Regular exercisers, defined as individuals who voluntarily seek out moderate to vigorous physical activity on a weekly or even daily basis, have a different psychological profile than non-exercisers. Regular exercisers score lower on neuroticism and higher on extraversion, conscientiousness, and sensation-seeking (De Moor et al., 2006; Hoyt et al., 2009; Rhodes & Smith, 2006). These stable differences in psychological traits are reflected in assessments of ongoing mood and one of the most compelling descriptions of the psychological profile of regular exercisers is that of the “iceberg profile” in Morgan’s mental health state model (Morgan & Johnson, 1977). Regular exercisers have higher vigor (the peak of the iceberg) but lower levels of anxiety, tension, apprehension, depression, and fatigue compared to the average of these mood states in non-exercisers.

Originally, the interest of sports psychologists in the psychological profile of exercisers was driven by the idea that personality and mood could help predict athletic performance in elite athletes. This did not turn out to be a very useful addition to the coach’s toolbox. A large meta-analysis, for instance, showed that Profile of Mood States scores accounted for less than 1% of athletic success (Rowley et al., 1995). However, Morgan’s research facilitated the growing interest in the relation between exercise and psychology in a different field, that of preventive medicine. The core idea there is that exercise (not necessarily at the elite level) increases psychological well-being and can attenuate or even prevent the development of anxiety and depressive disorders in the population at large. This converges with folk wisdom that exercise “makes you feel better” and can help combat stress. In the last two decades, this has become a dominant angle in sports psychology.

Exercise and Psychological Well-Being

When compared to sedentary individuals, regular exercisers have been found to have higher self-esteem (Sonstroem & Morgan, 1989), life satisfaction and happiness (Stubbe et al., 2006b), better perceived health, and quality of life (De Moor et al., 2007b; Klavestrand & Vingard, 2009). Most importantly, regular exercisers have lower levels of anxious and depressive symptoms in both adolescents and adults (Brown et al., 2005; Camacho et al., 1991; Cooper-Patrick et al., 1997; De Moor et al., 2006; Farmer et al., 1988; Kritz-Silverstein et al., 2001; McKercher et al., 2009; Rhodes & Smith, 2006; Stephens, 1988; Strawbridge et al., 2002; van Gool et al., 2003; Weiss et al., 2008; Weyerer, 1992; Wise et al., 2006). However, co-existence of a healthy mind and a healthy body does not prove that the healthy mind is a consequence of the healthy body (such causality was never suggested by Juvenal, the Roman satirist who originated the adage of “mens sana in corpore sano”—he just prayed for both). The association could as easily
reflect a reversed causality, where emotionally well-adjusted, agreeable, and self-confident individuals with low levels of stress are simply more attracted to sports and exercise, or that only such persons have the necessary energy and self-discipline to maintain an exercise regime. In short, the favorable psychological profile of exercisers may reflect self-selection.

To resolve causality, various studies have addressed the association in longitudinal designs (Brown et al., 2005; Camacho et al., 1991; Cooper-Patrick et al., 1997; Farmer et al., 1988; Kritz-Silverstein et al., 2001; Strawbridge et al., 2002; van Gool et al., 2003; Weyerer, 1992; Wise et al., 2006). Most of these longitudinal studies reported that regular exercise at baseline was associated with less depression and anxiety at follow-up. Some studies, however, did not find evidence for a longitudinal association (Cooper-Patrick et al., 1997; Kritz-Silverstein et al., 2001; Weyerer, 1992), and one study found a longitudinal association in White women but not in men and Black women (Farmer et al., 1988). More importantly, observational longitudinal studies cannot truly resolve causality. Higher psychological well-being in exercisers may reflect the operation of common underlying influences on both exercise behavior and psychological well-being.

These “third factors” may consist of environmental influences like low socio-economic status and poor social support networks that affect both exercise behavior and psychological well-being. Alternatively the association between regular exercise behavior and the psychological profile may be partly due to underlying genetic factors that have a favorable effect on both traits. This means that the genetic variation that leads to, for example, increased levels of depression may also influence voluntary exercise behavior. This phenomenon, where low-level biological variation has effects on multiple complex traits at the organ and behavioral level, is called genetic pleiotropy. If present in a time-lagged form, that is, when genetic effects on exercise behavior precede effects of the same genes on psychological health at a later time point, this phenomenon can cause longitudinal correlations that mimic the causal effects of exercise. To test for the presence of underlying genetic “third factors,” genetically informative designs are needed, for instance, a study in twins.

Twin studies can directly decompose familial resemblance into genetic and shared environmental influences by comparing the resemblance in exercise behavior between monozygotic (MZ) and dizygotic (DZ) twins. When twins are reared together, they share part of their environment, and this sharing of the family environment is postulated to be the same for MZ and DZ twins. The important difference between MZ and DZ twins is that the former share (close to) all of their genotypes, whereas the latter share on average only half of the genotypes segregating in that family. If the resemblance in exercise behavior within MZ pairs is larger than in DZ pairs, this suggests that genetic factors influence exercise behavior. If the resemblance in exercise behavior is as large in DZ twins as it is in MZ twins, this points to shared environmental factors as the cause of family resemblance (Boomsma et al., 2002). As opposed to parent–offspring family designs, a twin study estimates heritability within members of the same generation, which avoids dilution of within-family resemblance by cohort effects.

In a twin study, four possible components and their interactions and correlations are thought to contribute to the total variance in a trait: unique environmental factors (“E”), shared environmental factors (“C”), additive genetic factors (“A”), and dominant genetic factors (“D”). Shared environmental factors (“C”), and additive (“A”) and dominant (“D”) genetic factors can cause twin resemblance, whereas the extent to which twins do not resemble each other is ascribed to the unique (or non-shared) environmental factors. These include all unique experiences like differential jobs or lifestyle, accidents or other life events, and in childhood, differential treatment by the parents, and non-shared peers. Using twins, we can only estimate three components of variance at the same time (A, C, and E, or A, D, and E). One solution is to add parents or offspring of twins to the
design (Keller et al., 2009). If data on parents are not available, one needs to make the assumption that either C or D is absent. The presence of dominance can be inferred from the pattern of twin correlations because it yields DZ correlations that are much lower than half the MZ correlation. In contrast, the presence of shared environmental effects yields DZ correlations that are much higher than half the MZ correlations.

Twin researchers typically use structural equation modeling to estimate the relative contribution of A, D/C, and E to the individual differences in the trait. In structural equation modeling, the relationships between several latent unobserved variables (e.g., genetic and environmental factors) and observed variables are summarized by a series of equations. Additional equations can specify the correlation between the latent genetic and environmental factors if these are known. It is possible to derive the variance–covariance matrix implied by the total set of equations (the model) through the use of covariance algebra. When the complexity and number of the equations increase, the structural equation model can be formulated more easily by application of path-tracing rules on the complete representation of all relationships between observed and unobserved variables in a so-called path diagram. An example is depicted in Figure 25.1 where exercise behavior has been measured in DZ and MZ twin pairs. In this example inspection of the twin correlations had suggested that dominance does not play a role and that all the genetic variance in exercise behavior is additive genetic variance. Hence only the latent factors A, C, and E are used in the diagram, and the latent D factor was omitted.

Using maximum likelihood estimation, we can iteratively test the fit of the expected covariances/variances to the actual observed covariances/variances in a sample of hundreds or thousands of twins over a range of possible values for the path coefficients. From the best fitting model, we take the estimates for the path coefficients (e.g., a, c, and e) and determine the relative contribution of the latent factors to the total variance in leisure-time exercise behavior. Heritability of this behavior, defined as the relative proportion of the total variance explained by genetic factors, is obtained as the ratio of \(a^2/(a^2+e^2+c^2)\). The heritability can also be expressed as a percentage by multiplying this ratio by a hundred.

**Heritability of Exercise Behavior**

Using the twin design, it has been established that genetic factors importantly contribute to individual differences in exercise participation and measures of exercise frequency, duration and/or intensity. An overview of these twin studies is given in Table 25.1. We focused on voluntary leisure-time exercise behavior and it is important to note that different heritability estimates may be obtained for total physical activity that includes strenuous activities at the workplace or commuting by bicycle. Indeed, the factors underlying total physical activity need not overlap with the factors that underlie leisure-time
## Table 25.1 Twin studies on exercise behavior

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Phenotype(s)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carlsson et al. (2006)</td>
<td>5334 MZ and 8028 DZ pairs (aged 14–46 years)</td>
<td>Leisure-time PA</td>
<td>( h^2 = 64% ); ( c^2 = 7% ) for males 14–28 years ( h^2 = 51% ); ( c^2 = 15% ) for females 14–28 years ( h^2 = 40% ); ( c^2 = 0% ) for males 29–46 years ( h^2 = 41% ); ( c^2 = 0% ) for females 29–46 years</td>
</tr>
<tr>
<td>Eriksson et al. (2006)</td>
<td>1022 Swedish male twin pairs (aged 19–29 years)</td>
<td>Total PA, leisure-time PA incl. and excl. sport, sport during leisure-time, occupational PA</td>
<td>( h^2 = 40%–65% ); ( c^2 = 0% )</td>
</tr>
<tr>
<td>Stubbe et al. (2006a)</td>
<td>13,676 MZ and 23,375 DZ pairs from seven different countries in Europe and Australia (aged 19–40 years)</td>
<td>Leisure-time exercise participation</td>
<td>( h^2 = 27%–67% ); ( c^2 = 0%–37% ) for males ( h^2 = 48%–71% ); ( c^2 = 0% ) for females</td>
</tr>
<tr>
<td>Stubbe et al. (2005a)</td>
<td>2628 Dutch twin pairs (aged 13–14, 15–16, 17–18, 19–20 years)</td>
<td>Leisure-time exercise participation</td>
<td>( h^2 = 0% ); ( c^2 = 84% ) for 13- to 14-year-old twins ( h^2 = 0% ); ( c^2 = 78% ) for 15- to 16-year-old twins ( h^2 = 36% ); ( c^2 = 47% ) for 17- to 18-year-old twins ( h^2 = 85% ); ( c^2 = 0% ) for 19- to 20-year-old twins</td>
</tr>
<tr>
<td>Beunen &amp; Thomis (1999)</td>
<td>92 male and 91 female Belgium twin pairs (aged 15 years)</td>
<td>Number of hours spent on sports each week</td>
<td>( h^2 = 83% ); ( c^2 = 0% ) for males ( h^2 = 44% ); ( c^2 = 54% ) for females</td>
</tr>
<tr>
<td>de Geus et al. (2003)</td>
<td>157 adolescent (aged 13–22 years) and 208 middle-aged Dutch twin pairs (aged 35–62 years)</td>
<td>Weekly METs for vigorous leisure-time exercise</td>
<td>( h^2 = 79% ); ( c^2 = 0% ) for adolescent twins ( h^2 = 41% ); ( c^2 = 0% ) for middle-aged twins</td>
</tr>
<tr>
<td>Frederiksen &amp; Christensen (2003)</td>
<td>616 MZ and 642 same-sex DZ twin pairs (aged 45–68 years)</td>
<td>Leisure-time exercise participation in any of 11 activities</td>
<td>( h^2 = 49% ); ( c^2 = 0% ) for males and females</td>
</tr>
<tr>
<td>Kujala et al. (2002)</td>
<td>Data on both members of 1772 MZ and 3551 DZ same-sex twin pairs (aged 24–60 years)</td>
<td>Participation in vigorous PA</td>
<td>( h^2 = 56% ); ( c^2 = 4% ) for vigorous activity</td>
</tr>
<tr>
<td>Maia et al. (2002)</td>
<td>411 Portuguese twin pairs (aged 12–25 years)</td>
<td>Sports participation</td>
<td>( h^2 = 68% ); ( c^2 = 20% ) for males ( h^2 = 40% ); ( c^2 = 26% ) for females</td>
</tr>
<tr>
<td>Aarnio et al. (1997)</td>
<td>3254 twins at age 16, their parents and grandparents</td>
<td>Engagement in five types of PA</td>
<td>( h^2 = 54% ); ( c^2 = 18% ) for males ( h^2 = 46% ); ( c^2 = 18% ) for females</td>
</tr>
<tr>
<td>Lauderdale et al. (1997)</td>
<td>3344 male twin pairs of the Vietnam Era Twin Registry (aged 33–51 years)</td>
<td>Regular participation in five types of sports</td>
<td>( h^2 = 53% ) for jogging ( h^2 = 48% ); ( c^2 = 4% ) for racquet sports ( h^2 = 30% ); ( c^2 = 17% ) for strenuous sports ( h^2 = 58% ) for bicycling ( h^2 = 8% ); ( c^2 = 31% ) for swimming</td>
</tr>
</tbody>
</table>

*MZ, monozygotic; DZ, dizygotic; PA, physical activity; \( h^2 \), heritability; \( c^2 \), shared environmental factors.*
activity, or they may even be negatively correlated as high-energy expenditure demands at work or during commuting may countermand voluntary exercise behavior.

A striking finding in these studies is that the genetic architecture of leisure-time exercise behavior is vastly different across the life span. Studies conducted in adult twins aged between 19 and 68 years (Beunen & Thomis, 1999; Carlsson et al., 2006; Eriksson et al., 2006; Frederiksen & Christensen, 2003; Kujala et al., 2002; Lauderdale et al., 1997; Stubbe et al., 2006a) show that variation in exercise behavior is accounted for by genetic and non-shared environmental factors, with heritability estimates ranging between 35% and 83% of the variance in exercise. Twin studies in adolescence (Aarnio et al., 1997; Carlsson et al., 2006; Maia et al., 2002; Stubbe et al., 2005a) show that variation in adolescent leisure-time exercise behavior is explained by a combination of genetic, shared environmental, and unique environmental factors. In a study of adolescent twins aged 13–20 years (Stubbe et al., 2005a), it was observed that exercise behavior in young adolescents (up to 16 years) is largely determined by shared environmental factors. The influence of these factors rapidly wanes when adolescents become young adults and genetic factors start to appear. After age 18, heritability estimates for exercise behavior are as high as 80% (de Geus et al., 2003; Stubbe et al., 2005a).

**Bivariate Heritability of Exercise Behavior and Psychological Well-Being**

We now deal with the question of whether the genetic factors underlying exercise behavior also play a role in well-being. First it is important to note that a number of (twin) family studies have demonstrated that general well-being and aspects of it, such as life satisfaction and happiness, are influenced by genetic factors just like anxiety and depression (Hettema et al., 2001; Lykken & Tellegen, 1996; Nes et al., 2006; Stubbe et al., 2005b; Sullivan et al., 2000). Similarly, significant genetic influences have been reported for self-rated health and quality of life (De Moor et al., 2007b; Svedberg et al., 2005). To test for an overlap in the genetic factors for exercise behavior and well-being we used a bivariate extension of the structural equation model for twin data (Neale & Cardon, 1992). This allows a whole new set of hypotheses to be tested because the observed information now includes all possible cross-twin cross-trait correlations, for instance the correlation of exercise behavior in a twin with the psychological well-being of his or her co-twin.

Using this addition to the covariance matrix we can test the extent to which the heritability of these traits is caused by common genetic factors that influence all of the traits, as well as the extent to which heritability is caused by genetic factors that are specific to each trait. As shown in Figure 25.2, there are now two genetic factors: common genetic factor A1 influences regular exercise as well as psychological well-being, whereas specific genetic factor A2 influences well-being only. When multivariate models are depicted in a path diagram, the number of arrows (and path loadings) can become overwhelming so

![Figure 25.2: A bivariate ACE model for exercise behavior and psychological well-being.](image-url)
Figure 25.2 differs from Figure 25.1 in that the part of only one twin is depicted (the other twin and non-twin sibling is still used in the analyses with their latent factors correlated as before; they are just no longer drawn).

Path coefficient $a_{11}$ quantifies the effect of genetic factor $A_1$ on regular exercise; $a_{21}$ quantifies the pleiotropic genetic effect of $A_1$ on well-being. Coefficient $a_{22}$ quantifies the effect of specific genetic factor $A_2$ on well-being. If $a_{21}$ is zero and $a_{22}$ is significantly different from zero, the association between exercise and well-being does not derive from the same genetic factor and there is no evidence of pleiotropy. In a similar way, path coefficients $e_{11}$, $c_{11}$, $e_{21}$, $c_{21}$, $e_{22}$, and $c_{22}$ quantify the effects of common and specific factors $E$ and $C$ on exercise and well-being. If $c_{21}$ is non-significant but $c_{22}$ significantly differs from zero, the association between exercise and well-being does not derive from the same common environmental factor.

Alternatively, the bivariate twin model in Figure 25.2 can be used to decompose a phenotypic correlation between two traits into its three possible sources: overlapping genetic, overlapping shared environmental, or overlapping unique environmental factors. The word overlapping can be defined more precisely as the correlation between the latent genetic ($R_g$), shared environmental ($R_c$), or unique environmental ($R_e$) factors influencing regular exercise ($A_1$, $C_1$, $E_1$) and psychological well-being ($A_2$, $C_2$, $E_2$). More generally, $R_g$ between two traits is derived as the genetic covariance divided by the square root of the product of the environmental variances of the two traits ($R_g = (c_{11} * c_{21}) / \sqrt{(c_{11}^2 + c_{21}^2)}$).

Computation of genetic and environmental correlations in longitudinal data across 2-, 4-, 7-, 9-, and 11-year follow-up periods from 8558 twins and their family members was used to test a crucial prediction from the causal hypothesis (De Moor et al., 2008). If exercise causally influences symptoms of anxiety and depression, all genetic and environmental factors that influence variance in exercise behavior will, through the causal chain, also influence the variance in these symptoms. Translating this to the structural equation models used on twin family data, this means that, if $A$, $C$, and $E$ contribute to both traits, the genetic ($R_g$) and environmental ($R_e$, $R_c$) correlations between exercise and symptoms must both be significantly different from zero. Furthermore, this should apply to the cross-sectional cross-trait correlations as well as the longitudinal cross-trait correlations (De Moor et al., 2008). In spite of sufficient power, we found only the genetic correlation to be significant (ranging between $-0.16$ and $-0.44$ for different symptom scales and different time-lags). Environmental correlations, however, were essentially zero. This means that the environmental factors that cause a person to take up exercise do not cause lower anxiety or depressive symptoms in that person, currently or at any future time point. In contrast, the genetic factors that cause a person to take up exercise also cause lower anxiety or depressive symptoms in that person at the present and all future time points.

We have also addressed the association between exercise and well-being in a sample of 5140 Dutch adult twins and their non-twin siblings from 2831 families using self-rated health as an index of well-being (De Moor et al., 2007b). Bivariate genetic models tested the contribution of genetic and environmental factors to the observed correlation between exercise participation and self-rated health. We showed that the genetic factors influencing exercise participation and self-rated health partially overlap ($R_g = 0.36$) and, importantly, this overlap fully explains their association. Again this argues in favor of genetic pleiotropy.
and suggests that the well-being of genetically identical individuals shows a high resemblance, even if one is a fervent exerciser and the other is a couch potato.

**Training Studies**

Based on the work described above, we conclude that, in the population at large, exercise participation is associated with higher levels of perceived health, life satisfaction, and happiness, as well as lower levels of anxiety and depression, largely through genetic factors that influence both exercise behavior and psychological well-being. At first sight, these pleiotropic effects would suggest that recruitment of “genetic non-exercisers” in exercise activities would do little to change well-being because exercising would not change their genotype. However, it is important to recognize that we assessed leisure-time exercise behavior that is completely initiated and maintained by individuals on a voluntary basis. Although the association between such voluntary self-chosen exercise behavior and well-being does not reflect a causal effect, it still does not rule out the possibility that successful recruitment of sedentary individuals, for instance as part of a (cardiac) rehabilitation or psychiatric therapy program, might have an effect on well-being.

To test the potential of exercise to change the well-being of individuals who do not voluntarily engage in exercise, an experimental manipulation of exercise behavior in these individuals is needed. Several well-designed training studies have reported improved mood and coping behavior or reduction in depression and anxiety after a program of aerobic exercise training in comparison to control manipulations (Barbour & Blumenthal, 2002; Brosse et al., 2002; Steptoe et al., 1989). Unfortunately, many others have failed to replicate these training effects (de Geus et al., 1993; King et al., 1989). Without denying the potential of exercise to change well-being in subsets of individuals, critical reviews on this topic express only cautious optimism about the use of exercise for the enhancement of well-being in the population at large (Dunn et al., 2005; Lawlor & Hopker, 2001).

The most promising evidence comes from studies in individuals who had low initial levels of well-being at the start of the exercise program, like depression patients. Various randomized controlled trials showed that regular exercise can be used as a treatment to relieve symptoms in these patients (Babyak et al., 2000; Blumenthal et al., 2007). These studies reported beneficial psychological effects of exercise that match or even exceed those of pharmacological treatment. Although these results are promising it should be kept in mind that these studies examined the effects of prescribed and externally monitored exercise treatments in select subgroups. Whether these individuals are able to maintain exercise behavior in the long run is a serious concern, since up to 50% of individuals recruited in exercise programs may drop out within the first few months (Dishman & Ickes, 1981). Moreover, due to the strong societal beliefs about the efficacy of this intervention, severe methodological problems cling to even the most well-designed randomized controlled trial (Ekkekakis, 2008).

At present, to assume that regular exercise may prevent depression in a non-clinical population sample, because it has been successfully used as a therapy in subsets of clinically depressed patients, is still a leap of faith. What is needed is a better understanding of why non-exercisers chose not to exercise in spite of the well-advertised benefits in many domains. Below we argue that increased knowledge of the genetic factors determining the acute psychological response to exercise may be a powerful way forward.

**Genes for Exercise Behavior**

What types of genes are relevant to exercise behavior? As with any other behavior, for exercise behavior to be repeated time and again, the net rewarding effects of exercise would need to outweigh the net aversive effects. Although emphasis traditionally is put on “feeling good” after exercise, the reality of sedentariness dictates that many individuals may be “feeling bad” after exercise. Figure 25.3 proposes that individuals for whom the aversive effects are stronger than the rewarding effects will become non-exercisers. In contrast,
individuals for whom the rewarding effects are dominant will repeat the behavior and become regular lifetime exercisers. The figure proposes that, to become an exerciser, the rewarding effects must outweigh the aversive effects to a substantial degree. It also proposes that this may be the case for a modest percentage of the population, in keeping with the low percentage of individuals (17% of the Dutch population) that regularly engage in vigorous exercise (De Moor et al., 2007b).

Whether the rewarding or punishing effects of a behavior affect the future frequency of the behavior strongly depends on the contingency in time of behavior and reinforcement. Hence, the psychological effects during and shortly after exercising, often termed the acute effects of exercise will be especially important. Among the hypothesized factors that determine the acute psychological effects of exercise, a homeostatic “need for activity” should probably be first on the list. The motivation to exercise may be a real drive in the classical Hullian sense, not different from sex drive, hunger, or thirst (Rowland, 1998). Hypothalamic and brain stem control systems are likely biased to food intake over energy expenditure, but large individual differences in this homeostatic system may exist with some individual intrinsically driven to more exercise than others. Fulfillment of this homeostatic drive may be directly coupled to dopaminergic midbrain reward systems, not unlike eating and drinking.

Additional activation of the rewarding system may come from two well-known social psychological mechanisms. The first may be specific to individuals with above-average exercise abilities. People generally like doing what they are good at, and will pursue those activities in leisure time as much as possible. Taken the strong positive cultural attitudes toward exercise ability, individuals who notice that they gain more in performance than others (that nonetheless follow the same exercise regime) will experience strong feelings of competence and mastery. A second mechanism may be limited to individuals who have strong self-regulatory skills, including self-discipline. These individuals may experience reward by the sheer accomplishment of an exercise challenge, even when exercising has strong aversive effects.

Among the aversive effects of exercise, the first one to list is that the person may need to abort other ongoing activities. Put otherwise, exercise has to compete with other, potentially more pleasurable, activities available to the individual. But the aversive effects of exercise may also be direct through feelings of pain, fatigue, or even exertion. According to Ekkekakis and colleagues (Ekkekakis et al., 2005, 2008), intensity is an important determinant of the aversive responses to exercise. At intensities that exceed the individuals’ ventilatory threshold, strong interoceptive cues, inherently charged with negative affect, may present a major obstacle to perceiving pleasure. Tolerance for aversive interoceptive cues may depend on the same serotonergic punishment systems in the brain that are also involved in the pathogenesis of depression and anxiety. Many novice exercisers may lack the skills to adequately regulate the intensity of exercise at the optimal level and fail to use their felt discomfort as a meaningful guideline, because they may have been brainwashed to push harder by their coaches, parents, or peers (“no pain, no gain”).

In the less able exercisers, the aversive effects may also stem from the reverse variant of the psychosocial mechanisms that make exercise rewarding for those who have above-average exercise abilities.
Put otherwise, people generally don’t like doing things they are not good at. Individuals who achieve low levels of performance, even after substantial training, may feel disappointment and even shame, particularly when the exercise is performed in a competitive context. In this regard, it is perhaps not striking that the highest heritabilities of exercise behavior are achieved during adolescence (Stubbe & de Geus, 2009), when the sensitivity to one’s own relative ranking among peers may be the largest.

We have previously hypothesized that the acute aversive and rewarding effects of exercise show strong individual differences and that these differences may be strongly genetically determined (de Geus & De Moor, 2008). That is, there are gene-by-exercise interaction effects for the acute psychological effects of exercise. Furthermore, in keeping with the finding that regular exercisers report greater acute exercise-induced mood enhancement than non-exercisers (Hoffman & Hoffman, 2008), we predicted that genes determining individual differences in the acute psychological effects of exercise to a large extent explain the heritability of voluntary exercise behavior as tabulated in Table 25.1. More specifically we may predict that the heritability of exercise behavior reflects genes influencing individual differences in the immediate rewarding and aversive effects, which may directly depend on genetic variation in the homeostatic exercise drive, exercise-induced engagement of the opioid and dopamine reward systems, exercise-induced engagement of punishment systems or, indirectly, on exercise ability.

These predictions can be most optimally tested in a training study in twins by showing significant genetic correlation between the exercise participation and individual differences in the acute psychological response to exercise, for instance as assessed by a change in mood. To our knowledge, no such studies have been performed to date. Below, we follow an alternative strategy by examining the genes currently implicated in variation in exercise behavior and see whether they fit our theoretical model. In total, nine genes have been found to be associated with exercise behavior, or more broadly defined physical activity phenotypes, in six candidate gene association studies (Loos et al., 2005; Lorentzon et al., 2001; Salmen et al., 2003; Simonen et al., 2003a; Stefan et al., 2002; Winnicki et al., 2004), three genome-wide linkage studies (Cai et al., 2006; De Moor et al., 2007a; Simonen et al., 2003b), and one genome-wide association study (GWAS) (De Moor et al., 2009).

Two genes were identified that are highly expressed in the hypothalamic area and may fit our idea of genetic variation in the “need for activity.” The leptin receptor (LEPR) gene was associated with total physical activity in Pima Indians (Stefan et al., 2002) and was also associated with leisure-time exercise participation in a sample of American Caucasians (De Moor et al., 2002) and in both studies independent of BMI. The melanocortin-4 receptor (MC4R) gene was associated with daily physical activity levels in a combined sample of adult men and women (Loos et al., 2005), and the same region on chromosome 18 was also identified in a linkage study on daily physical activity in children (Cai et al., 2006).

Two of the exercise genes identified could influence the reward or aversive experience of exercise directly. In a candidate gene study, the dopamine 2 receptor (DRD2) gene was found to be associated with physical activity, sports participation, and occupational physical activity in adult females (Simonen et al., 2003a). In the GWAS, the GABRG3 gene was associated with exercise participation in a combined sample of 2622 Dutch and American individuals (De Moor et al., 2009) and one of the linkage studies had also pointed to the 15q12-13 region that harbors the GABRG3 gene (Simonen et al., 2003b). The GABRG3 gene may be involved in the aversive effects of exercise-induced fatigue as shown in an elegant study on physical exercise-associated gene expression that found higher expression levels of the GABRG3 gene after a bout of exhaustive exercise but not after aerobic exercise at 60% V̇O₂max (Kawai et al., 2007).

Three of the exercise genes identified may specifically act to increase or decrease exercise ability. In a study of adolescent females, the calcium-sensing receptor (CASR) gene was associated with hours spent on physical activities per week (Lorentzon et al., 2001). The GWAS further strongly pointed to the PAPSS2 gene on chromosome 10q23 (De Moor et al., 2009). This gene is
widely expressed in skeletal and smooth muscles and the brain and has previously been linked to maximal exercise capacity in a genome-wide linkage study of 453 sib pairs (Rico-Sanz et al., 2004). Finally, in a study of mild male and female hypertensives, the angiotensin-converting enzyme (*ACE*) gene accounted for 21% of the variation in leisure-time physical activity (Winnicki et al., 2004). The regular exercisers had the same genotype (I/I) that has been associated with high exercise ability and, in particular, an increased responsiveness to training (Williams et al., 2000; Woods et al., 2000).

**Conclusion**

In the population at large, regular leisure-time exercise is associated with better mental health largely through genetic pleiotropic effects. Genetic factors that increase the chances that an individual engages in voluntary exercise behavior also influence the risk for anxiety and depression. These genetic factors may in part reflect a differential sensitivity to the acute psychological effects of exercise. For exercisers, exercising may be associated with a strong “feel good” experience and constitute an excellent short-term coping strategy that helps to unwind more rapidly from daily pressures experienced in the school, job, or home environment, up to a point where stopping exercise could lead to loss of well-being and self-esteem. In fact, most of the popular ideas on the psychological benefits of exercise may stem from exercisers themselves. For persistent sedentary individuals the aversive effects of exercise, at least in the forms that they tried so far, may greatly overwhelm the rewarding effects, causing them to drop out. Increased understanding of the genetic factors influencing the psychological response to exercise may help create better exercise programs to re-engage these individuals in some form of regular exercise.

**References**


Exercise treatment for depression—


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