Published in final edited form as:

Med Sci Sports Exerc. 2012 January ; 44(1): . doi:10.1249/MSS.0b013e31822676e8.

Attenuated inheritance of body weight by running in monozygotic twins

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Abstract

Purpose—Genetic factors account for 40%–70% of the population variation in body mass index (BMI), suggesting that genetic predisposition is a major risk factor for excess weight. The purpose of this study was to test whether exercise attenuates the inherited risk for excess body weight.

Methods—Survey questionnaires of exercise (usual running distance) and BMI were obtained from a national sample of 582 female and 344 male self-identified monozygotic (MZ) twins. Regression analyses were used to test whether running disparity diminished the inheritance of BMI when adjusted for age, education, cigarette use, and selected dietary variables.

Results—The active twins ran between 0 and 10.7 km/d more than their less active twins if female (mean±SD: 1.61±1.50 km/d) and between 0 and 13.7 km/d more if male (1.88 ± 1.78 km/d). Average BMIs of the less active twins were 22.38±3.56 and 24.59±3.08 kg/m² in females and males, respectively. Within-twin correlations were significant ($P < 0.0001$) for usual distance run (females: $r = 0.64$; males: $r = 0.61$) and BMI (females: $r = 0.67$; males: $r = 0.71$). Greater running differences (km/d) attenuated the effect of the less active twins' BMIs on their active MZ twins' BMI (females: -14.3% per km/d, $P < 10^{-7}$; males: -7.4% per km/d, $P = 0.004$), such that by 4 km/d, the inherited risk was reduced by 58.8% in females and 29.6% in males.

Conclusions—These results are consistent with the attenuation of the inherited risk of excess body weight by running, which is remarkable because BMI regulation is assumed to be multifactorial, its genetic inheritance is polygenic, and no single genetic polymorphism currently explains >1% of the BMI variance.

Sixty-four percent of US adults were overweight in 2008, and 34% were obese (6). The annual economic cost of obesity is purported to have been in the US \$147 billion in 2008 and to represent 10% of all medical expenditures (5). Even within the ostensibly “healthy weight” range, greater body weight significantly increases the risks for hypertension, diabetes, high cholesterol, and coronary heart disease (39,40). The national Institute of Medicine currently recommends the energy equivalent of 60 min of walking per day to maintain a healthy weight (10). Sustained vigorous exercise, in particular, may inhibit age-related weight gain (33,34).

Family and twin studies show that genetic factors account for 40%–70% of the population variation in body mass index (BMI) (14,18,23); however, specific single nucleotide polymorphisms (SNPs) tend to be only weakly related to body weight (9,17,24,27). To date, at least 17 SNPs have been shown to be relevant to adult BMI in genome-wide association studies (9,17,24,27). Polymorphisms within the fat mass– and obesity-associated (FTO) gene and the melanocortin 4 receptor gene (MC4R) show the strongest consistent associations with body weight and yet, together, account for <1% of the BMI variance (9).

Genetic predisposition for obesity may be the result of genes maladapted to the calorie-rich and sedentary lifestyles that characterize Western societies (19). Before the industrial revolution, and in hunter–gatherer societies, vigorous physical activity was a regular part of daily existence (15). Studies by others have shown that physical activity suppresses the effect of the FTO genotypes on BMI (1,20,22,25). In addition, we have shown that BMIs were uncorrelated in monozygotic (MZ) twins selected to be discordant for exercise (37), in contrast to their characteristically strong correlation in unselected twins (14,18,23). Gene–environment interactions between physical activity and BMI inheritance have also been suggested by structural equation modeling of Vietnam-era twins (16) and in association studies of genetic risk scores (13).

This report examines the dose–response relationship between twin pair differences in exercise levels and their BMI concordance in a large sample of MZ twins. An advantage to this approach is that the specific genes involved do not need to be identified to test for gene–environment interactions. Moreover, whereas the aforementioned interactions between physical activity and FTO genotypes can affect only a very small proportion of the population, the suppression of BMI inheritance in MZ twins must necessarily involve most genetic influences. Although previous studies, including our own, have shown that physical activity attenuates genetic predisposition to excess body weight, to our knowledge, this is among the first studies to estimate quantitatively the dose–response relationship relative to a specific vigorous physical activity.

Methods

Subjects

Self-identified MZ twins were recruited during screening for a study of lipoproteins in MZ twins discordant for exercise. The MZ twin pairs were participants of the National Runners' Health Study who reported being an identical twin (28,29) or respondents to fliers at race events soliciting MZ twins. The accuracy of self-identified MZ seems to be high for this population, i.e., 96.5% of the sample correctly self-identified themselves as MZ in a subset of 226 twin pairs who were genotyped directly. The twins completed questionnaires that solicited information on demographics, exercise, body weight, smoking habits, medical histories, medications, and selected dietary variables. The study protocol was approved by the Committee for the Protection of Human Subjects, University of California at Berkeley, and all participants signed committee-approved informed consents.

Measurements

BMI was calculated as weight in kilograms divided by the square of height in meters. Elsewhere we have reported strong correlations between self-reported and clinically measured heights ($r = 0.96$) and weights ($r = 0.96$) in runners (32). Runners also reported their usual distances run per week, pace (mi/min), and other exercise activities (type and duration) on the questionnaires. The test–retest correlation for self-reported distance run ($r = 0.89$) compares favorably with other physical activity scores, and the measure correlates significantly with resting heart rate (28,29), a measure commonly used to validate physical activity assessment. Self-reported running distances have been reported to correlate significantly with reported BMI cross-sectionally and BMI longitudinally (28–30,34), and with incident hypertension, hypercholesterolemia, diabetes and other disease end points, prospectively (35). Dietary intake was characterized by usual weekly servings of meat and fish, pieces of fruit consumed, and alcohol intake as computed from reported 12-oz bottles of beer, 4-oz glasses of wine, and glasses of hard liquor or cocktails.

Statistics

Multiple regression analyses (JMP software version 5.0; SAS Institute, Cary, NC) were used to test whether the relationship between the MZ twins' BMI was attenuated with their discordance in reported running distance. Specifically, the model took the form (excluding covariates):

$$\text{BMI}_{\text{Active Twin}} = \beta_0 + \beta_1 \text{Exercise}_{\text{Twin}} + \beta_2 \text{BMI}_{\text{Less-active Twin}} + \beta_3 \text{Exercise}_{\text{Twin}} \times \text{BMI}_{\text{Less-active Twin}}$$

where “ $\text{BMI}_{\text{Active Twin}}$ ” is the BMI of the active twin, “ $\text{Exercise}_{\text{Twin}}$ ” is the twin pair's difference in exercise levels expressed as km/day of running, “ $\text{BMI}_{\text{Less-active Twin}}$ ” is the BMI of the less-active twin, and the cross-product “ $\text{Exercise}_{\text{Twin}} \times \text{BMI}_{\text{Less-active Twin}}$ ” is the interaction between inheritance and exercise. The test for significant interaction is whether the coefficient “ β_3 ” differs significantly from zero. The above equation can be re-expressed as:

$$\text{BMI}_{\text{Active Twin}} = \beta_0 + \beta_1 \text{Exercise}_{\text{Twin}} + [1 + (\beta_3 / \beta_2) \times \text{Exercise}_{\text{Twin}}] \times \text{BMI}_{\text{Less-active Twin}}$$

where $[1 + (\beta_3 / \beta_2) \times \text{Exercise}_{\text{Twin}}]$ is the attenuating effect of exercise on the coefficient for $\text{BMI}_{\text{Less-active Twin}}$. Covariates used in the analyses were age, and within twin-pair differences in cigarette/day smoked, education, and reported intakes of meat, fish, fruit, and alcohol. The occasional missing covariate values were imputed from sex-specific regression analyses with age as the dependent variable (<2% of values).

Results

Survey questionnaires were obtained from 582 female and 344 male self-identified MZ twin pairs identified through a physically active proband who reported a positive running distance. Table 1 presents their sample characteristics. On average, the active twin ran (mean difference $\pm$ SD) 1.61 ± 1.50 km/d more if female and 1.88 ± 1.78 km/d more if male than her or his less active twin ($P < 10^{-15}$ for both). The active females also weighed significantly less (-0.55 ± 2.71 kg/m², $P < 10^{-5}$) and tended to be slightly more educated (0.17 ± 1.82 yr, $P = 0.03$), smoked less (-0.31 ± 2.38 cigarettes per day, $P = 0.002$), and eat less meat (-0.06 ± 0.55 servings per day, $P = 0.008$) and more fish (0.02 ± 0.26 servings per day, $P = 0.04$) and fruit (0.13 ± 0.98 pieces per day, $P = 0.001$) than their less active twin. The active males weighed significantly less (-0.84 ± 2.19 kg/m², $P < 10^{-10}$), smoked less (-0.38 ± 3.23 cigarettes per day, $P = 0.03$), and tended to eat more fruit (0.13 ± 0.98 pieces per day, $P = 0.0002$) than their less active twin. The minor age difference between MZ twins is due to the differences in the dates they completed their survey questionnaires. Consistent with their monozygosity, Table 2 shows that the MZ twins were highly correlated for height. They were also strongly correlated for years of education, pack-years of cigarettes smoked, and intake of meat and fish (particularly males), fruit, and alcohol.

Attenuating the inheritance of body weight

Figure 1 compares the regression slopes for the active versus the sedentary twins' BMI in two distinct groups of twins: those pairs with substantial differences in usual running distances (≥ 4 km/d) and those with minor differences (<0.5 km/d). The regression slopes were significantly greater for those twin pairs whose running distances differed by <0.5 km/d vis-a-vis those whose differences differed by ≥ 4.0 km/d.

Table 3 presents the regression analyses used to test whether the active twin's BMI ($\text{BMI}_{\text{Active Twin}}$, the dependent variable) simply represents the additive effects of exercise (km/d) and inheritance ($\text{BMI}_{\text{Less active Twin}}$) or whether it includes his/her interaction (i.e., a significant $\text{km/d} \times \text{BMI}_{\text{Less active Twin}}$ interaction). The analyses show that $\text{BMI}_{\text{Active Twin}}$

was significantly related to $BMI_{\text{Less active Twin}}$ ($P < 10^{-15}$ for both sexes) and effects of exercise (km/d; $P < 10^{-5}$). The analyses reject the additive model in favor of significant interactions between inheritance and activity in both women ($P < 10^{-7}$) and men ($P = 0.004$). On average, each 1-km/d difference in running distance was associated with a 14.3% reduction in the effect of $BMI_{\text{Less active Twin}}$ on $BMI_{\text{Active Twin}}$ if female (i.e., 100 (0.100/0.697)) and a 7.4% reduction if male. The interactions between $BMI_{\text{Active Twin}}$ (y axis) to $BMI_{\text{Less active Twin}}$ (x axis) for varying levels of exercise disparity (e.g., 0, 1, 2, ..., 7 km/d) are displayed in Figure 2. The lines would be parallel if $BMI_{\text{Active Twin}}$ were simply the additive combination of effects of exercise (km/d; represented by shifts in the y intercept) and inheritance (represented by a constant slope). In fact, the slopes become progressively more horizontal with increasing exercise and are estimated to be horizontal by 7 km/d in women and 13.5 km/d in men. The significance of the interaction was not dependent on the adjustment of the covariates, i.e., nearly identical results were obtained when the covariates were removed from the regression model (i.e., significance levels for the unadjusted interactions were $P < 10^{-7}$ in women and $P = 0.003$ in men, analyses not displayed). Note that whereas Figure 2 illustrates the regression slopes for the fitted model of Table 3, Figure 1 computes each group's regression slopes directly from the data.

The analyses were repeated excluding all twin pairs whose differences in physical activity were < 1 km/wk (60 female and 26 male pairs). The resulting analyses were consistent with the complete sample, i.e., on average, each 1-km/d difference in running distance was associated with a 14.0% reduction in the effect of $BMI_{\text{Less active Twin}}$ on $BMI_{\text{Active Twin}}$ if female and a 6.3% reduction if male. Although one female MZ twin pair, both of whom had $BMI > 40$ kg/m², were found to be overly influential on the estimates of the regression coefficients, their exclusion did not qualitatively affect the results, i.e., their exclusion reduced the attenuating effect of exercise from 14.3% to 11.1%, and the coefficient for the interaction in Table 3 reduced from -0.100 ± 0.018 ($P = 10^{-7}$) to -0.067 ± 0.018 ($P = 0.0003$). These results further suggest that disparity in running distance attenuated the concordance of the twins' BMIs.

Discussion

Twins offer an important advantage in the study of gene-environment interactions in that it is not necessary to identify the specific genotypes or mechanisms involved to test their significance. This is particularly important in studies of BMI because only a limited number of SNPs affecting BMI in the general population have been identified (9,17,24,27), and the statistical power to detect environmental interactions for specific SNPs will be even weaker than for the main effects of SNPs. In contrast, previous MZ twin studies provide solid evidence for gene-environment interactions, namely, concordant changes in twin's body weights in response to increased total energy intake (2), increased energy expenditure (3), and changing dietary fat intake (38).

The current article shows that vigorous physical activity (specifically running) significantly attenuated the inherited risk for excess body weight in a large sample of MZ twins. On average, each 1-km/d increment in running distance was associated with 14.2% and 7.4% reductions in inherited BMI in women and men, respectively. Although this would theoretically include the inheritance of both genetic and family environmental components, other data suggest that BMI inheritance is primarily genetic, with environmental factors tending to be specific to the individual rather than common to the twin pair (12,23,26). Extrapolating the coefficients of Table 3 shows that BMI inheritance might be eliminated completely by running 7.05 km/d (23 mi/wk) in women and 13.51 km/d (60 miles/wk) in men, a projection that is consistent with our previous finding of uncorrelated BMI values in 35 pairs of MZ twins whose running differed by an average of 8 km/d (37), but a projection

that should, nevertheless, be considered with caution. More conservatively, the coefficients suggest 58.8% and 29.6% reductions in BMI inheritance by 4 km/d in women and men, respectively.

Our analyses reveal stronger interactions between physical activity and the inheritance of body weight than have been described in the past, which may be due to our generally large sample size, our focus on running versus composite physical activity measures, and/or use of a quantitative measure of vigorous physical activity (kilometer-per-day run) rather than a simple dichotomization of the data by regular exercise. Samaras et al. (21) reported no significant gene–environment interaction in their comparison of 68 high-activity and 68 low-activity female twin pairs of mixed zygosity. Karnehed et al. (11) also failed to demonstrate that physical activity status affected change in BMI in 180 MZ male twin pairs at high and low genetic risk for obesity. McCaffery et al. (16) reported that relative to those reporting no vigorous exercise, BMI heritability was significantly reduced ($P < 0.001$) in those who ran or jogged >10 miles/wk play strenuous racquet sports >5 h/wk, cycled >50 miles/wk, swam >2 miles/wk, or played other strenuous sports in 2710 MZ and 2327 dizygotic male–male twin pairs from the Vietnam Era Twin Registry. BMI heritabilities were reduced from 0.72 to 0.66 at 38 yr old, from 0.68 to 0.59 at 41 yr old, and from 0.61 to 0.55 at 44 yr old (16). In contrast to our Table 3 and Vietnamera twins (16), Heitmann et al. (8) reported greater MZ twin concordance for 6-yr BMI change in the more active twin in men but not women, i.e., greater genetic regulation of men's BMI in physically active MZ twins. Li et al. showed that physical activity reduced the effects of genetic risk scores on obesity (13). Their genetic risk score, accounting for 0.6%–1.2% of the BMI variance (13), could only account for a small proportion of the diminished BMI concordance for MZ twins reported here.

Others have reported that the FTO rs9939609 genotype is associated with BMI, and its effect on BMI is exercise dependent. Compared with TT homozygotes, AA homozygotes and heterozygotes averaged 1.95 and 0.38 kg/m² heavier, respectively, if passively active; 0.69 and 0.37 kg/m² heavier, respectively, if moderately active; and 0.47 and –0.11 kg/m² heavier, respectively, if very active (1). The FTO genotypes cannot account for the results of Table 3 and the figures because they explain less than three fourths of 1% of the BMI variance (24). Conversely, Table 3 and Figure 1 cannot predict whether exercise will attenuate the effect of any particular SNP on BMI when the proportion of the variance explained by the SNP is minor. However, if inheritance of BMI involves a multitude of individual genetic effects, then our results suggest that many of these individual effects must be attenuated by exercise. Such interactions may be the rule rather than the exception.

The limitations of the current analyses warrant recognition. Table 2 shows twin concordance for diet, education, and other nongenetic factors that may contribute to their concordance in weight. The study may be biased by the volunteer nature of the samples and ascertainment of twin pairs through a physically active proband; however, body size was never considered as part of the recruitment requirements. Twins also tend to have lower BMI than do singletons (4) and may differ in other ways from the nontwin population. We also acknowledge that runners may differ genetically and in other ways from the rest of the population as well; however, we expect that the basic metabolic processes that regulate body weight are common to the population. Self-selection does not account entirely for the leanness of high-mileage runners (36). It needs to be determined whether the same benefits observed for runners applies to other types of vigorous exercise (i.e., exercise requiring more than six-fold the energy expended at rest) and to equivalent energy expenditure by less intense exercise.

We conclude by noting that the role of exercise in attenuating the inheritance of obesity may be underappreciated. Genetics, aging, and high-fat/low-CHO diets are risk factors for

excessive weight gain (18). In addition to attenuating the inherited risk for excess weight gain (Figs. 1 and 2), vigorous exercise has been shown to attenuate middle-age weight gain in proportion to the exercise dose (30,33). This prophylactic benefit may require that exercise be sustained without extended interruption. Prospectively, it seems that the amount of weight gained by men and women who stop running is greater than the amount of weight lost by those who start running, suggesting a potential net weight gain by runners who take an exercise hiatus, even after they resume their former level of activity (34). Exercise may also be a prophylactic for unhealthy food choices, but it is not a guarantee against diet-induced risk. Cross-sectionally, associations between BMI and diets characterized by high meat and low fruit intake were observed to be substantially less in high-mileage than low-mileage runners (31). The exercise dose required for these prophylactic benefits are generally greater than the minimum guideline levels currently recommended for health (7), and correspond more closely to the Institute of Medicine's recommendations for weight maintenance (10).

Acknowledgments

This research was supported by grants from the National Heart, Lung, and Blood Institute (HL072110) and the Institute of Aging (AG032004) and was conducted at the Ernest Orlando Lawrence Berkeley National Laboratory (Department of Energy DE-AC03-76SF00098 to the University of California). The author thanks Ms. Kathryn Hoffman for her help in collecting the data and reviewing the article.

References

1. Andreassen CH, Stender-Petersen KL, Mogensen MS, et al. Low physical activity accentuates the effect of the FTO rs9939609 polymorphism on body fat accumulation. *Diabetes*. 2008; 57:95–101. [PubMed: 17942823]
2. Bouchard C, Tremblay A, Despre's JP, et al. The response to longterm overfeeding in identical twins. *N Engl J Med*. 1990; 322:1477–1482. [PubMed: 2336074]
3. Bouchard C, Tremblay A, Despre's JP, et al. The response to exercise with constant energy intake in identical twins. *Obes Res*. 1994; 2:400–410. [PubMed: 16358397]
4. Estourgie-van Burk GF, Bartels M, van Beijsterveldt TC, Deleamarre-van de Waal HA, Boomsma DI. Body size in five-yearold twins: heritability and comparison to singleton standards. *Twin Res Hum Genet*. 2006; 9:646–655. [PubMed: 17032545]
5. Finkelstein EA, Trogdon JG, Cohen JW, Dietz W. Annual medical spending attributable to obesity: payer- and service-specific estimates. *Health Aff (Millwood)*. 2009; 28:w822–w831. [PubMed: 19635784]
6. Flegal KM, Carroll MD, Ogden CL, Curtin LR. Prevalence and trends in obesity among US adults, 1999–2008. *JAMA*. 2010; 303:235–241. [PubMed: 20071471]
7. Haskell WL, Lee IM, Pate RR, et al. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. *Circulation*. 2007; 116:1081–1093. [PubMed: 17671237]
8. Heitmann BL, Kaprio J, Harris JR, Rissanen A, Korkeila M, Koskenvuo M. Are genetic determinants of weight gain modified by leisure-time physical activity? A prospective study of Finnish twins. *Am J Clin Nutr*. 1997; 66:672–678. [PubMed: 9280191]
9. Hinney A, Hebebrand J. Three at one swoop! *Obes Facts*. 2009; 2:3–8. [PubMed: 20054198]
10. Institute of Medicine. Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). Washington (DC): The National Academies Press; 2005. p. 880-935.
11. Karnehed N, Tynelius P, Heitmann BL, Rasmussen F. Physical activity, diet and gene–environment interactions in relation to body mass index and waist circumference: the Swedish young male twins study. *Public Health Nutr*. 2006; 9:851–858. [PubMed: 17010250]
12. Koeppen-Schomerus G, Wardle J, Plomin R. A genetic analysis of weight and overweight in 4-year-old twin pairs. *Int J Obes Relat Metab Disord*. 2001; 25:838–844. [PubMed: 11439298]

13. Li S, Zhao JH, Luan J, et al. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPICNorfolk prospective population study. *PloS Med.* 2010; 7(8 suppl) pii: e1000332.
14. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. *Behav Genet.* 1997; 27:325–351. [PubMed: 9519560]
15. Malina RM, Little BB. Physical activity: the present in the context of the past. *Am J Hum Biol.* 2008; 20:373–391. [PubMed: 18433002]
16. McCaffery JM, Papandonatos GD, Bond DS, Lyons MJ, Wing RR. Gene environment interaction of vigorous exercise and body mass index among male Vietnam-era twins. *Am J Clin Nutr.* 2009; 89:1011–1018. [PubMed: 19225119]
17. Meyre D, Delplanque J, Chevre JC, et al. Genome-wide association study for early-onset and morbid adult obesity identifies three new risk loci in European populations. *Nat Genet.* 2009; 41:157–159. [PubMed: 19151714]
18. National Institutes of Health. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults—the Evidence Report. National Institutes of Health. *Obes Res.* 1998; 6(suppl 2):51–209S.
19. Neel JV. Diabetes mellitus: a “thrifty” genotype rendered detrimental by “progress”? *Am J Hum Genet.* 1962; 14:353–362. [PubMed: 13937884]
20. Rampersaud E, Mitchell BD, Pollin TI, et al. Physical activity and the association of common FTO gene variants with body mass index and obesity. *Arch Intern Med.* 2008; 168:1791–1797. [PubMed: 18779467]
21. Samaras K, Kelly PJ, Chiano MN, Spector TD, Campbell LV. Genetic and environmental influences on total-body and central abdominal fat: the effect of physical activity in female twins. *Ann Intern Med.* 1999; 130:873–882. [PubMed: 10375335]
22. Scott RA, Bailey ME, Moran CN, et al. FTO genotype and adiposity in children: physical activity levels influence the effect of the risk genotype in adolescent males. *Eur J Hum Genet.* 2010; 18:1339–1343. [PubMed: 20717169]
23. Stunkard AJ, Harris JR, Pedersen NL, et al. The body mass index of twins who have been reared apart. *N Engl J Med.* 1990; 322:1483–1487. [PubMed: 2336075]
24. Thorleifsson G, Walters GB, Gudbjartsson DF, et al. Genomewide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet.* 2009; 41:18–24. [PubMed: 19079260]
25. Vimalaewaran KS, Li S, Zhao JH, et al. Physical activity attenuates the body mass index—increasing influence of genetic variation in the FTO gene. *Am J Clin Nutr.* 2009; 90:425–428. [PubMed: 19553294]
26. Wardle J, Carnell S, Haworth CM, Plomin R. Evidence for a strong genetic influence on childhood adiposity despite the force of the obesogenic environment. *Am J Clin Nutr.* 2008; 87:398–404. [PubMed: 18258631]
27. Willer CJ, Speliotes EK, Loos RJ, et al. Six new loci associated with body mass index highlight a neuronal influence on body weight regulation. *Nat Genet.* 2009; 41:25–34. [PubMed: 19079261]
28. Williams PT. High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. *N Engl J Med.* 1996; 334:1298–1303. [PubMed: 8609947]
29. Williams PT. Relationship of distance run per week to coronary heart disease risk factors in 8283 male runners: the National Runners’ Health Study. *Arch Intern Med.* 1997; 157:191–198. [PubMed: 9009976]
30. Williams PT. Evidence for the incompatibility of age-neutral overweight and age-neutral physical activity standards from runners. *Am J Clin Nutr.* 1997; 65:1391–1396. [PubMed: 9129467]
31. Williams PT. Interactive effects of exercise, alcohol, and vegetarian diet on coronary artery disease risk factors in 9242 runners: the National Runners’ Health Study. *Am J Clin Nutr.* 1997; 66:1197–1206. [PubMed: 9356539]
32. Williams PT. Vigorous exercise and the population distribution of body weight. *Int J Obes Relat Metab Disord.* 2004; 28:120–128. [PubMed: 14569277]
33. Williams PT. Maintaining vigorous activity attenuates 7-yr weight gain in 8340 runners. *Med Sci Sports Exerc.* 2007; 39(5):801–809. [PubMed: 17468577]

34. Williams PT. Asymmetric weight gain and loss from increasing and decreasing exercise. *Med Sci Sports Exerc.* 2008; 40(2):296–302. [PubMed: 18202572]
35. Williams PT. Vigorous exercise, fitness and incident hypertension, high cholesterol, and diabetes. *Med Sci Sports Exerc.* 2008; 40(6):998–1006. [PubMed: 18461008]
36. Williams PT. Self-selection accounts for inverse association between weight and cardiorespiratory fitness. *Obesity (Silver Spring).* 2008; 16:102–106. [PubMed: 18223620]
37. Williams PT, Blanche PJ, Krauss RM. Behavioral versus genetic correlates of lipoproteins and adiposity in identical twins discordant for exercise. *Circulation.* 2005; 112:350–356. [PubMed: 16009789]
38. Williams PT, Blanche PJ, Rawlings R, Krauss RM. Concordant lipoprotein and weight responses to dietary fat change in identical twins with divergent exercise levels. *Am J Clin Nutr.* 2005; 82:181–187. [PubMed: 16002817]
39. Williams PT, Hoffman K, La I. Weight-related increases in hypertension, hypercholesterolemia, and diabetes risk in normal weight male and female runners. *Arterioscler Thromb Vasc Biol.* 2007; 27:1811–1819. [PubMed: 17510467]
40. Williams PT, Hoffman KM. Optimal body weight for the prevention of coronary heart disease in normal-weight physically active men. *Obesity.* 2009; 17:1428–1434. [PubMed: 19553927]

FIGURE 1.

Regression slopes between the active and less active twins' BMI in pairs with minor (<0.5 km/d) and substantial (≥ 4 km/d) differences in usual running distances. There were 70 male and 149 female pairs having minor differences in their usual running distances and 40 male and 48 female pairs with major differences in their usual running distances. The regression slopes are computed for both groups from the data directly, and include adjustment for average age and twin differences in education, smoking, and reported intakes of meat, fish, fruit, and alcohol. Significance levels refer to the difference in slope.

FIGURE 2.

Relationship between the active and less active twins' BMI by the difference between the twins' reported running distances (females, $N = 582$; males, $N = 344$). Plotted lines depict the regression coefficients of Table 3. Dashed lines are outside the 95th percentile of the effects of exercise (km/d) distribution and are presented to demonstrate consistency of the current data with our previous analyses showing no BMI concordance for 35 MZ twin pairs whose running distance differed by an average of 8 km/d (37).

Table 1

Characteristics of MZ twins (means $\pm$ SD) by sex and physical activity.

	Females (N=582)		Males (N=344)	
	Active	Less active	Active	Less active
Age	36.64 $\pm$ 11.74	36.83 $\pm$ 11.93	41.52 $\pm$ 14.11	41.41 $\pm$ 14.09
Education (years)	16.14 $\pm$ 2.18	15.97 $\pm$ 2.11	16.15 $\pm$ 2.27	16.16 $\pm$ 2.26
Smoking (cigarettes/day)	0.12 $\pm$ 0.96	0.43 $\pm$ 2.40	0.11 $\pm$ 1.05	0.50 $\pm$ 3.04
Meat (servings/day)	0.31 $\pm$ 0.31	0.37 $\pm$ 0.54	0.50 $\pm$ 0.42	0.51 $\pm$ 0.41
Fish (servings/day)	0.18 $\pm$ 0.22	0.16 $\pm$ 0.21	0.18 $\pm$ 0.19	0.18 $\pm$ 0.23
Fruit (pieces/day)	1.39 $\pm$ 0.97	1.26 $\pm$ 0.90	1.44 $\pm$ 1.07	1.21 $\pm$ 1.01
Alcohol (ml/day)	6.19 $\pm$ 9.86	6.40 $\pm$ 9.55	9.75 $\pm$ 13.86	10.60 $\pm$ 13.87
Distance run (km/day)	2.67 $\pm$ 1.89	1.06 $\pm$ 1.50	3.01 $\pm$ 2.22	1.14 $\pm$ 1.61
BMI (kg/m ²)	21.82 $\pm$ 2.88	22.38 $\pm$ 3.56	23.75 $\pm$ 2.58	24.59 $\pm$ 3.08

Table 2

Age-adjusted MZ twin correlations.

	Females	Males
Height (m)	0.92	0.92
Education (years)	0.64	0.56
Smoking (pack years)	0.54	0.65
Current smoking (cigarettes/day)	0.22	−0.01
Meat (servings/day)	0.26	0.41
Fish (servings/day)	0.26	0.44
Fruit (pieces/day)	0.46	0.39
Alcohol (ml/day)	0.44	0.55
Distance run (km/day)	0.64	0.61
BMI (kg/m ²)	0.66	0.71

582 female and 344 male MZ twin pairs. Age-adjusted partial correlation coefficients, all significant at $P < 0.0001$ except current smoking in men, which is not significant.

Table 3

Regression analyses for testing for a significant gene-environment interaction. The dependent variable is the active twin's BMI. Covariates are age and within twin pair differences in education, cigarettes smoked, and intakes of meat, fish, fruit and alcohol.

	Females		Males	
	All N=582	km/wk 1 N=522	All N=344	km/wk 1 N=318
Intercept	6.642 ± 0.882 [§]	7.245 ± 0.998 [§]	7.032 ± 1.135 [§]	8.001 ± 1.264 [§]
Age (years)	0.001 ± 0.008	0.000 ± 0.008	0.007 ± 0.007	0.006 ± 0.007
education (years)	0.091 ± 0.047 [*]	0.095 ± 0.051 [*]	0.020 ± 0.048	0.021 ± 0.050
smoking (cig/d)	-0.039 ± 0.037	-0.047 ± 0.038	-0.020 ± 0.030	-0.017 ± 0.030
meat (servings/d)	0.023 ± 0.022	0.017 ± 0.024	0.041 ± 0.031	0.038 ± 0.032
fish (servings/d)	-0.073 ± 0.048	-0.084 ± 0.051	-0.057 ± 0.062	-0.053 ± 0.064
fruit (pieces/d)	-0.036 ± 0.013 [‡]	-0.037 ± 0.014 [‡]	-0.009 ± 0.012 [‡]	-0.008 ± 0.013 [‡]
alcohol (ml/d)	-0.004 ± 0.009	-0.002 ± 0.009	0.004 ± 0.007	0.002 ± 0.008
exercise (km/d run)	1.955 ± 0.399 [§]	1.823 ± 0.435 [§]	0.978 ± 0.434 [*]	0.725 ± 0.461 [*]
BMI _{less-active twin} (kg/m ²)	0.697 ± 0.039 [§]	0.674 ± 0.043 [§]	0.690 ± 0.046 [§]	0.652 ± 0.051 [§]
Interaction exercise * BMI_{less-active twin}	-0.100 ± 0.018[§]	-0.094 ± 0.020[§]	-0.051 ± 0.018[‡]	-0.041 ± 0.019[*]
Significance of interaction	P<10⁻⁷	P=2.2×10⁻⁶	P=0.004	P=0.03
R ²	0.49	0.48	0.56	0.54

Significance levels coded * P 0.05;

[‡]P 0.01;

[‡]P 0.001;

[§]P 0.0001