Are genetic determinants of weight gain modified by leisure-time physical activity? A prospective study of Finnish twins

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ABSTRACT A large number of studies have shown that obesity is both under genetic control and influenced by several environmental factors, including energy expenditure and intake. Several studies in animals and humans have furthermore suggested that certain environmental factors, such as a high fat intake, may modify the expression of the genes responsible for weight gain. The present study examined whether physical activity, measured at the baseline examination in 1975, was likely to play a differential role in subsequent weight changes in the following 6 y in 1571 monozygotic and 3029 dizygotic, same-sex twin pairs from the Finnish Twin Cohort Study. A hierarchical multiple-regression analysis was used to test for gene-environment interactions by identifying significant three-way interactions between genetic factors, physical activity, and weight change. The results showed that associations between weight change in twin A and twin B were significantly stronger for monozygotic than for same-sex dizygotic twins at all levels of physical activity. Additionally, in the monozygotic men the strength of the association varied with physical activity level, and the association between the change in body mass index between the twin pairs with the highest physical activity level was about three times stronger ($\beta = 0.40$) than the association in twin pairs with the lowest physical activity level ($\beta = 0.15, P$ for trend $= 0.002$). In pairs of dizygotic men, and in both monozygotic and dizygotic women, similarity in body mass index change was independent of physical activity level (all $P > 0.14$). The present study showed that genetic factors may modify the effects of physical activity on weight change, and suggests that a sedentary lifestyle may have an obesity-promoting effect in men with a genetic predisposition. Am J Clin Nutr 1997;66:672-8.

KEY WORDS Weight change, physical activity, genetic predisposition, obesity, twins, Finnish Twin Study

INTRODUCTION

It is generally accepted that obesity develops from an imbalance between energy ingested and expended. Although studies using twin-pair designs and families with adopted children have shown that body mass index (BMI) and other measures of fatness are under strong genetic control (1), there is no doubt that environmental factors, such as food intake, smoking status, and physical activity level, also influence the development of obesity (1). Several studies indicate that both food intake and spontaneous physical activity levels are influenced partly by genetic factors, with heritability (ie, the ratio of genetic variance to total phenotypic variance of the trait) up to 40% (1). Furthermore, it has been hypothesized that development of obesity is, in part, due to differential effects of environmental influences for those who are genetically predisposed compared with those who are not (1, 2). In this context, a few studies in animals and humans have shown that food intake seems to play a specific role for obesity development in association with a predisposition to obesity (3-5).

For instance, obesity-prone mice have been found to gain weight at a much faster rate than wild-type mice fed the same high-fat diets (3), suggesting a gene-environment interaction between the high-fat diet and subsequent weight gain. Furthermore, compared with nonobese control subjects, an impaired ability to increase the ratio of fat to carbohydrate oxidation in response to a high-fat diet has been shown in postobese women (4), suggesting that this obesity-prone group is particularly susceptible to weight gain when consuming such a diet. Finally, we found that with a high-fat diet, obese women with a familial history of obesity had a risk of major weight gain almost 10 times that of women without such a predisposition (5). It may be hypothesized that a genetic susceptibility to obesity modifies the responses to the other aspect of energy balance, namely physical inactivity, although, to our knowledge, this has never been examined. The purpose of the present study was, therefore, to investigate whether physical activity modifies the expression of those genes responsible for weight gain. This was done by examining effects of both genetic factors and physical activity for subsequent weight changes over 6 y in adult Finnish twins.

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SUBJECTS AND METHODS

Subjects

The original part of the Finnish Twin Cohort Study was compiled from a national population registry of Finnish citizens in 1974 (6). This cohort consists of all same-sex pairs born before 1958 with both members of a pair alive in 1967. The twins completed a mailed questionnaire on medical and psychosocial factors in the autumn of 1975, providing their baseline characteristics. A follow-up questionnaire in 1981 included identical items on weight, height, physical activity at leisure, and smoking status. The response rate of the whole cohort was 89% in 1975 (7) and 84% in 1981 (8).

The general ethical guidelines for epidemiologic research based on the Helsinki Declaration were followed. Subjects provided informed consent and were given several feedback letters about the study over the past 20 y. The study was initiated with approval from the Ministry of Social Affairs and Health, the Central Population Registry of Finland, and the University of Helsinki. Furthermore, the Ethical Committee of the Department of Public Health approved the study.

Zygosity determination

Zygosity was determined from responses to two questions in the 1975 questionnaire on the similarity of appearance of a twin pair during the school years (8). Ninety-three percent of respondents were classified as a monozygotic or dizygotic twin based on these questions. The accuracy of this procedure was ascertained by determining genetic polymorphisms in a subsample of 104 twin pairs from southern Finland. The agreement between the blood tests and the questionnaire was 100%. The probability of misclassified zygosity based on blood tests in this subsample was determined to be 1.7% (9). Only same-sex dizygotic twins were studied.

The study base

The present study included 4600 twin pairs younger than 40 y in 1975 who were free of major disease (prevalent cancer or cardiovascular disease, or receiving disability pension) and hypertension, and who provided complete data for zygosity classification, for weight from the surveys in 1975 and 1981, and for height at one or both of the surveys. Subjects with major disease were excluded because they were likely to be experiencing weight changes due to their underlying illness rather than in response to environmental influences. We included only adult twins aged < 40 y to minimize the influence of age-related weight changes on the results presented here, and hence to obtain a sample as homogeneous as possible with respect to causes of weight gain. The resulting sample for analysis consisted of 687 monozygotic and 1423 dizygotic male and 884 monozygotic and 1606 dizygotic female pairs aged 18–39 y.

Measures

Weight was reported in kilograms and height in centimeters, which, when necessary, were rounded off to the nearest integers. Self-reported weights have been shown to be accurate across age and sex (10). BMI [weight (in kg) divided by height" (in m)] was used as a measure of relative body weight. Change in BMI was determined as the difference between the two BMI values at baseline and at follow-up, a positive number representing a gain.

Physical activity

Physical activity during leisure time was assessed by three questions. The first question asked whether the average level of the respondents leisure-time physical activity was as tiring as (ie, generally equivalent to) walking, alternating walking and jogging, jogging, or running. The second question asked how long each session of physical activity generally lasted: < 15 min, 15–30 min, 30–60 min, 1–2 h, or ≥ 2 h. The third question asked how many such sessions were engaged in each month: < 1 time/mo, 1–2 times/mo, 3–5 times/mo, 6–10 times/mo, 11–19 times/mo, and ≥ 20 times/mo (11). On the basis of the responses to these three questions, the item on intensity was then used to estimate the leisure aerobic activity index (MET) values. The MET value is derived from the resting rate of oxygen consumption. One MET equals ≈ 3.5 mL · kg−1 · min−1, which is the approximate rate of oxygen consumption of a seated individual at rest (12). Walking was assumed to correspond to 4 METs, rapid walking and the mixture of walking and jogging to 6 METs, light jogging to 10 METs, and running to 13 METs (13). Total MET values were computed from the product of estimated MET value of intensity, the time of one physical activity session, and the number of physical activity sessions per month using the class midpoint (11). In the present study, tertiles of the MET values from all 4600 subjects were used to classify subjects into low, medium, and high physical activity levels.

Smoking

Information about smoking habits was obtained by questionnaire. Subjects were considered to be never-smokers if they reported never smoking more than a total of 5–10 packs of cigarettes in their lifetime and never smoked daily or almost daily. Current smokers were those ever-smokers who smoked at the time of the questionnaire study, and exsmokers were noncurrent ever-smokers (8). Dummy-coded variables were created for the ever-smokers and current smokers.

Statistical methods

Phenotypic resemblance between twins was measured by using intraclass correlations (14), stratified by zygosity and physical activity level. Intraclass correlations (simple and partial) were used to assess twin similarity across zygosity at different levels of physical activity (15). A double-entry file was used. The intraclass correlations were calculated by treating each pair of twins as a class, and represent the proportion of total variance (between plus within-group variance) that is explained by the variance between groups. Between-group influences include all shared sources of variation due to common genes and common environments, and within group influences include all sources of variation including those due to environmental effects not shared by members of a twin pair.

Because monozygotic and dizygotic twins differ in the extent to which genes contribute to twin resemblance, the intraclass correlations are informative regarding genetic and environmental sources of variance. Specifically, members of monozygotic pairs are perfectly correlated for genetic effects, but members of dizygotic pairs share, on average, only half of their segregating genes and are correlated ≈0.5 for effects due to additive genes. Thus, under the assumption of equal environments for monozygotic and dizygotic twins, genes contribute only to
similarity among members of monozygotic pairs, but to similarity and differences among members of dizygotic pairs. Comparison of the pattern of correlations across zygozy groups provides a simple approach for identifying the types of effects contributing to variation and estimating their relative importance. For example, evidence for additive genetic effects is indicated by greater monozygotic than dizygotic correlations, and is calculated as twice the difference between monozygotic and dizygotic values. The influence of shared environment is reflected by the extent to which twice the dizygotic correlation exceeds the monozygotic correlation. Less than perfect monozygotic correlations suggest that a nonshared environment accounts for some of the variation in the phenotype.

A hierarchical multiple-regression approach was used to model the influence of cotwin effects on the trait being studied, while taking into account other covariates of the twin and variables common to both twins, such as zygozy. In particular, the model permits us to test for interactions between genetic factors, physical activity, and weight change. Genetic effects are present when monozygotic twins are more similar (eg, for weight change) than dizygotic twins. Gene-environment interactions are present if the greater similarity among monozygotic twins compared with dizygotic twins is furthermore modified by environmental factors, for instance physical activity level. In the hierarchical multiple-regression model, both BMI, change in BMI, and physical activity level are tested by using all continuous data. The hierarchical multiple-regression models predict weight change in one twin (twin A) from weight change in the other (twin B); the pair's zygozy; the baseline physical activity level for twin A; and two-way cross-product terms of zygozy and twin-B weight change, zygozy and twin-A physical activity, and twin-A weight change and twin-A physical activity; as well as the three-way interaction term among zygozy, physical activity, and twin-B weight change. The analyses yield significance tests for genetic effects, and more importantly, evaluate the modulation of such genetic effects by the weight change of the cotwin and physical activity level (16). Furthermore, all models included main effects of smoking status and BMI.

To examine main and interactive effects separately, a hierarchical procedure was conducted in which model 1 consisted of main effects only. This was expanded in model 2 by adding variables describing the two-way interactions; finally, the three-way interaction was included in model 3. A significant two-way interaction between zygozy and twin-B weight change tests for genetic effects on weight change, but the other two-way interactions were of little substantive interest and were only included for statistical reasons.

Furthermore, our main interest was the significant three-way interaction among zygozy, twin-A physical activity, and twin-B weight change, which is an indicator that physical activity modifies the expression of the genes responsible for weight gain, eg, the three-way term tests for gene-environment interactions (17, 18). Strictly speaking, we tested whether the phenotype of physical activity moderated the effect of the genotype on weight change. However, physical activity generates a change in the environment of the cells and organs to which there is a metabolic response. Although patterns of physical activity aggregate in families, and are, to some extent more similar for monozygotic than for dizygotic twins, the genetic component is relatively weak and most likely to be indirect, through personality and attitude predispositions on the one hand and structural and fitness components on the other. Therefore, we considered the concept of physical activity as an external environmental agent.

Twins within a pair were randomly assigned to be either twin A or twin B. Twin A was the first twin in a pair in the data set, and first and second-born twins were equally represented in groups A and B. Thus.

Twin A weight change =

\[ \text{twin B weight change + zygozy} \]
\[ + \text{twin A physical activity} \]
\[ + \text{twin A smoking} \]
\[ + \text{twin A baseline body mass index} \]
\[ + \text{age} \]
\[ + \text{zygozy \times twin A physical activity} \]
\[ + \text{zygozy \times twin B weight change} \]
\[ + \text{twin A physical activity \times twin B weight change} \]
\[ + \text{zygozy \times twin A physical activity \times twin B weight change} \]

(1)

When significant three-way interactions are found, the gene-environment interactions can be examined more closely by using a model that includes dummy variables coding for the six strata defined by zygozy and physical activity level (model 4). This procedure of stratification was described previously (19) and involves including information about the cotwin by creating dummy-coded variables of BMI change (as a continuous variable) in twin B groups of zygozy by physical activity level (slopes and intercepts). Accordingly, differences in associations between twin A weight change and twin-B weight change for monozygotic and dizygotic pairs can be examined at different physical activity levels. The equation for model 4 is as follows:

Model 4: Twin A weight change =

\[ + \text{twin A physical activity + twin A smoking} \]
\[ + \text{twin A baseline body mass index + age} \]
\[ + \text{twin B weight change for monozygotic twins with a low physical activity level,} \]
\[ + \text{twin B weight change for monozygotic twins with a medium physical activity level,} \]
\[ + \text{twin B weight change for monozygotic twins with a high physical activity level,} \]
\[ + \text{twin B weight change for dizygotic twins with a low physical activity level,} \]
\[ + \text{twin B weight change for dizygotic twins with a medium physical activity level,} \]
\[ + \text{twin B weight change for dizygotic twins with a high physical activity level.} \]

(2)

SAS software (version 6, 1990; SAS Institute Inc, Cary, NC) was used for the analyses.
RESULTS

Characteristics of the participants

A total of 2110 male and 2490 female twin pairs aged 18–39 years with complete data on age and zygosity; on baseline weight, height, leisure-time physical activity, and smoking; and on follow-up weight and height participated in this study. At baseline 42% of the men and 30% of the women smoked, whereas 31% of the men and 59% of the women had never smoked. Mean (± SD) BMIs at baseline and follow-up, respectively, were 23.0 ± 2.7 and 23.9 ± 2.9 for men and 21.0 ± 2.6 and 21.8 ± 2.9 for women. These 6-y changes in BMI were significant for both sexes and were described previously (20). There were no significant differences between cotwins in mean BMIs but after adjustment for age differences, dizygotic twins were found to be slightly heavier than monozygotic twins (all P < 0.05; data not shown). Descriptive values for BMI at baseline and follow-up by sex and physical activity level are listed in Table 1.

Simple correlations revealed negative and insignificant associations between physical activity level and weight gain in men (r = −0.028, P = 0.19) and women (r = −0.034, P = 0.08). However, a significant negative correlation was found in the monozygotic men (r = −0.098, P = 0.009), but the association was only marginally significant in monozygotic women (r = −0.056, P = 0.08) and not significant for either dizygotic men (r = 0.008, P = 0.77) or dizygotic women (r = −0.02, P = 0.36). MET values for physical activity level varied between 0 and 27. Medians and ranges (25–75th percentiles) were 1.25 METs (range: 0.2–2.5 METs) in men and 0.60 METs (range: 0.15–1.5 METs) in women.

Correlation analyses

Intraclass correlations between twin and cotwin change in BMI are given by twin A physical activity level, zygosity, and sex in Table 2.

Among active men (medium and high physical activity levels), the monozygotic correlations were much stronger than the dizygotic correlations whereas no significant differences were seen in correlations between monozygotic and dizygotic inactive men, suggesting that genetic effects on BMI change depend on physical activity level. Among women, the monozygotic correlations were consistently higher than the dizygotic correlations across the full range of physical activity levels, suggesting that genetic effects operate independently of physical activity level in women. Because of the overall relatively weak simple correlations between weight change and physical activity level, intraclass correlations for weight change are not expected to be confounded by a discordant twin B physical activity level. Indeed, irrespective of sex, only ≈12% of the monozygotic pairs and 19% of the dizygotic pairs were discordant (one twin with a high and one with a low physical activity level). Similar results were obtained (ie, smaller differences in correlations between monozygotic and dizygotic inactive men than in men with medium or high physical activity levels, and no trends in women) when twin resemblance for weight change was classified according to twin B physical activity level rather than by twin A physical activity level. The results remained virtually unchanged when partial (adjusted for age and smoking) rather than simple intraclass correlations were considered (data not shown).

Hierarchical multiple-regression approach

A hierarchical multiple-regression approach was used to test for significant three-way interactions among genetic factors, physical activity, and weight change (gene-environment interactions). The model predicts weight change in one twin from weight change in the other.

In the main-effects model, for both men and women, smoking, baseline BMI, and cotwin change in BMI were independent predictors of twin A BMI change (all P < 0.01), but physical activity level was unrelated to weight change (both P > 0.24). In these models R² was 0.08 for the men and 0.05 for the women (Table 3). When the two-way interaction terms were added, R² increased to 0.09 in men but did not change in women. Independent of the main effects and two-way interaction terms, the three-way interaction term among zygosity, physical activity level, and cotwin BMI change was significant in men (P = 0.05, R² = 0.10), indicating that the differences in twin resemblance on BMI change between monozygotic and dizygotic twins were dependent on physical activity level (Table 4). No such three-way interaction was seen in the women (P = 0.87, R² = 0.05).

The significant three-way interaction in the men was evidence for a gene-environment interaction, which was explored further by dummy-coding variables for groups of zygosity by physical activity level (slopes and intercepts) in the hierarchical regression model (model 4) Table 5. This analysis showed that associations between weight change in twin A and twin B were significantly stronger for the monozygotic than for the dizy-

### Table 1

Characteristics of the subjects, by sex and physical activity level

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<th>Physical activity level</th>
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<td></td>
<td>Low</td>
<td>Medium</td>
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<td>Unadjusted</td>
<td>Age adjusted</td>
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<td>Men</td>
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<tr>
<td>Age (y)</td>
<td>26.8 ± 6.0 [683]</td>
<td>27.5 ± 6.1 [623]</td>
<td>26.7 ± 6.0 [804]</td>
<td>0.04</td>
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<tr>
<td>BMI₁₀⁻²⁵ (kg/m²)</td>
<td>23.0 ± 2.8 [683]</td>
<td>23.2 ± 2.7 [623]</td>
<td>22.8 ± 2.6 [804]</td>
<td>0.14</td>
<td>0.08</td>
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<tr>
<td>BMI₁₀⁻¹ (kg/m²)</td>
<td>24.0 ± 3.0 [683]</td>
<td>24.0 ± 2.9 [623]</td>
<td>23.6 ± 2.7 [804]</td>
<td>0.09</td>
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<td>Women</td>
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<td>Age (y)</td>
<td>26.1 ± 6.0 [846]</td>
<td>26.3 ± 5.9 [774]</td>
<td>26.4 ± 6.1 [870]</td>
<td>0.51</td>
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<tr>
<td>BMI₁₀⁻²⁵ (kg/m²)</td>
<td>21.1 ± 2.7 [846]</td>
<td>21.1 ± 2.6 [774]</td>
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<td>0.14</td>
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x ± SD; n in brackets.
Dizygotic twins at all physical activity levels. Furthermore, in monozygotic men the strength of the association varied with physical activity level, and the association between twin and cotwin change in BMI for monozygotic men with a high physical activity level was about three times stronger ($\beta = 0.40$) than the association in men with a low physical activity level ($\beta = 0.15$, $P$ for trend $= 0.002$, $F_{[2109, 21]}$). In pairs of dizygotic men and in both monozygotic and dizygotic women, similarity in BMI change was independent of physical activity level (all $P > 0.09$). These results were similar but slightly weaker when subjects with disease (prevalent cancer or cardiovascular disease, or receiving disability pension), hypertension, or both were included (data not shown). Furthermore, the results remained unchanged after twin pairs who reported they were pregnant at either baseline or the follow-up examination were excluded (data not shown).

**DISCUSSION**

This study showed that both genetic factors and physical activity level played a significant independent role in weight changes. Because monozygotic twins share all their segregating genes but dizygotic twins share only 50% of their genes, the finding that associations between BMI change in twin A and twin B were stronger for monozygotic than for dizygotic pairs was evidence of a genetic contribution to the variability in weight change. However, there was additional evidence of a gene-environment interaction in men, indicating that genetic effects on weight gain may be dependent on physical activity level. Closer analysis of this interaction revealed that the genetic influence on BMI change in men was detected at medium and high physical activity levels only. A basic assumption of the monozygotic-dizygotic comparison is that the two types of twins are otherwise comparable, but differ only in the degree of genetic relatedness. Because we have no data to indicate otherwise, this is a reasonable assumption. Additionally, BMI itself may not be the best measure for obesity, especially in relation to physical activity because different types of change in weight may be compared. However, unless there is a major change in physical activity level, the change is mostly due to fat in an adult population. Furthermore, in the present study height and weight were self-reported. Although underreported weights and overreported heights may occur, it has been found that use of self-reported height and weight is indeed very accurate (10). Furthermore, it was unlikely in the present study that such bias in height and weight would affect the results, showing greater similarity for weight change in monozygotic twins with a high physical activity level than in dizygotic twins with a high physical activity level. We therefore hypothesize that genes modify the association between physical activity and weight changes in such a way that either the "right" genes were necessary to suppress weight gain at high physical activity levels, or the "right" genes suppress weight gain only among physically active men. In men who were sedentary, weight-modifying genes did not seem to be expressed, eg, the observed weight changes must have depended primarily on environmental factors other than physical activity (eg, diet).
In women, similarity in BMI change between twins was largely independent of physical activity level, suggesting the same genetic effect on weight change in sedentary and active women. In a sample of Swedish women we showed previously that a high-fat diet promoted weight gain only in the women with a familial predisposition to obesity. Hence, the results from the present study suggest that susceptibility to weight gain depends on different gene-environment interactions in men and women, eg, physical activity and diet, respectively. However, interactions with diet could not be tested in the present sample of Finnish twins, in whom no information on nutrient intakes were available. In addition, various environmental factors may interact with each other independent of genes. In this context we showed in adult women that weight gain, as a function of fat intake, may occur primarily in connection with sedentary activity level (21).

Although the underlying mechanisms are unknown, the results of the present study suggest that there are sex differences in response to physical activity for the expression of genes that affect weight change. Indeed, sex-specific genetic effects for BMI were reported in a study of twins younger than those in the present study (20, 22). The results suggested that some of the variation in BMI was explained by different sets of genes in males and females.

Finally, it is likely that the physical activity index, used in the present study, measures different characteristics in men and women and that it may account for some of the differential findings between men and women. In support of this, associations between weight changes and the measures of duration, intensity, or type of leisure physical activity were found to be much weaker for women than for men. The overall lower physical activity level and the lower variation in physical activity among the women may partly explain why the three-way interactions were not significant in women. Additionally, responses to the same questions about physical activity may vary between men and women depending on sex differences in the perception of intensity, duration, and frequency of engagement in sessions related to physical activities. Alternatively, physical activity itself may play a different role in weight changes in men and women because of sex differences in body composition. Finally, the differences observed between the two sexes may be that other factors, for instance childbearing, override physical activity as a major explanatory factor for weight changes in women in the age range that we studied. The present study suggests that sex as well as genes may modify the effects of physical activity for subsequent change in weight.

REFERENCES