smoking (2).
Zutphen Elderly Study 10-yr follow-up of 802 middle-aged Dutch men (5)	Significant linear trend for reduced risk of CVD mortality with increasing leisure-time physical activity. Adjustment for BMI did not affect the strength of the association. BMI was not different across physical activity tertiles (5).
Israeli 15-yr follow-up of 5288 men and 5229 women living in collective settlements (10)	The risk of primary myocardial infarction was 60% less in nonsedentary than in sedentary male workers. Nonsedentary workers leaner, but no adjustment for adiposity (10).
Evans County 7.25-yr follow-up of white male farmers and nonfarmers (11)	Farmers had 51% lower CHD incidence than nonfarmers, and since they were heavier for their height than nonfarmers, leanness is unlikely to explain the farmers' lower risk (11).
German 11-yr follow-up of 1904 vegetarians (12)	Compared to low activity vegetarians, more active vegetarians had fatal CVD risk that was 50% lower. BMI unrelated to CVD risk and not used as covariate (12).
British 8.5-yr follow-up of 3591 male civil servants (13)	Men who exercised vigorously during leisure time had significantly fewer CHD deaths. No adjustment for adiposity (13).
Honolulu Heart Program 12-yr follow-up of 7644 Japanese-American men (15)	Men in the upper tertile of total activity (occupational plus leisure-time) had significantly lower CHD risk than bottom tertile, adjustment for BMI had little effect on risk reduction (15).
Israeli Ischemic Heart Disease Study 21-yr follow-up of 8463 men (16)	Leisure-time physical activity associated with a 21% reduction in CHD mortality when adjusted for potentially confounding effects (Quetelet index not selected as a significant covariate) (16).
Atherosclerosis Risk in Communities Study 4- to 7-yr follow-up of 6188 men and 7852 women (23)	A 1-SD increase in the leisure-time physical activity index produced a statistically significant 22% reduction in the age, race, and center adjusted relative risk for CHD, which became nonsignificant when adjusted for regional adiposity and other potential confounding effects (23).
Puerto Rico Heart Health Program 8.25-yr follow-up of 5802 urban and 2419 rural men (25)	Inverse dose-response relationship between CHD incidence and physical activity index (occupational plus leisure-time) when adjusted for BMI in rural ( $P = 0.04$ ) and urban samples ( $P = 0.02$ ) (25).
Finnish 10.8-yr follow-up of 1072 men (26)	Men who expended at least 2100 kcal · wk <sup>-1</sup> had 72% reduction in CVD mortality compared with men expending under 800 kcal · wk <sup>-1</sup> . BMI not found to confound relationship (26).
Finnish 10-yr follow-up of 842 men and 953 women in three northern municipalities (27)	In men, the CHD risk reduction for high vs low energy expenditure was significant both before (relative risk = 0.51) and after adjustment for BMI (relative risk = 0.52). High vs low energy expenditure unrelated to CHD risk in women, regardless of whether the data were adjusted (27).
Copenhagen Male Study 17-yr follow-up of 4859 men (31)	Least active men have 70% increased risk of ischemic heart disease as those who are more active. No adjustment for adiposity (31).
Primary Prevention Study 11.8-yr follow-up of 7395 men in Göteborg, Sweden (34)	No dose-response relationship with leisure-time physical activity. BMI not used among covariates (unclear if excluded for nonsignificance or other reason) (34).
Male postal workers ( $N = 1664$ ) employed between 1906 and 1940 and followed through December 1961 (35)	64% lower risk of fatal CHD in carriers than clerks. Only 0.5-lb difference between carriers and clerks, thus difference in adiposity unlikely to explain risk reduction (35).
Framingham Study 14-yr follow-up of 1909 men and 2311 women (36)	Significant (one-sided) inverse association with ischemic heart disease mortality in men. No adjustment for adiposity (36).
Framingham Study 24-yr follow-up of 1166 men (37)	Inverse associations of fatal and total CHD and CVD with total physical activity index (occupational plus leisure-time) significant both before and after adjustment for relative weight (37).
Alameda County Study 28-yr follow-up of 6131 adults (38)	A one-interquartile-range difference in the leisure-time physical activity score was associated with significant reduction in the relative risk for CVD before (relative risk = 0.82) and after (relative risk = 0.85) adjustment for BMI and other covariates (38).
Finnish 19-yr follow-up of 8177 twins (39)	Compared with sedentary men, the age-adjusted CHD risk was reduced by 23% for occasional exercisers and 48% for conditioning exercisers ( $P = 0.0001$ for trend). The corresponding values when adjusted for BMI, smoking, hypertension, and diabetes were 16% and 32% (39).
Postmenopausal Iowa women ( $N = 32,763$ ) who were followed for 4 yr (44)	When adjusted for current BMI, BMI at age 18, and other covariates, the relative risk for CVD mortality decreased significantly as physical activity increased (relative risk from lowest to highest activity: 1.0, 0.86, 0.55; $P = 0.002$ ) (44).
HMO members ( $N = 615$ men and 1030 women) $\geq 65$ yr old followed for 4.2 yr (45)	Adjustment for BMI only slightly diminished the risk reduction associated with walking >4 hr compared with under 1 hr (45).
Kuopio Ischemic Heart Disease Risk Factor Study 4.9-yr follow-up of 1166 men (46)	Adjustment for BMI had minor impact on the relative risk of myocardial infarction in the highest vs lowest third of physical activity (relative risk went from 0.31 to 0.34, both significant) (46).
Gothenburg Study 12-yr follow-up of 1424 women (47)	Incidence of myocardial infarction greater in women reporting low leisure-time physical activity than in other women. No adjustment for adiposity (47).
Multiple Risk Factor Intervention Trial 7-yr follow-up of 12,138 men (51)	Significantly lower risk for lowest vs second and third tertiles of leisure-time physical activity. BMI not used for adjustment; however, mean BMI identical across activity tertiles (51).
Multiple Risk Factor Intervention Trial 10.5-yr follow-up of 12,138 middle-aged men (52)	Compared with the lowest tertile of physical activity, the second tertile had 22% and 27% lower CVD and CHD mortality rates ( $P < 0.05$ ). Corresponding reductions in the third tertile (21% and 16%, respectively) not significantly different from first tertile. Mean BMI identical across tertiles of leisure-time physical activity; not used as covariate in proportional hazards models (52).
Multiple Risk Factor Intervention Trial 16-yr follow-up of 12,138 middle-aged men (53)	Adjustment for BMI and other potential covariates slightly diminished the reduction in CHD risk associated with increased levels of leisure time physical activity (age-adjusted risk ratios went from 1.0, 0.71, 0.75, 0.69 to 1.0, 0.75, 0.81, 0.75) for the 1st, 2nd–4th, 5th–7th, and 8th–10th deciles, respectively; however, all but the 5th–7th remained significant after adjustment for BMI and other covariates (53).
Adventist Mortality Study 26-yr follow-up of 9484 men (57)	CVD risk greater in men reporting no or slight exercise during work or play compared with more active men, which persists when adjusted for BMI and other covariates (57).
Gothenburg Study 20-yr follow-up of 1405 women (58)	No significant reduction for risk of fatal myocardial infarction (age-adjusted relative risk 0.41 changed to 0.36 with additional adjustments for waist/hip ratio and other covariates) (58).
Finnish 8.9-yr follow-up of 8869 men and 9.2-yr follow-up of 10,105 women (59)	Physical inactivity (<2–3 times · mo <sup>-1</sup> ) associated with significantly higher cardiovascular mortality in women ( $P < 0.01$ ) but not men ( $P = 0.28$ ) when adjusted for BMI and other covariates (59).
Nurse's Health Study 7.7-yr follow-up of 72,488 women (60)	The trend for a lower risk for CHD going from the least to most physical active quintiles (1.0, 0.77, 0.65, 0.54, 0.46; $P < 0.001$ for trend) was only slightly weakened by adjustment for BMI (1, 0.88, 0.81, 0.74, 0.61; $P = 0.002$ ) (60).
Italian 5-yr follow-up of 99,029 male railroad employees (63)	Men who expended > 3000 kcal · d <sup>-1</sup> at work had significantly less risk of fatal myocardial infarction than men with less strenuous jobs ( $P < 0.001$ ). No adjustment for adiposity (63).
German Cardiovascular Prevention Study involving 6658 and 7993 person-years of experience for males and females, respectively (64)	When adjusted for BMI, men who had engaged in high activity had lower relative risk for CVD than those who did not (64).

TABLE 1. Continued

Study	Adjustment for Adiposity
Male drivers and conductors of London Transport Executive (65)	Risk of first coronary episode 30% lower in conductors than drivers. No adjustment for adiposity (65).
London 5-yr follow-up of 667 bus drivers and conductors (67)	Conductors have 47% lower risk for ischemic heart disease than drivers. Skinfold thickness does not appear to explain the association (67).
British 8.5-yr follow-up of 17,944 male civil servants (68)	Compared with men who reported no vigorous activity during leisure time, those who exercised vigorously had 55% lower incidence of coronary heart disease. When stratified for weight, the risks were 0.46 for BMI $\leq$ 23; 0.43 for 23 < BMI $\leq$ 25; and 0.64 for 25 < BMI $\leq$ 28 (68).
British 9.34-yr follow-up of 9376 male civil servants (69)	CHD inversely related to frequency of vigorous aerobic activity, significant both before ( $P < 0.005$ ) and after ( $P < 0.025$ ) adjustment for BMI and other covariates (69).
Longshoremen ( $N = 6351$ ) followed for 22 yr (72)	Risk of fatal heart attack 44% lower in high-energy compared with the low-energy occupational category. Significance persists when adjusted for BMI and other risk factors (72).
Longshoremen ( $N = 3686$ ) followed for 22 yr (73)	Risk of fatal heart attack 37% lower in high-energy compared with the low-energy occupational category. BMI only weakly related to risk (73).
Harvard Alumni Study 6.9-yr follow-up 16,936 men (74)	The RR for heart attack was 0.65 for men who expended $> 2000 \text{ kcal} \cdot \text{wk}^{-1}$ at walking, stair climbing, and sports play compared with other men. Significant when adjusted for BMI. The risk reduction was similar for men with higher (relative risk = 0.75) and lower BMI (relative risk = 0.60) (74).
Harvard Alumni Study 12.62-yr follow-up of 16,936 men (75)	Inverse dose-response relationship between CHD and physical activity when stratified by BMI ( $P < 0.001$ ). Increased risk associated with $< 2000 \text{ kcal} \cdot \text{wk}^{-1}$ when BMI used as a covariate ( $P < 0.001$ ) (75).
Harvard Alumni Study 8.8-yr follow-up of 10,269 men (76)	Men who climbed fewer than 20 flights of stairs per week and did not engage in moderately vigorous activity were at 56% and 51% greater risk for fatal CHD than men who climbed more stairs or engaged in moderately vigorous activity when adjusted for age, smoking, BMI $> 26$ , and family history (76).
Finnish 20-yr follow-up of 636 men (78)	Men who worked hard in their occupation and also walked, cycled, or skied cross-country had lower CHD mortality than less active men (R.R. = 0.71, $P = 0.11$ ), which was weakened slightly when adjusted for BMI and other risk factors (R.R. = 0.77, $P = 0.13$ ) (78).
Iowa study of occupation listed on 61,922 death certificates (80)	Significantly lower standardized mortality ratios for ischemic heart disease in farmers than all Iowa men. Probably not because of adiposity, since farmers heavier than townsmen (80).
Iowa women drivers (32,898) followed for 4.3 yr (81)	Leisure-time physical activity unrelated to age-adjusted risk of fatal myocardial infarction (81).
Honolulu Heart Program 23-yr follow-up of 7074 Japanese men (84)	Adjustment for BMI increased the relative risk of CHD in the highest tertile of physical activity from 0.83 (95% confidence interval; 0.70–0.99) to 0.89 (0.75–1.06) (84).
Göteborg Primary Prevention Study 20-yr follow-up of 7142 men (85)	Adjustment for BMI and other potential confounders reduced the relative risk of CHD mortality in the two most active groups from 0.55 to 0.72 when compared with the sedentary group, but did not eliminate the significance of the risk reduction (85).
Federal employee 3-yr follow-up study of 1741 men (86)	Total activity unrelated to CHD when adjusted for other risk factors (not including BMI) (86).
Finnish study of approximately 7-yr follow-up 3978 men and 3688 women (89)	Adjustment for BMI and other risk factors eliminated the significant associations between age-adjustment leisure-time physical activity and acute myocardial infarction in both men and women, and the significant association between leisure-time physical activity and fatal ischemic heart disease in men (89).
Finnish 6-yr follow-up of 15,088 men and women (90)	Age-adjusted leisure-time physical activity inversely related to fatal ischemic heart disease, but not when adjusted for various covariates (BMI not included). Excess risk of fatal ischemic heart disease in men with low leisure-time physical activity was marginally greater in obese men than in nonobese men (90).
Northern and Central Italian 25-yr follow-up study of 1712 men (96)	The relative risk for CHD mortality was 0.81 for strenuous workers compared with sedentary workers ( $P < 0.01$ ). No adjustment for adiposity (96).
University of Pennsylvania 22.4-yr follow-up of 1564 female alumnae (99)	The age-adjusted relative risks for CVD were 1.0, 0.99 and 0.86 for $< 500$ , 500–999, and $\geq 1000 \text{ kcal} \cdot \text{wk}^{-1}$ from stairs climbed, blocks walked, and sports played ( $P = 0.37$ for trend). When adjusted for BMI and other covariates, the corresponding values were 1.0, 0.99, and 0.86 ( $P = 0.45$ ) (99).
Harvard Alumni Study 13.3-yr follow-up of 12,516 men (100)	Compared with men who expended under $2100 \text{ kJ} \cdot \text{wk}^{-1}$ at climbing steps, blocks walked, and sports, the age-adjusted risks for CHD was reduced by 15%, 25%, 27%, and 27% ( $P < 0.001$ for trend) for 2100–4199, 4200–8399, and 8400–1599 $\text{kJ} \cdot \text{wk}^{-1}$ . The corresponding risk reductions were 10%, 19%, 20%, and 19% when further adjusted for BMI and other covariates (100).
British Regional Heart Study 8-yr follow-up of 5714 men (101)	When adjusted for BMI, there was a strong inverse association between heart attacks and physical activity (101).
Framingham Study 16-yr follow-up of 1404 women (103)	No dose-response relationship with physical activity index (occupational plus leisure-time). Metropolitan ideal weight used as covariate in proportional hazards regression mode (103).
U.S. Railroad Study 17- to 20-yr follow-up of 2562 men (105)	Significantly lower CHD risk associated with any light to moderate activity or any intense leisure-time physical activity. BMI not used as covariate because it showed no relationship to CHD mortality (105).
Belgian Physical Fitness Study 5-yr follow-up of 2106 men (106)	Both occupational and leisure-time physical activity unrelated to ischemic heart disease. No adjustment for adiposity (106).
Nurses Health Study 14-yr follow-up of 84,129 women (109)	The age-related relative risks for CVD were 1.0, 0.87, 0.84, 0.74, and 0.71 for $< 1$ , 1–2.2, 2.3–3.5, 3.6–5.5 and $> 5.5 \text{ hr} \cdot \text{wk}^{-1}$ of moderate to vigorous activity. Exercising $> 5.5 \text{ hr}$ significantly lower risk compared with $< 1$ . BMI significantly related to CVD risk but not selected as covariate (109).

activity (125), and additional articles identified through electronic literature search. Rather than directly measuring the body fat, an index of weight adjusted for height was used in these studies.

Eleven of the 64 articles listed in Table 1 found no relationship between physical activity and disease, and 53 found at least some significant relationship. Among the latter, 11 reported no adjustment for weight, nine cited

TABLE 1. Continued

Study	Adjustment for Adiposity
Norwegian 14.6-yr follow-up study of 25,058 middle-aged men and 24,535 women (111)	Unadjusted relative risk for coronary deaths unrelated to leisure-time physical activity (111).
Two-yr follow-up of 191,609 male railroad employees (112)	Death rate for arteriosclerotic heart disease in the section men (the most active occupational group) was 51% lower than in clerks and 28% lower than switchmen. No adjustment for adiposity (112).
Scottish Heart Health Cohort Study of 5754 men and 5875 women who were followed for 7.6 yr (119)	Hazard ratio for CHD increased significantly with increasing levels of inactivity at work in men and women and during leisure in men. No adjustment for weight (119).
British Regional Heart Study 3-yr follow-up of 4311 men (121)	CVD mortality lower in moderately active (risk ratio = 0.26) and vigorously active (risk ratio = 0.43) men compared with inactive men. When adjusted for BMI and other covariates, risk ratios continue to be significantly less than 1 for moderate but not vigorous activity (121).
Canadian Survey Fitness cohort 7-yr follow-up of 6620 women (123)	Physical activity significantly associated with CVD, no adjustment for BMI reported (123).
Gothenburg 8-yr follow-up study of 775 men born in 1913, and Primary Prevention Trial 2.5- to 5.5-yr follow-up of 8125 men in Göteborg (124)	No significant relationships between leisure-time physical activity and myocardial infarctions when adjusted for covariates (adiposity not included among covariates) (124).
Honolulu Heart Program 10-yr follow-up of 7705 Japanese-American men (141)	Men who developed CHD were significantly less physically active and heavier than those without disease at baseline. Total physical activity inversely related to CHD risk when adjusted for BMI and other potential confounders (141).

reasons that weight differences should not explain the observed association (the active group is not leaner than the sedentary group, weight is unrelated to CHD or CVD, or the association persists when the observations are stratified by weight), and 33 present findings adjusted for weight (if necessary, i.e., also included are those studies that did not select weight as a required covariate in a stepwise selection process). Only three of these 33 articles found that adjustment for weight changed the associations between physical activity and disease from significant to nonsignificant.

The 16 reports of cardiorespiratory fitness all reported at least some significant association of fitness with CHD or CVD (Table 2). Five of these did not adjust for weight and one argued that weight adjustment was unnecessary because weight was unrelated to fitness. None of the remaining 10 reports changed the significance of their findings when they adjusted for body weight.

These studies suggest that statistical adjustments for body weight had little impact on the associations of physical activity or cardiorespiratory fitness with CVD or CHD. We cannot exclude the possibility that the published articles represent a biased sample of studies. It is possible that the articles that adjusted away the association between physical activity and disease were less likely to be submitted or accepted for publication, or that adjusted results were not reported when they eliminated significant findings. However, the articles that omitted weight adjustment tended to have earlier publication dates and to have studied occupations. It is likely that multivariate statistics were less accessible for early publications and that occupational studies may have lacked data on body weight.

## POPULATION STUDIES OF PLASMA HDL AND OTHER LIPOPROTEINS

Although the mechanisms for protective effects of exercise are not well understood, it is probable that the creation of more favorable plasma lipoprotein profiles are partly involved. Low CHD risk is associated with higher concentration of HDLs, particularly the HDL<sub>2</sub> subfraction, and lower concentrations of LDLs, triglycerides, and small dense LDL particles (3,33). The reduction in risk may

accrue from both the atherogenic and thrombotic properties of these lipoproteins (87).

Numerous population studies show higher HDL-cholesterol concentrations in vigorously active men and women compared with their sedentary counterparts (1,3,14,28–30,50,55,61,62,70,71,83,93–95,108,114–116,118,133,138). Most purport that the relationship between physical activity and plasma HDL concentrations is not attributable to body fat because: 1) the difference persists when adjusted for weight by ANCOVA (29,30,133); 2) long-distance runners have significantly higher HDL-cholesterol levels than naturally lean, sedentary men (55,71,95); and 3) HDL-cholesterol and adiposity levels are only weakly correlated within the sample of runners or sedentary men (1,62,138). Two large studies have recently documented the relationship of HDL-cholesterol to exercise amount (43,130). HDL-cholesterol was associated with a 0.005 mmol·L<sup>-1</sup> increase per kilometer run in 2906 students and employees of the National Defense University (43). Physician-supplied medical records for men who participated in the National Runners' Health Study showed that each 16-km incremental increase in weekly running distance between 0 and 80 km·wk<sup>-1</sup> was associated with a significant increase in HDL-cholesterol (130). Figure 1 shows that adjustment for BMI by ANCOVA accounted for only 25% of the HDL-cholesterol difference between runners who ran under 16 km·wk<sup>-1</sup> and those that exceeded 80 km·wk<sup>-1</sup>.

## INTERVENTION STUDIES

In contrast to population (cross-sectional) studies, intervention studies show that runners' changes in HDL-cholesterol are strongly dependent on loss of weight. In one study, Wood et al. assigned men at random to vigorous exercise (primarily running, *N* = 48) or to control (*N* = 33) over a 1-yr period (132,134,139). Within the exercise group, changes in HDL-cholesterol were significantly correlated with weekly running distance (*r* = 0.44), changes in total body mass (*r* = -0.53), and changes in percent body fat (*r* = -0.47). Forty-six percent of the variance of the runners' HDL-cholesterol changes were accounted for by changes in body composition and running distance. However, when

TABLE 2. Population-based studies of the association of cardiorespiratory fitness with CVD or CHD.

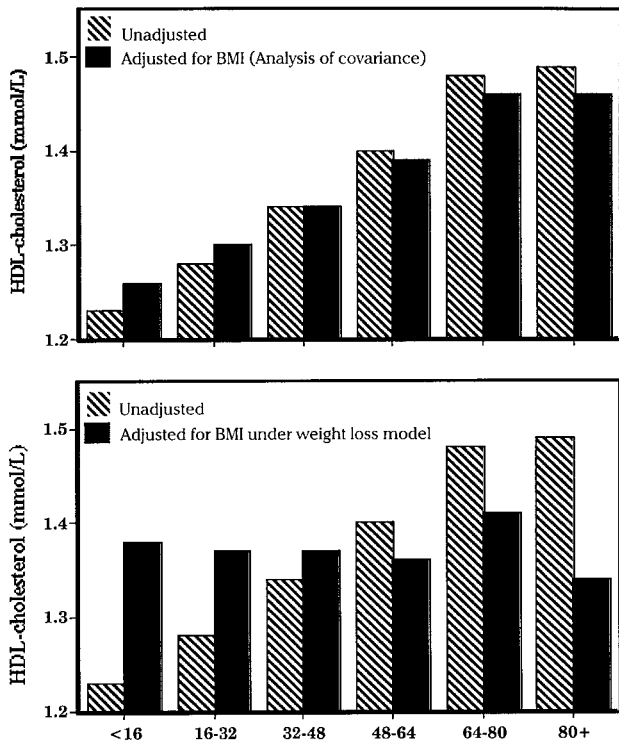
Study	Adjustment for Adiposity
Canadian Health Survey 7-yr follow-up study in men and women (2)	Subjects who did not pass or who were ineligible for the Canadian home fitness test had significantly higher risk for CVD mortality than those that passed when adjusted for BMI, sex, age, and smoking (2).
Aerobic Center Longitudinal Study 8.32-yr follow-up of 10,224 men and 8.15-yr follow-up of 3120 women (6)	Longer treadmill test duration predicted significantly lower risk of CVD mortality in men. BMI $\geq 26.9$ unrelated to all-cause mortality. Adjustment for BMI and other covariates did not eliminate the association between fitness and all-cause mortality (effects of adjustment not reported for cardiovascular mortality) (6).
Aerobic Center Longitudinal Study of 5.1-yr follow-up of 9777 men having two fitness measurements 4.9 yr apart (7)	Rates of CVD mortality were highest in men who were unfit at two visits (i.e., lowest quintile for treadmill test duration), intermediate in men who were fit at only one visit, and lowest in men who were fit at both visits. These differences were significant when adjusted for BMI and other covariates (7). (See caveat in 131.)
Aerobics Center Longitudinal Study 8.4-yr follow-up of 25,341 men and 7.5-yr follow-up of 7080 women (8)	The relative risk of CVD for fitness $> 20$ th sample percentile was 0.37 for men (0.59 when adjusted for BMI and other covariates) and 0.36 for women (0.41 when adjusted) (both significant) (8).
Seattle Heart Watch study 5.6-yr follow-up of 2365 men (9)	Activity unrelated to CHD risk; however, a treadmill test duration of 6 min or less was associated with 12-fold increase in risk. Risk adjusted for age and BMI not reported (9).
Lipid Research Clinics Mortality Follow-up Study 8.5-yr follow-up of 3106 men (17)	Compared with the most fit men (defined by submaximal heart rate during a treadmill test), the least fit had 8.5 times higher rate of CHD and 6.5 times higher risk of CVD. Quetelet index unrelated to fitness and not included among covariates in multivariate adjustment (17).
Norwegian 9- to 11-yr follow-up of 1832 middle-aged men (18)	Risk of CHD deaths greatest for the lowest fitness quartile (i.e., cumulative work performed on a bicycle ergometer divided by body weight). No statistical test for trend, and no adjustment for adiposity (18).
Norwegian 12-yr follow-up of 1428 middle-aged men (19)	When adjusted for BMI and other covariates, the relative risks by quartile of fitness were 1.0, 0.66, 0.50 ( $P < 0.05$ ), and 0.47 ( $P < 0.05$ ) (19).
Aerobics Center Longitudinal Study 8.4-yr follow-up of 25,341 men (20)	When adjusted for age, fatal CVD rates decreased with increasing levels of fitness in men having a BMI $< 27 \text{ kg} \cdot \text{m}^{-2}$ (14.5, 9.6, and 6.7 deaths per 10,000 man-years, $P = 0.001$ ), but not in those having a higher BMI (17.9, 10.6, and 9.5 deaths per 10,000 man-years, $P = 0.24$ ) (20).
Copenhagen Male Study 17-yr follow-up of 4999 men (31)	Among men who did a minimum of light physical activity for $4 \text{ h} \cdot \text{wk}^{-1}$ , survivors had higher baseline fitness (indirect estimates of $\dot{V}O_{2\text{max}}$ on cycle ergometers) than men who died from ischemic heart disease. BMI inversely related to cardiorespiratory fitness ( $P < 0.001$ ) but not used in adjustment (31).
Kuopio Ischemic Heart Disease Risk Factor Study 4.9-yr follow-up of 1166 men (46)	Adjustment for BMI had minor impact on the relative risk of myocardial infarction in the highest vs lowest third of physical fitness (relative risk = 0.26–0.35). Significant both before and after adjustment (46).
Norwegian 7-yr follow-up of 2014 middle-aged men (56)	Risk of CHD deaths greatest for the lowest fitness quartile (difference among fitness quartiles, $P < 0.001$ ). No adjustment for adiposity (56).
4.8-yr follow-up of 2,779 Firemen and police men (77)	Men who were above the median fitness (highest work load sustained for 5 min on cycle ergometer) had 55% lower risk for systematic myocardial infarction. Significant when adjusted for other covariates (lean body mass not selected among covariates in stepwise procedure) (77).
Norwegian 15.9-yr follow-up of 1960 middle-aged men (91)	The highest fitness quartile (i.e., differences between observed and expected work capacity according to body weight) had 70% lower CVD risk than the least fit quartile ( $P < 0.001$ ), which was decreased to 59% ( $P = 0.01$ ) when adjusted for BMI and other risk factors (91).
U.S. Railroad Study 20-yr follow-up of 2431 men (104)	Men with lower exercise heart rates had lower death rates from CVD and CHD. BMI not included in proportional hazards regression analysis (104).
Belgian Physical Fitness Study 5-yr follow-up of 2109 men (106)	Interpolated physical working capacities per kilogram body weight was inversely related to ischemic heart disease both before and after adjustment for BMI and other risk factors. Mean BMI identical in men with and without ischemic events (106).

adjusted for changes in body composition, the runners' changes in HDL-cholesterol were no longer significantly related to weekly running distance (132).

A second study by this group compared the lipoprotein changes of men who dieted ( $N = 42$ ), or exercised vigorously (primarily running,  $N = 47$ ) to nondieting sedentary controls ( $N = 42$ ) (135,140). All were sedentary and moderately overweight at baseline. During the 1-yr trial, the exercisers ran (mean  $\pm$  SD)  $18.9 \pm 13.1 \text{ km} \cdot \text{wk}^{-1}$  and lost  $4.0 \pm 3.9 \text{ kg}$  of body weight, whereas the controls' weights remained stable (mean gain of  $0.6 \pm 3.7 \text{ kg}$ ). Compared with mean changes in controls, the exercisers significantly increased their HDL-cholesterol levels (difference  $\pm$  SE,  $0.13 \pm 0.03 \text{ mmol} \cdot \text{L}^{-1}$  or  $5.05 \pm 1.17 \text{ mg} \cdot \text{dL}^{-1}$ ), but this difference was eliminated by adjustment for changes in BMI ( $0.04 \pm 0.04 \text{ mmol} \cdot \text{L}^{-1}$  or  $1.46 \pm 1.44 \text{ mg} \cdot \text{dL}^{-1}$ ). Within the exercise group, changes in HDL-cholesterol during the 1-yr study were correlated with running distances ( $r = 0.45$ ) and changes in BMI ( $r = -0.58$ ). Changes in HDL-cholesterol were no longer significantly correlated with running distance when adjusted for changes in BMI, whereas changes in BMI remained significantly correlated with the exercisers'

changes in HDL-cholesterol ( $r = -0.39$ ) when adjusted for weekly running distance.

In another study, Thompson et al. showed that weight loss was not required to achieve modest increases in HDL-cholesterol with exercise. They trained 17 sedentary men  $4 \text{ hr} \cdot \text{wk}^{-1}$  while keeping both body weight and percent body fat constant over 1 yr by overfeeding (117). By the end of the study, HDL-cholesterol had increased by  $0.1 \text{ mmol} \cdot \text{L}^{-1}$  ( $3.8 \text{ mg} \cdot \text{dL}^{-1}$ ), caused primarily by a 33% increase ( $0.06 \text{ mmol} \cdot \text{L}^{-1}$  or  $2.3 \text{ mg} \cdot \text{dL}^{-1}$ ) in HDL<sub>2</sub>. However, the maintenance of body weight through overfeeding does not reflect the usual condition of men who exercise vigorously. Significant loss of total weight and percent body fat occurs usually within the first 6 months of training. The contribution of weight loss to lipoprotein levels in these 17 men was investigated through further experimentation by Thompson and colleagues (113). On completion of the 1-yr weight stable phase; the 17 men were assigned at random to either a weight stable group (i.e., continuing the previous year's protocol) or a weight loss group. The lipoprotein changes in the weight stable group were not sustained by 18 months, i.e., HDL-cholesterol decreased  $0.05 \text{ mmol} \cdot \text{L}^{-1}$  ( $2.0 \text{ mg} \cdot \text{dL}^{-1}$ ) and



**FIGURE 1**—Distribution of mean plasma HDL-cholesterol concentrations by reported weekly distance run in 7059 male runners (130). Upper panel: *Solid bars* show the effects of adjustment by traditional analysis of variance, which uses the cross-sectional relationship between BMI and HDL-cholesterol to adjust for weight differences between distance groups. Bottom panel: *Solid bars* show the effects of using the coefficient relating weight loss to HDL-cholesterol changes ( $4.28 \text{ mg}\cdot\text{dL}^{-1}$  per unit decrease in BMI) (126) to adjust for weight differences between distance groups.

HDL<sub>2</sub>-cholesterol decreased  $0.03 \text{ mmol}\cdot\text{L}^{-1}$  ( $1.3 \text{ mg}\cdot\text{dL}^{-1}$ ). The weight loss group lost 9.4 kg, resulting in additional increases of  $0.8 \text{ mmol}\cdot\text{L}^{-1}$  ( $3.3 \text{ mg}\cdot\text{dL}^{-1}$ ) in HDL-cholesterol and  $0.11 \text{ mmol}\cdot\text{L}^{-1}$  ( $4.3 \text{ mg}\cdot\text{dL}^{-1}$ ) in HDL<sub>2</sub>-cholesterol concentrations. This suggests that at the end of the 18-month period, weight loss accounted for most of the increases in plasma HDL-cholesterol (75%) and HDL<sub>2</sub> (85%) from baseline.

These results suggest that the increases in HDL in sedentary men who begin exercising vigorously arise primarily from processes associated with weight loss. They agree with observations by Katzell et al. and Sopko et al. showing only small changes in HDL-cholesterol in the absence of weight change (40,107), and with the observations by Leon et al. that training-induced changes in HDL-cholesterol are related to changes in percent body fat but not  $\dot{V}O_{2\text{max}}$  (51).

**Previously obese runners.** If HDL-cholesterol levels in runners are principally related to historical weight loss rather than current adiposity levels, then previously obese runners would be expected to have higher HDL-cholesterol than runners who were always lean. In one study, we found that HDL-cholesterol concentrations were unrelated to training level or running performance, but strongly related to the difference between the runners' greatest and current BMI. HDL-cholesterol levels were increased  $3.0 \text{ mg}\cdot\text{dL}^{-1}$  for every kilogram per square

meter below greatest weight. This association largely reflected the elevated HDL-cholesterol levels of five men who lost more than  $6 \text{ kg}\cdot\text{m}^{-2}$  since their greatest weight (126). The association between weight history and lipoprotein concentrations was also examined in the National Runners' Health Study (129). Current HDL-cholesterol levels were greatest in those runners with the greatest weight loss since their maximum lifetime weight, as well as the runners with the greatest reductions in circumference of their waist, hip, and chest since their maximum weight. These results remained significant when adjusted for current BMI and running mileage.

**The trouble with statistics.** The intervention studies suggest a prominent role for the metabolic processes associated with weight loss in the etiology of the runners' lipoprotein profiles. Thus, it would be misguided to dismiss the importance of these processes simply because the HDL differences in population studies persist when statistically adjusted for BMI. It may also be misguided to dismiss the importance of weight loss in lowering CHD and CVD risk among active individuals. However, there are no intervention studies having CHD or CVD as endpoints to provide guidance on this issue.

There are the obvious limitations to statistical adjustment for BMI in population studies. The adjustment for indices of weight for height (including BMI) are valid only to the extent that these measures reflect the biologically relevant parameters of body fat. Measurement error associated with BMI may also reduce its effectiveness of the covariate. Some reports cite evidence of interactions between fitness and weight and between activity and weight in their relationship to disease that is contrary to the statistical models (48,69). However, a more fundamental issue concerns the meaning of statistical adjustment and the assumptions made in its calculation. As traditionally applied, the adjustment uses the cross-sectional relationships between weight and the health outcomes. It therefore invokes a frame of reference of a population that is static in time. This is appropriate if the leanness of physically active individuals is because of self-selection, i.e., if lean individuals take up sports and lead more physically active lives than overweight men and women. For example, it is apropos to conduct comparisons of bus drivers and conductors, since London bus drivers are heavier when hired than conductors (66). As applied to Tables 1 and 2, the statistical adjustments suggest that CHD, CVD, and lipoprotein differences between active and inactive men are not simply the consequence of lean and healthy subjects choosing to be active whereas overweight unhealthy subjects lead sedentary lives (i.e., they rule out the effects of self-selection).

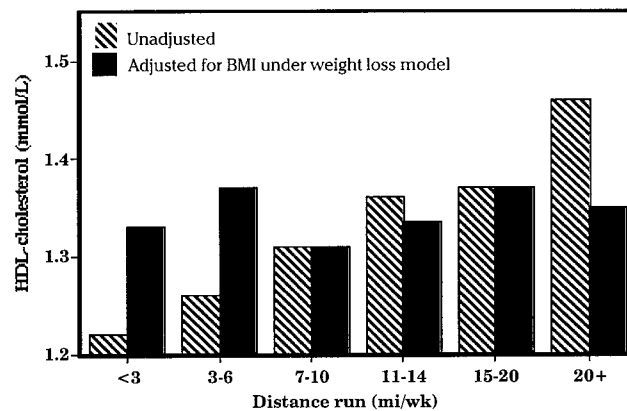
A separate issue is whether the metabolic processes associated with weight loss produce the high HDL-cholesterol levels of runners. For this, the static model requires justification. Vigorous physical activity causes loss of weight and body fat (138–140). Higher mileage runners are leaner because they have lost more weight or avoided weight gain. Although lean individuals may be more likely to take up running as a sport (self-selection), the leanness of runners is

also caused in large measure by weight loss as a consequence of running. The validity of using weight as a covariate in ANCOVA, logistic regression, or survival analysis depends critically on whether the cross-sectional relationship between weight and health outcomes can be used to estimate the dynamic effects of weight loss on these health outcomes.

This critical assumption has been shown to be invalid for plasma HDL-cholesterol concentrations. We have found that initially sedentary men who began running were able to increase their HDL cholesterol by  $0.11 \text{ mmol}\cdot\text{L}^{-1}$  ( $4.28 \text{ mg}\cdot\text{dL}^{-1}$ ) for each unit decrease in BMI over the 1-yr study (135). This change in HDL-cholesterol is fivefold greater than the cross-sectional data implied at baseline ( $0.02 \text{ mmol}\cdot\text{L}^{-1}$  or  $0.78 \text{ mg}\cdot\text{dL}^{-1}$  increase per unit decrease in BMI) or at the end of the 1-yr study ( $0.01 \text{ mmol}\cdot\text{L}^{-1}$  or  $0.57 \text{ mg}\cdot\text{dL}^{-1}$  increase per unit decrease in BMI). This suggests that standard epidemiological methods for adjusting for weight are likely to seriously underestimate the confounding effects of weight loss.

Studies carried out by our group suggest that expected HDL-cholesterol for a given weight depends in part on whether the current weight is relatively high or low within the historical range of weights experienced by the individual. Williams compared the cross-sectional HDL levels of runners with their current weights (as traditionally used for adjustment) and their weight loss since they began running 1 yr ago (127). In all cases, current BMI showed little relationship to current HDL levels, which is consistent with the conclusions of most population studies. However, there was a strong relationship between previous weight loss since starting to run and current HDL levels. Thus, the actual relationship depends on past weight history in addition to current weight (126,127,136). Runner A could be heavier than runner B but have higher HDL-cholesterol than B if A had lost more weight than person B. This supposes a frame of reference within each person, a frame of reference also invoked when postulating the existence of a weight set point (126,127).

**Reassessing statistical adjustment.** ANCOVA uses the following method of correction. To correct for differences in BMI, the mean differences in BMI between runners and nonrunners is multiplied by the expected change in HDL per unit difference in BMI. This value is then subtracted from the mean difference in HDL-cholesterol to get the corrected mean difference, i.e., (average HDL-cholesterol difference)  $- \beta \times$  (average BMI difference), where  $\beta$  is the expected HDL difference per unit difference in BMI. ANCOVA uses the cross-sectional (static) relationship between HDL-cholesterol and BMI to estimate  $\beta$ . For example, we have reported that average HDL-cholesterol concentrations were  $0.39 \text{ mmol}\cdot\text{L}^{-1}$  ( $15.33 \text{ mg}\cdot\text{dL}^{-1}$ ) higher in runners than sedentary men and that the runners were also  $2.48 \text{ kg}\cdot\text{m}^{-2}$  leaner (133). Cross-sectionally, we found that HDL-cholesterol was  $0.03 \text{ mmol}\cdot\text{L}^{-1}$  ( $1.065 \text{ mg}\cdot\text{dL}^{-1}$ ) higher for each unit decrease in BMI ( $\beta = -1.065 \text{ mg}\cdot\text{dL}^{-1}\cdot\text{kg}^{-1}\cdot\text{m}^{-2}$ ). Thus, the standard application of ANCOVA suggests that only  $0.07 \text{ mmol}\cdot\text{L}^{-1}$  ( $2.64 \text{ mg}\cdot\text{dL}^{-1}$ ) of the differ-



**FIGURE 2**—Distribution of mean plasma HDL-cholesterol concentrations by reported weekly distance run in 2906 male runners (43). *Solid bars* show the effects of using the coefficient relating weight loss to HDL-cholesterol changes ( $4.28 \text{ mg}\cdot\text{dL}^{-1}$  per unit decrease in BMI) (126) to adjust for weight differences between distance groups. Ninety-two percent of the HDL-cholesterol difference between the high- and low-distance runners ( $0.24 \text{ mmol}\cdot\text{L}^{-1}$ ) can be explained by the  $2 \text{ kg}\cdot\text{m}^{-2}$  difference in their mean BMI ( $2 \text{ kg}\cdot\text{m}^{-2} \times 0.11 \text{ mmol}\cdot\text{L}^{-1}\cdot\text{kg}^{-1}\cdot\text{m}^{-2} = 0.22 \text{ mmol}\cdot\text{L}^{-1}$ ).

ence was because of BMI, and that  $0.33 \text{ mmol}\cdot\text{L}^{-1}$  ( $12.69 \text{ mg}\cdot\text{dL}^{-1}$ ) was the corrected difference between runners and nonrunners, i.e., ( $15.33 \text{ mg}\cdot\text{dL}^{-1}$ )  $- (-1.065 \text{ mg}\cdot\text{dL}^{-1}\cdot\text{kg}^{-1}\cdot\text{m}^{-2}) \times (-2.48 \text{ kg}\cdot\text{m}^{-2})$ . However, if we use the coefficient for weight loss ( $-0.11 \text{ mmol}\cdot\text{L}^{-1}$  or  $-4.28 \text{ mg}\cdot\text{dL}^{-1}$ ) to estimate how a one-unit difference in BMI affects HDL, then  $0.27 \text{ mmol}\cdot\text{L}^{-1}$  ( $10.61 \text{ mg}\cdot\text{dL}^{-1}$ ) of the difference is because of BMI, and that  $0.12 \text{ mmol}\cdot\text{L}^{-1}$  ( $4.6 \text{ mg}\cdot\text{dL}^{-1}$ ) is the corrected difference between runners and nonrunners, i.e., ( $15.33 \text{ mg}\cdot\text{dL}^{-1}$ )  $- (-4.28 \text{ mg}\cdot\text{dL}^{-1}\cdot\text{kg}^{-1}\cdot\text{m}^{-2}) \times (-2.48 \text{ kg}\cdot\text{m}^{-2})$ . The choice of models very much affects the conclusion reached about exercise versus body fat. The traditional (static) ANCOVA model suggests that metabolic processes associated with BMI have minor roles (17%) in producing high HDL in runners, whereas the weight loss model predicts the metabolic processes associated with BMI are pivotal (i.e., accounting for 70%).

In another example (Fig. 1, upper panel), the traditional (static) ANCOVA model suggested that only 25% of the HDL-cholesterol difference between high-mileage and low-mileage runners was explained by BMI. In contrast, the dynamic weight loss model (i.e.,  $4.28 \text{ mg}\cdot\text{dL}^{-1}$  increase per kilogram per square meter of weight loss) eliminates all of the differences in HDL-cholesterol between high- and low-mileage runners (Fig. 1, lower panel). We also estimate that 92% of the HDL-cholesterol difference reported in the other large study of lipoproteins in runners is attributable to their difference in BMI (Fig. 2). Finally, elsewhere we have plotted the HDL-cholesterol differences reported in 23 published cross-sectional comparisons between runners and sedentary controls against their predicted differences on the basis of our model. Assuming that all of the HDL-cholesterol differences are the consequence of the metabolic processes associated with the lower body weights of the runners, the model predicts with a high correlation the published differences between runners and sedentary men ( $r = 0.80$ ) (132).

The above examples demonstrate that standard statistical adjustment by ANCOVA may substantially underestimate the effects of weight on the lipoprotein profiles of runners. Running is a vigorous activity, and it is not possible to determine to what extent our findings apply to population studies of total physical activity and CHD and CVD. Some studies attribute the lower CHD and CVD risk in active individuals to vigorous activity alone, others negate any advantage of vigorous over nonvigorous activity, and still others assign greater risk reduction to vigorous activity although recognizing the contribution of moderate intensity activity. The relationship between disease risk and weight history is seldom reported. One study that did, by Paffenbarger et al., found a significant dose-response relationship between exercise and CHD risk when adjusted for weight gain since college (75). However, even this may not be an appropriate measure of the difference between a person's current weight and their expected sedentary weight because even long-distance runners appear to gain weight as they age (128).

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## FUTURE RESEARCH PRIORITIES

Population studies that examine disease endpoints will forever be restricted to measurements of adiposity that are practical for large samples. These measurements are adequate for testing whether the associations observed between disease and physical activity are the artifact of self-selection for weight, but not for testing whether metabolic processes associated with weight loss are involved in the etiology of the disease (e.g., dyslipoproteinemias and physical activity). This will require detailed studies of the physiological mechanisms responsible for these health outcomes in runners and other physically active individuals.

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