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A genetic perspective on the association between exercise and mental health

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ABSTRACT

Regular exercise is associated with better mental health. This association is widely assumed to reflect causal effects of exercise. In this paper we propose that two additional mechanisms contribute to the association between exercise and mental health in the population-at-large: genetic pleiotropy and gene-by-exercise interaction. Both mechanisms assume heritability of exercise behavior and a partial overlap between the genes influencing exercise behavior and mental health. We review a number of large-scale studies in monozygotic and dizygotic twins that support these assumptions. Based on the importance of genetic factors in exercise behavior we develop a model for gene-by-exercise interaction that explains differences in voluntary exercise behavior by differential genetic sensitivity to the mental health benefits of exercise. We focus on the genetic modulation of acute mood effects of exercise and longer-term effects on self-esteem through genetic effects on exercise ability. If correct, our model calls for a change from 'population-based' to 'personalized' intervention strategies.

1. Introduction

Regular exercisers have reduced cardiovascular morbidity and mortality (Kaplan, Strawbridge, Cohen, & Hungerford, 1996). In addition, exercisers are characterized by higher psychological well-being and sharper minds. They have a lower incidence of depression and anxiety disorders (De Moor, Boomsma, Stubbe, Willemsen, & de Geus, 2008) and show cognitive advantages, specifically in frontal executive functions (Hillman, Erickson, & Kramer, 2008). Current population-based intervention campaigns tacitly assume that these associations found at a population level (a) mainly reflect causal effects of exercise, and (b) that exercise programs exert beneficial effects on *all* participants. In this paper we will challenge these assumptions on two grounds.

First, the association between regular exercise behavior and health outcomes 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, decreased risk for blood pressure or 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 health at a later time point, this phenomenon can mimic the causal effects of exercise and, consequently, overestimate the beneficial effects of exercise. Second, even if causal effects of exercise are established in experimental training studies, the magnitude of these effects, even in standardized training regimes, is far from uniform across all participants. Some participants will respond very favorably, whereas others hardly respond at all, or even respond unfavorably. If these individual differences in beneficial training effects derive from genetic variation between the trainees, the exercise effects are more accurately described as *gene-by-exercise interaction*.

Below we will review a number of studies that provide evidence for pleiotropy and gene-by-exercise interaction effects in the link between exercise and health. First, we focus on the field of physical health, where research on these topics has progressed most strongly. This will help us conceptualize the main principles and research strategies. Next, we turn to the field of mental health where these effects have been less often addressed, but, as we will argue, deserve our full attention if we want a better grasp on why exercisers exercise, and why non-exercisers do not. Since pleiotropy and gene-by-exercise interaction logically require individual differences in exercise behavior to be partly under genetic control, we begin by a brief summary of twin studies demonstrating heritability of this lifestyle.

2. Heritability of exercise behavior

Until recently, the bulk of studies on the determinants of voluntary exercise behavior has attempted to explain low exercise prevalence in terms of social and environmental barriers. These include, amongst others, poor access to facilities (Matson-Koffman, Brownstein, Neiner, & Greaney, 2005; Varo et al., 2003), low socioeconomic status (Haase, Steptoe, Sallis, & Wardle, 2004; Varo

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et al., 2003), non-Caucasian race (Kaplan, Lazarus, Cohen, & Leu, 1991), high job strain (van Loon, Tijhuis, Surtees, & Ormel, 2000; Payne, Jones, & Harris, 2005), subjective "lack of time" (Sherwood & Jeffery, 2000; Tzormpatzakis & Sleap, 2007), inadequate health beliefs (Haase et al., 2004), and low social support by family, peers or colleagues (King et al., 1992; Orleans, Kraft, Marx, & McGinnis, 2003; Sherwood & Jeffery, 2000). Despite their face validity, none of these factors has emerged as a strong causal determinant of exercise behavior (Dishman, 1988; Seefeldt, Malina, & Clark, 2002). Adding to this the observation that exercise behavior appears to "run in the family" (Koopmans, van Doornen, & Boomsma, 1994; Perusse, Tremblay, LeBlanc, & Bouchard, 1989; Simonen et al., 2002) genetic factors have been increasingly invoked as potential determinants of this behavior.

One of the strongest designs to demonstrate the heritability of a trait is the twin design. 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. MZ twin pairs share all of their genetic material and their family environment. DZ twin pairs and siblings also share the same family environment, but share on average only half of their genetic material. 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, Busjahn, & Peltonen, 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. A variety of twin studies have shown that genetic factors contribute to individual differences in exercise participation and measures of exercise frequency, duration and/or intensity (Aarnio, Winter, Kujala, & Kaprio, 1997; Beunen & Thomis, 1999; Boomsma, Vandenbree, Orlebeke, & Molenaar, 1989; Carlsson, Andersson, Lichtenstein, Michaelsson, & Ahlbom, 2006; Frederiksen & Christensen, 2003; de Geus, Boomsma, & Snieder, 2003; Heller et al., 1988; Koopmans et al., 1994; Kujala, Kaprio, & Koskenvuo, 2002; Lauderdale et al., 1997; Maia, Thomis, & Beunen, 2002; Perusse et al., 1989; Seabra, Mendonca, Goring, Thomis, & Maia, 2008; Stubbe, Boomsma, et al., 2006; Stubbe, Boomsma, & de Geus, 2005).

A striking finding in these studies is that the genetic architecture of exercise behavior is vastly different across the life span. The largest change is seen during adolescence. In childhood and early adolescence, up till the age of 13, genes are of no importance in explaining individual differences in exercise participation, whereas a huge familial resemblance is found through common environmental effects. In mid- to late-adolescence, the effects of common environment gradually wane, and genetic factors start to dominate individual differences in exercise behavior, with a peak heritability of 85% around the age 19–20. Heritability then decreases again to reach a stable value of about 50% in adult participants. All studies in *adult* twins consistently suggest a significant genetic contribution to leisure-time exercise participation. This was further confirmed in a multinational collaboration of 7 Twin Registries ("the GenomEUtwin project") in which exercise behavior was assessed in 37,051 twin pairs (mean age 28.5 years) from 7 countries (Stubbe, Boomsma, et al., 2006). Table 1 shows the heritabilities in each of the countries. In view of the sample sizes, these results leave very little doubt about the importance of genetic factors in voluntary exercise behavior.

Table 1
Heritability of voluntary exercise participation (more than 60 min a week of leisure-time exercise activities requiring 4 METs or more) in subjects aged 21–40 in 7 countries participating in the collaborative GenomEUtwin project.

	N twin pairs	Percentage exercisers	Heritability of exercise participation
Australia	2728	59	48%
Denmark	9456	40	52%
Finland	8842	33	62%
The Netherlands	2681	59	67%
Norway	3995	57	26%/57%[a]
Sweden	8927	31	59%
UK	422	56	70%[b]

[a] Estimates in males/females.
[b] Only female twins participated.

3. Genetic pleiotropy in physical health

We now deal with the question of whether the genetic factors underlying exercise behavior also play a role in physical health. To test these potential pleiotropic effects studies have used the "discordant monozygotic twin design" (Carlsson et al., 2006; Kujala et al., 2002). As outlined above, monozygotic twins share 100% of their genetic variation, with a few rare exceptions (Martin, Boomsma, & Machin, 1997). Due to environmental influences, a number of these twin pairs will be discordant for exercise behavior such that one twin is a regular exerciser, whereas the co-twin is sedentary. Under the causal hypothesis, the exercising twin should be less often affected by disease than the non-exercising twin. That is, the twins should also be discordant for morbidity and mortality. In contrast, pleiotropy predicts that the genetic protection against disease is still effective in the non-exercising twin and that the twins should be concordant for morbidity and mortality.

A study in Finnish twins on all-cause mortality yielded evidence in favor of such a scenario (Kujala et al., 2002). In discordant MZ pairs, the twin who exercised was not more likely to survive than the co-twin who did not exercise. Controlling for genetics, therefore, removed the health effect of exercise. In contrast, similar analyses in Swedish twins showed that the high active twin was about 20% less likely to die than the low active co-twin (Carlsson et al., 2006). Because this within-pair association was smaller than the association found at the population level (high active persons 30% less likely to have died than low active persons) these results are still compatible with a pleiotropic effect. However, a significant reduction in mortality remained in the within-MZ pair analysis, suggesting additional causal effects of exercise. A strength of the Swedish study was the 20-fold larger sample size, but the assessment of exercise behavior (a single question) was much less convincing than the detailed instruments used in the Finnish study. Also, by including twins with cardiovascular disease at baseline the Swedish study was vulnerable to the effects of reversed causality, where unhealthy twins cease to exercise because of their symptoms. A fair summary is that the verdict of whether exercise protects against mortality or whether regular exercisers simply happen to have more 'healthy genes' is still out. Importantly, both studies are compatible with the existence of genetic pleiotropy.

Evidence for pleiotropy also exists at the level of established risk factors. Hernelahti and colleagues (Hernelahti, Levalahti, et al., 2004; Hernelahti, Kujala, & Kaprio, 2004; Hernelahti, Kujala, Kaprio, & Sarna, 2002; Hernelahti, Tikkanen, Karjalainen, & Kujala, 2005) showed that regular exercise in adolescence was associated with significantly lower diastolic blood pressure in adulthood, 19 years later. This 'predictive' effect of exercise disappeared when muscle-type distribution, a highly genetically determined trait (Bassett, 1994; Spangenburg & Booth, 2003) was included into the model (Hernelahti et al., 2005). Type I muscles boost aerobic endurance but are also linked to an increased number of capillaries which may buffer blood pressure. Perhaps possessing many type I fibers predisposes adolescents to choose to engage in (vigorous) exercise but also acts to attenuate the gradual rise in blood pressure

seen across the life span. Pleiotropy was also found in the association between heart rate and exercise behavior. Using cross-trait correlations in monozygotic (MZ) and dizygotic (DZ) twin pairs we showed that the exercise behavior of a twin could be successfully used to predict the co-twin's heart rate, but that this effect was much stronger in the genetically identical MZ twins, than in the DZ twins who share on average only 50% of their genetic variation. The observed correlations between heart rate and weekly energy expenditure in exercise in adolescent ($r = 0.35$) and middle-aged ($r = 0.18$) twins derived largely from common genetic factors accounting for 84% and 88% of the heart rate/exercise covariance, respectively (de Geus et al., 2003).

At first sight, these pleiotropic effects would suggests that recruitment of 'genetic non-exercisers' in exercise activities would do little to prevent hypertension, since exercising would not change their genotype. Fortunately, experimental studies have shown that things are not so bleak. The plausibility of an additional true causal effect of exercise is supported by many training studies showing that taking up exercise decreases blood pressure (e.g. de Geus, van Doornen, & Orlebeke, 1993; de Geus, van Doornen, de Visser, & Orlebeke, 1990; Hagberg, Ferrell, Dengel, & Wilund, 1999; Hagberg, Park, & Brown, 2000; Svedenhag, Martinsson, Ekblom, & Hjemdahl, 1991) and heart rate (de Geus et al., 1990, 1996; Fagard & Cornelissen, 2007; Loimaala, Huikuri, Oja, Pasanen, & Vuori, 2000; Mujika & Padilla, 2000; Shi, Stevens, Foresman, Stern, & Raven, 1995), whereas forced de-training restores these variables to their pre-training levels (Bonaduce et al., 1998; de Geus et al., 1996; Mujika & Padilla, 2001). In short, although heart rate and blood pressure share genes in common with exercise behavior, this pleiotropic effect seems to co-exist with true causal effects of exercise. This suggests that the association between these risk factors and exercise behavior seen in the population-at-large reflects a mixture of pleiotropic genetic effects and true causal effects.

4. Gene-by-exercise interaction in physical health

A simple inspection of the ranges and standard deviations in training studies immediately suggests that the effects of exercise may not be uniform across individuals. Even in carefully standardized exercise programs, heart rate and blood pressure changes in response to training typically follow a normal distribution, where some individuals show strong decreases in heart rate or blood pressure, whereas only modest, or even no effects are found in others (Bouchard & Rankinen, 2001; de Geus et al., 1990, 1993, 1996; Hagberg et al., 1999, 2000). This suggests that individuals can strongly differ in their sensitivity to the beneficial effects of exercise. Part of the individual differences in the sensitivity to exercise ('trainability') may be due to genetic variation. If trainability is indeed heritable, this would be an instance of gene-by-exercise interaction.

To empirically test the existence of gene-by-exercise interaction, a candidate gene approach can be used in which participants with known different genotypes can be subjected to a standardized aerobic training program. A now almost 'classical' study using this approach was performed on the variable that is most clearly causally influenced by training: physical fitness. Montgomery and colleagues (Williams et al., 2000; Woods, Humphries, & Montgomery, 2000) determined genotypes for an insertion/deletion (I/D) polymorphism in the Angiotensin Converting Enzyme (ACE) gene in British army recruits who were tested for a number of fitness traits before and after a 10-week training program. Efficiency of the muscles, or delta efficiency, computed as the increase in power output for a given increase in oxygen consumption, was found to increase almost 9-fold more in participants homozygous for the I allele. Almost no training effect was found in those homozygous for the D allele. This constituted clear evidence of gene-by-exercise interaction.

Even if no actual genes are measured it is feasible to establish the presence and the extent of gene-by-exercise interaction by performing a controlled training study in genetically related individuals. Already in 1952, Falconer had the useful insight that a trait (e.g. heart rate) measured in two environments (e.g. before and after training) can be treated as two different traits (Falconer, 1952). Genotype-by-environment interaction can then be detected from the genetic correlation between these two traits (e.g. heart rate before and after training). This principle was successfully exploited in the HERITAGE study by Bouchard and colleagues (Bouchard et al., 1999). In over 200 families, both parents and three or more biological offspring were recruited, tested on multiple fitness traits, exercise-trained in the laboratory with the same program for 20 weeks, and re-tested on the same traits.

This large-scale training study showed an astounding variation in the response to exercise, not just in aerobic gain but also in muscular strength phenotypes. Virtually all the fitness traits examined showed evidence of gene-by-exercise interaction. For instance, a heritability estimate of 47% was obtained for the training-induced increase in aerobic endurance, measured as the maximal oxygen consumption (VO_2max) during an exhaustive exercise test (Bouchard et al., 1999). More importantly, large genetic variance in the training response appears to be also present for many risk markers for cardiovascular disease, including heart rate and blood pressure (An et al., 2003; Rice, An, et al., 2002) but also the amount and distribution of subcutaneous fat (Perusse et al., 2000), HDL and LDL cholesterol (Rice, Despres, et al., 2002), C-reactive protein (Lakka et al., 2005), insulin sensitivity and glucose effectiveness (Boule et al., 2005; Kilpelainen et al., 2007; Teran-Garcia et al., 2005, 2007).

These gene-by-exercise interaction effects may be caused by the emergence of new genetic variance when polymorphic genes that are quiescent in the sedentary state become expressed during exercise, or it may be caused by the amplification or de-amplification of existing genetic variance. In a variant of "the rich getting richer", those who already have a favorable genotype in the sedentary state may see their innate advantage even further expand in response to exercise. The reverse and more optimistic scenario, however, may also apply when the impact of detrimental genetic variation is de-amplified by exercise. For example, sedentary individuals who are simultaneously Arg64 carriers of the ß3-ADR gene and Glu27 carriers of the ß2-ADR gene have an unfavorable body composition. Exactly these individuals, however, were shown to experience a significantly greater loss of total percent body fat, trunk fat, and fat mass with 24 weeks aerobic training compared with all other genotypes groups (Phares et al., 2004). Thus, the combination of gene variants that confers disadvantageous body fat characteristics in a sedentary population was associated with a more favorable response to an exercise training intervention. The latter type of gene-by-exercise interaction is in line with a recent theory that the human genome requires regular exercise to promote normal function and health and that an evolutionary unexpected state of chronic physical inactivity induces abnormal phenotypic expression of our genes (Booth, Chakravarthy, & Spangenburg, 2002).

5. Pleiotropy in mental health

A major question for the readership of this journal is whether genetic pleiotropy can also be found in the realm of mental health benefits of exercise. The dominant hypothesis seems to be that the increased levels of psychological well-being found in exercisers reflects a causal effect of exercise. This converges with folk wisdom that exercise "makes you feel better" and can help "combat stress". In parallel to the findings for physical health, we should consider the alternative possibility that the association between exercise behavior and mental health reflects the effects of genes that

influence the propensity to exercise as well as a disposition for well-being or, framed inversely, that genes preventing people to exercise are also involved in the risk for anxious and depressive symptoms.

To address this question we have used the discordant twin design outlined previously to assess the association between exercise participation and positive well-being in 162 discordant monozygotic (MZ) twin pairs, 174 discordant dizygotic (DZ) twin or sibling pairs, and 2842 unrelated individuals (age range 18–65 years) from the Netherlands Twin Registry (Stubbe, De Moor, Boomsma, & de Geus, 2006). Type, frequency and duration of leisure-time exercise activities were obtained by survey and metabolic equivalent (MET) values were assigned, using Ainsworth's Compendium of physical activity (Ainsworth et al., 2000). Exercise participation was quantified as yes/no, where individuals counted as a regular exerciser when they exceeded a minimum threshold of 1 h weekly spent in exercise activities with a minimal intensity of 4 MET hours for at least 6 months, and as sedentary otherwise. As expected, in unrelated pairs the exercisers were more satisfied with their life and happier than non-exercisers at all ages (ORhappiness = 1.38; ORsatisfaction = 1.25). However, these odds ratios were attenuated and no longer significant in the exercise-discordant DZ and MZ pairs (e.g. DZ, ORsatisfaction = 1.05; MZ ORsatisfaction = 1.00). These results argue against causality and in favor of "an underlying factor" influencing both exercise participation and well-being in members of the same family.

We then readdressed this question in a sample of 5140 Dutch adult twins and their non-twin siblings from 2831 families using self-rated health (De Moor, Posthuma et al., 2007). Exercise participation was quantified using two different thresholds (4 MET hours weekly and 8 MET hours weekly) to obtain sedentary, light or moderate, and vigorous exercise participation. Rather than using a discordant MZ twin design we exploited the full information in all participating siblings in a bivariate genetic model that quantified the observed correlation between exercise participation and self-rated health ($r = 0.20$), and the contribution of genetic and environmental factors to this association. We showed that the genetic factors influencing exercise participation and self-rated health partially overlap ($r_{genetic} = 0.36$) 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.

Additional evidence for genetic pleiotropy was obtained in a third study in Dutch twins that focused on the inverse of well-being, the occurrence of symptoms of anxiety and depression (De Moor et al., 2008). The study was set up to perform a rigorous test of the hypothesis that the association between exercise and anxious/depressive symptoms is due to a causal effect of exercise. To this end, we used longitudinal data across 2-, 4-, 7-, 9-, and 11-year follow-up periods from 8558 twins and their family members. A number of predictions of the causal hypothesis were tested. The first prediction is that, 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 both genetic and environmental correlations between exercise and symptoms must 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). The environmental correlations 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.

A second prediction made by the causal hypothesis is that in genetically identical (MZ) twins the within-twin pair differences in weekly MET hours should be associated with within-twin pair differences in anxious and depressive symptoms. This is conceptually identical to the discordant MZ twin design above, but is more powerful because it uses information from all pairs, not just the pairs discordant for reaching a minimal exercise criterion. Correlation of the intra-pair differences scores in anxious and depressive symptoms with the intra-pair differences in weekly MET hours ranged from −0.04 to 0.03 and were all non-significant. Finally, within-subject changes in exercise behavior across time did not predict parallel changes in anxious and depressive symptoms, such that increases in frequency and intensity of exercise behavior over time reduced symptoms of anxiety and depression, or that, vice versa, decreases in frequency and intensity of exercise behavior over time increased symptoms of anxiety and depression. The causal hypothesis clearly predicts significant correlations, but the actually observed correlations between the change scores ranged from −0.05 to 0.05 and were all non-significant.

Taken together these results argue against causal effects of exercise but in favor of genetic pleiotropy. It is important to note that this does not rule out causal effects on well-being in specific subpopulations like vigorous exercisers (to which we return below) nor does our finding contradicts randomized controlled trials showing that regular exercise can be used as a treatment to relieve symptoms in both subclinical individuals and patients diagnosed with an anxiety and depressive disorder (Babyak et al., 2000; Blumenthal et al., 2007; Brosse, Sheets, Lett, & Blumenthal, 2002; Craft & Landers, 1998; North, McCullagh, & Tran, 1990). These latter studies examined the effects of prescribed and externally monitored exercise treatments in select subgroups, whereas we focus on the effects of voluntary leisure-time exercise behavior at the level of the population-at-large.

Based on the work described above we conclude that, in the population-at-large, exercise participation is associated with higher levels of life satisfaction and happiness and lower levels of anxiety and depression largely through genetic factors that influence both exercise behavior and well-being. This working hypothesis can in principle be tested by identifying the genetic variants influencing exercise behavior and well-being, and then establishing overlap. In practice, this is not so simple. Although the success rate of gene finding for traits like diabetes and cardiovascular disease is rapidly increasing thanks to genome wide association approaches (Samani et al., 2007; The Wellcome Trust Case Control Consortium, 2007) no genes that influence either well-being or exercise behavior have been detected at the level of 'proof beyond reasonable doubt'. For exercise behavior, a number of genomic regions have been implied (Cai et al., 2006; De Moor, Stubbe, Boomsma, & de Geus, 2007; Simonen, Rankinen, Perusse, Rice, et al., 2003) and successful association to a number of candidate genes has been found (Loos et al., 2005; Lorentzon, Lorentzon, Lerner, & Nordstrom, 2001; Salmen et al., 2003; Simonen, Rankinen, Perusse, Leon, et al., 2003; Winnicki et al., 2004). In view of the vulnerability of single-study based gene finding, extensive replication and functional annotation is needed to confirm that these genes indeed explain part of the heritability of exercise behavior. The next step then, is to test their effect on psychological well-being.

6. Gene-by-exercise interaction in mental health

With regard to gene-by-exercise interaction in mental health benefits, there is a surprising paucity of empirical data. In principle,

all that is required is a training study in (twin) family members and to examine familial resemblance in the direction and degree of changes in psychological state after training. To our knowledge, such data have not been collected. We consider this an unfortunate state of affairs. Not only do we predict the existence of such gene-by-exercise interactive effects, we here assert that they will contain the answer to most vexing questions in the field of exercise intervention: why exercisers exercise, and why non-exercisers do not. This assertion is explained in some detail in Fig. 1.

As with any other behavior, for exercise behavior to be repeated time and again, the net appetitive effects of exercise would need to outweigh the net aversive effects. This is depicted in the top half of Fig. 1. For ease of presentation we have divided the population into individuals where appetitive effects outweigh aversive effects and vice versa. In reality this trait will be continuous rather than discrete and dynamic over time rather than fixed for life. This model predicts that individuals for who the aversive effects of exercise, including the commitment of a substantial amount of (scarce) free time, are stronger than the rewarding effects will gradually decrease their regular exercise behavior after initial exposure, all the way up to becoming sedentary. In contrast, individuals for who the appetitive effects are dominant will repeat the behavior and become regular lifetime exercisers. Extensive interviews with persistent exercisers, recent adopters, fitness program dropouts and persistent sedentary individuals indeed suggested that exercisers differed from individuals with less active lifestyles mainly in that they enjoyed *the exercise itself* and felt that something was missing in their life when they did not regularly exercise (Gauvin, 1990).

The repeated 'feel good' experiences after an acute bout of exercise may be an important component of the higher well-being reported by regular exercisers. In fact, we hold that, *for regular exercisers*, exercise does seem to cause well-being. At first sight this seems to contradict our previous findings on the importance of genetic pleiotropy in explaining this association. An important addition to the basic behaviorist scheme in Fig. 1, however, is that we incorporate genes as the major source of the individual differences in the effects of exercise on the acute mood response. We suggest that the genetic make-up of exercisers tips the balance of the appetitive and aversive effects of exercise in favor of the appetitive effects, whereas in non-exercisers the aversive effects may prevail This gene-by-exercise interactive effect not only explains why regular exercisers report greater acute exercise-induced mood enhancement than non-exercisers (Hoffman & Hoffman, 2008); it will also create a modest association between well-being and exercise behavior at the population level.

A major future challenge lies in the elucidation of the exact pathways explaining this gene-by-exercise interaction on mood effects, but existing studies already point to possible mechanisms. The *immediate* aversive effects caused by exercise-related fatigue related to monoamine depletion (Davis & Bailey, 1997) may depend on genetic differences in monoaminergic systems, whereas the extent of immediate rewarding effects may well depend on genetic variation in the opioid and dopamine systems (Simonen, Rankinen, Perusse, Leon, et al., 2003). Acute exercise has striking effects on neural activity, evident in EEG (Crabbe, Smith, & Dishman, 2007) and PET recordings (Williamson, McColl, & Mathews, 2003, 2004; Williamson, McColl, Mathews, Ginsburg, & Mitchell, 1999). This activity is partly caused by feed forward motor commands and partly by afferent feedback signals from active muscles. Interestingly, these areas (amygdala, dorsal anterior cingulated, subgenual cingulate, medial orbitofrontal) overlap with areas strongly involved in conscious visceral awareness and emotional appraisal (Critchley, 2002, 2005; Critchley, Wiens, Rotshtein, Ohman, & Dolan, 2004). Potentially, activity of these regions during exercise can help decouple ongoing arousal from (recent) negative emotional events, an idea closely linked to the concept of desensitization therapy in psychiatry. Because genes play a critical role in the size and function of these brain areas (Buckholtz et al., 2008; Munafo, Brown, & Hariri, 2008) this may be another source of gene-by-exercise interactive effects on mood.

Genetic differences in aversive/rewarding effects may also be found in the *period after exercise*. Studies of the acute effects of exercise often report a significant improvement in mood after exercise, including reduced feelings of tension, anxiety and anger, and increased feelings of vigor (Gauvin, Rejeski, & Reboussin, 2000; Gauvin & Spence, 1996; Smith, O'Connor, Crabbe, & Dishman, 2002; Steptoe, Kimbell, & Basford, 1998). Diverse explanations have been put forward to explain these positive aftereffects of exercise that are likely to co-exist: opioid (Thor, Floras, Hoffmann, & Seals, 1990) and monoaminergic (Chaouloff, 1989; Dishman, 1997) mechanisms, (post-exercise) changes in regional cerebral blood flow (Herholz et al., 1987), and strong peripheral physiological effects lasting from 2 to 4 h up to 13 h after exercise (Halliwill, 2001) that include

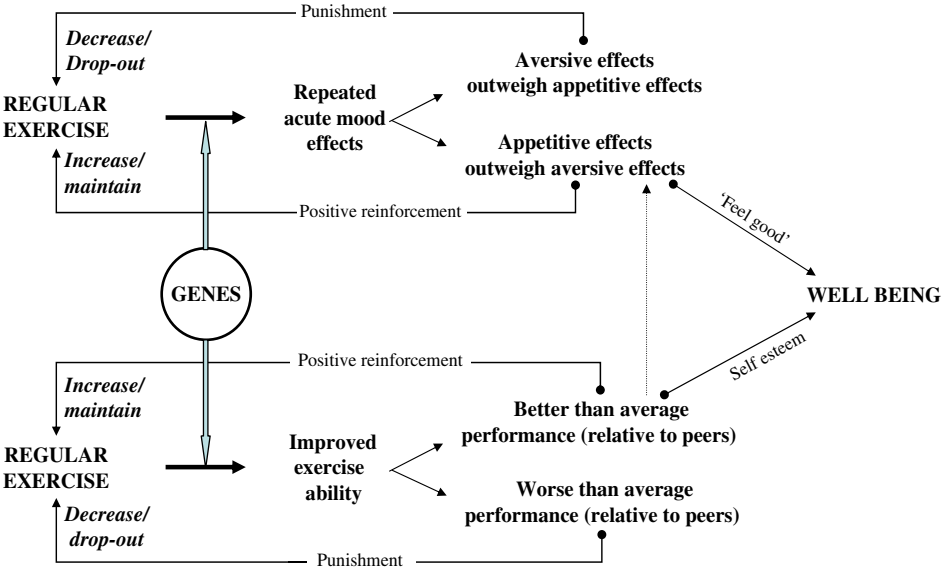

Fig. 1. Gene-by-exercise interaction in the effects on acute mood and exercise ability.

reduced activity of the sympathetic nervous system (Floras et al., 1989; Yamamoto, Miyachi, Saitoh, Yoshioka, & Onodera, 2001) and cardiovascular under-responsiveness to psychological stressors (Hamer, Taylor, & Steptoe, 2006; Hamer, Jones & Boutcher, 2006). The magnitude, or even the direction, of each of these effects may depend on variation in the gene networks involved in these systems. Likewise, the post-exercise aversive effects may be more prominent in some genotypes than in others. By enabling faster heart rate recovery, for instance, strong vagal control over heart rate, a partly genetic trait (Kupper et al., 2005), may reduce some of the aversive effects of exercise (e.g., prolonged palpitations).

In addition to differences in the acute mood effects, there is also a powerful social–psychological mechanism that may make some people more attracted to exercise than others. 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 towards exercise ability, people 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. People who achieve lower 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, in press). The hypothesized effects of performance differences on regular exercise behavior are depicted in the lower part of Fig. 1. In keeping with longstanding beliefs in the importance of self-esteem (Sonstroem & Morgan, 1989), the repeated sense of mastery may act to increase the sense of self-worth and exert long term effects on psychological well-being.

Although exercise tends to increase ability in all individuals, some clearly fare better than others. In the lower half of Fig. 1 genes are again thought to play a prominent role in explaining the differences in the exercise effects, and in this case evidence of gene-by-exercise interaction is already abundantly present. As we saw in the studies of the ACE I/D polymorphism (Williams et al., 2000; Woods et al., 2000) and the HERITAGE family study (Bouchard et al., 1999) differences in the gains in exercise performance during training are strongly heritable. From the reward/punishment loops in Fig. 1 we now additionally predict that these favorable trainability genes become genes that predispose to exercise behavior. In support of this "competence hypothesis" a multicentre study in Italian borderline hypertensives (Winnicki et al., 2004) showed that the ACE polymorphism accounted for 21% of the variance in exercise participation. The regular exercisers had a clear excess of the same genotype (I/I) that was associated with the largest training-induced increase in muscle efficiency in the British recruits (Williams et al., 2000; Woods et al., 2000). Here, at least, a gene for exercise *ability* indeed seems to be a gene for exercise *drive*.

We hasten to point out that the model in Fig. 1 should be regarded as a mere encouragement to take genetic factors into account, rather than a complete theory. In reality, the distinction between the lower part of the model and the upper part may blur. Perception of performing better than average, for instance, may constitute an important part of the appetitive effects of exercise (dotted arrow). Also, the genetic part of the model is very likely to be incomplete. Other genetic factors will play a role in the link between exercise and well-being. These include genes influencing known personality correlates of exercise like self-motivation, self-discipline, conscientiousness, and sensation seeking, and genes influencing exercise ability even in the untrained state. However, in its simplicity, the model already yields a number of testable predictions. It can, for instance, help explain why the psychological effects of training in population-based samples have differed greatly across controlled training studies, where some trials reported improved well-being (Barbour & Blumenthal, 2005; Brosse et al., 2002; Steptoe, Edwards, Moses, & Mathews, 1989) but others failed to note such effects (de Geus et al., 1993; King, Taylor, Haskell, & Debusk, 1989). Findings of such training studies will depend on the exact mix of genotypes recruited. Studies that use adults who have been completely sedentary for a long time may find less positive effects than studies that recruit previous exercisers who have only recently dropped out due to study or work pressure.

The strongest prediction of the model is that genetic variants, that amplify the short-term positive mood effects of exercise or longer-term effects of well-being through self-esteem and sense of accomplishment, will increase the likelihood of future exercise behavior. At the same time these 'exercise genes' will also act to increase well-being. In short, the genes involved in gene-by-exercise interaction will act like pleiotropic genes.

Current behavioral genetic models are able to test gene-by-environment interaction in combination with genetic pleiotropy (Purcell, 2002; Purcell & Sham, 2002), but models that incorporate behavioral feedback loops, for example, the effects of acute mood effects on future exercise behavior, have yet to be developed. This is a clear future challenge.

7. Perspectives on exercise intervention

Many countries have been campaigning for over 50 years to increase exercise behavior, and popular beliefs in its potential benefits on mental and physical health are extremely high, if not maximally saturated. Yet, a large part of the population does not exercise regularly. Using data from the Netherlands Twin Registry from the most recent wave in 2004, we find that between age 18 and 50 years (6453 individuals) the average prevalence of persons who exercised at least 60 min weekly at an intensity of 4 METs or better was 49.8%. When we apply a more stern criterion (a minimum of 3 times 20 min per week at an intensity of 6 METS or more) only 11.1% of the Dutch people between 18 and 50 years are sufficiently active to achieve aerobic fitness effects. Importantly, the percentage of sedentary Dutch adults *without any leisure-time exercise behavior* was 43.8%. We need to reach out to these people through other means than just repeating over and over that 'exercise will make you feel better'.

The notion of genetics sometimes meets with (c)overt hostility from professionals in the field of exercise intervention. Genetic influences are mistakenly interpreted as a life sentence for those who are sedentary. "If better health seen in exercisers reflects hard-wired genetic selection", the reasoning seems to go, "what is the use of our efforts to engage more people in regular exercise?" Such 'genetic determinism' is wrong on many accounts (Plomin, DeFries, McClearn, & McGuffin, 2000) but it is blatantly wrong for exercise if our hypothesis of gene-by-exercise interaction proves to be correct. Our model fully acknowledges that it may be harder to engage some people in exercise than others, but in no way suggests that we should stop trying. It does, however, suggest that we should not close our eyes to human genetic variation. Some individuals may require a different exercise program which emphasizes the appetitive aspects for an individual and reduces the aversive aspects. The exact strategy to optimize this balance requires a furthering of our understanding of genetic differences in the psychological responses to exercise. In some cases, obtaining increased adherence can be as simple as reducing exercise intensity and de-emphasizing the competitive aspect, presenting a larger selection of exercise activities, or a cognitive (realistic) restructuring of expected benefits, particularly in the initial phases of the exercise program.

Currently, the concept of 'personalized medicine' is increasingly being applied to curative medicine and pharmacological intervention. We need to dare to apply this concept also to preventive medicine and exercise intervention. This requires increased

understanding of the pathways from genes to exercise behavior and of the differences in genetic sensitivity to the mental health benefits of exercise. We hope to have provided a minimal framework to guide such research.

References

Aarnio, M., Winter, T., Kujala, U. M., & Kaprio, J. (1997). Familial aggregation of leisure-time physical activity – a three generation study. *International Journal of Sports Medicine, 18*, 549–556.

Ainsworth, B. E., Haskell, W. L., Whitt, M. C., Irwin, M. L., Swartz, A. M., Strath, S. J., et al. (2000). Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and Science in Sports and Exercise, 32*, S498–S516.

An, P., Perusse, L., Rankinen, T., Borecki, I. B., Gagnon, J., Leon, A. S., et al. (2003). Familial aggregation of exercise heart rate and blood pressure in response to 20 weeks of endurance training: the HERITAGE Family Study. *International Journal of Sports Medicine, 24*, 57–62.

Babyak, M., Blumenthal, J. A., Herman, S., Khatri, P., Doraiswamy, M., Moore, K., et al. (2000). Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. *Psychosomatic Medicine, 62*, 633–638.

Barbour, K. A., & Blumenthal, J. A. (2005). Exercise training and depression in older adults. *Neurobiology of Aging, 26*(Suppl. 1), 119–123.

Bassett, D. R., Jr. (1994). Skeletal muscle characteristics: relationships to cardiovascular risk factors. *Medicine and Science in Sports and Exercise, 26*, 957–966.

Beunen, G., & Thomis, M. (1999). Genetic determinants of sports participation and daily physical activity. *International Journal of Obesity, 23*, S55–S63.

Blumenthal, J. A., Babyak, M. A., Doraiswamy, P. M., Watkins, L., Hoffman, B. M., Barbour, K. A., et al. (2007). Exercise and pharmacotherapy in the treatment of major depressive disorder. *Psychosomatic Medicine, 69*, 587–596.

Bonaduce, D., Petretta, M., Cavallaro, V., Apicella, C., Ianniciello, A., Romano, M., et al. (1998). Intensive training and cardiac autonomic control in high level athletes. *Medicine and Science in Sports and Exercise, 30*, 691–696.

Boomsma, D., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics, 3*, 872–882.

Boomsma, D. I., Vandenbree, M. B. M., Orlebeke, J. F., & Molenaar, P. C. M. (1989). Resemblances of parents and twins in sports participation and heart-rate. *Behavior Genetics, 19*, 123–141.

Booth, F. W., Chakravarthy, M. V., & Spangenburg, E. E. (2002). Exercise and gene expression: physiological regulation of the human genome through physical activity. *Journal of Physiology-London, 543*, 399–411.

Bouchard, C., An, P., Rice, T., Skinner, J. S., Wilmore, J. H., Gagnon, J., et al. (1999). Familial aggregation of VO_2max response to exercise training: results from the HERITAGE family study. *Journal of Applied Physiology, 87*, 1003–1008.

Bouchard, C., & Rankinen, T. (2001). Individual differences in response to regular physical activity. *Medicine and Science in Sports and Exercise, 33*, S446–S451.

Boule, N. G., Weisnagel, S. J., Lakka, T. A., Tremblay, A., Bergman, R. N., Rankinen, T., et al. (2005). Effects of exercise training on glucose homeostasis. *Diabetes Care, 28*, 108–114.

Brosse, A. L., Sheets, E. S., Lett, H. S., & Blumenthal, J. A. (2002). Exercise and the treatment of clinical depression in adults – recent findings and future directions. *Sports Medicine, 32*, 741–760.

Buckholtz, J. W., Callicott, J. H., Kolachana, B., Hariri, A. R., Goldberg, T. E., Genderson, M., et al. (2008). Genetic variation in MAOA modulates ventromedial prefrontal circuitry mediating individual differences in human personality. *Molecular Psychiatry, 13*, 313–324.

Cai, G. W., Cole, S. A., Butte, N., Bacino, C., Diego, V., Tan, K., et al. (2006). A quantitative trait locus on chromosome 18q for physical activity and dietary intake in Hispanic children. *Obesity Research, 14*, 1596–1604.

Carlsson, S., Andersson, T., Lichtenstein, P., Michaelsson, K., & Ahlbom, A. (2006). Genetic effects on physical activity: results from the Swedish twin registry. *Medicine and Science in Sports and Exercise, 38*, 1396–1401.

Chaouloff, F. (1989). Physical exercise and brain monoamines: a review. *Acta Physiologica Scandinavia, 137*, 1–13.

Crabbe, J. B., Smith, J. C., & Dishman, R. K. (2007). Emotional & electroencephalographic responses during affective picture viewing after exercise. *Physiology & Behavior, 90*, 394–404.

Craft, L. L., & Landers, D. M. (1998). The effect of exercise on clinical depression and depression resulting from mental illness: a meta-analysis. *Journal of Sport and Exercise Psychology, 20*, 339–357.

Critchley, H. D. (2002). Electrodermal responses: what happens in the brain. *The Neuroscientist, 8*, 132–142.

Critchley, H. D. (2005). Neural mechanisms of autonomic, affective, and cognitive integration. *Journal of Comparative Neurology, 493*, 154–166.

Critchley, H. D., Wiens, S., Rotshtein, P., Ohman, A., & Dolan, R. J. (2004). Neural systems supporting interoceptive awareness. *Nature Neuroscience, 7*, 189–195.

Davis, J. M., & Bailey, S. P. (1997). Possible mechanisms of central nervous system fatigue during exercise. *Medicine and Science in Sports and Exercise, 29*, 45–57.

De Moor, M. H. M., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & de Geus, E. J. C. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives of General Psychiatry, 65*, 897–905.

De Moor, M. H. M., Posthuma, D., Hottenga, J. J., Willemsen, A. H. M., Boomsma, D. I., & de Geus, E. J. C. (2007). Genome-wide linkage scan for exercise participation in Dutch sibling pairs. *European Journal of Human Genetics, 15*, 1252–1259.

De Moor, M. H. M., Stubbe, J. H., Boomsma, D. I., & de Geus, E. J. C. (2007). Exercise participation and self-rated health: do common genes explain the association? *European Journal of Epidemiology, 22*, 27–32.

Dishman, R. K. (1988). Determinants of participation in physical activity. In C. Bouchard, R. J. Shepard, T. Stephens, J. R. Sutton, & B. D. McPherson (Eds.), *Exercise, fitness, and health; a consensus of current knowledge* (pp. 75–101). Champaign, IL: Human Kinetics Books.

Dishman, R. K. (1997). Brain monoamines, exercise, and behavioral stress: animal models. *Medicine and Science in Sports and Exercise, 29*, 63–74.

Fagard, R. H., & Cornelissen, V. A. (2007). Effect of exercise on blood pressure control in hypertensive patients. *European Journal of Cardiovascular Prevention & Rehabilitation, 14*, 12–17.

Falconer, D. S. (1952). The problem of environment and selection. *American Naturalist, 86*, 293–298.

Floras, J. S., Sinkey, C. A., Aylward, P. E., Seals, D. R., Thor, P., & Mark, A. L. (1989). Post-exercise hypotension and sympathoinhibition in borderline hypertensive men. *Hypertension, 14*, 28–35.

Frederiksen, H., & Christensen, K. (2003). The influence of genetic factors on physical functioning and exercise in second half of life. *Scandinavian Journal of Medicine and Science in Sports, 13*, 9–18.

Gauvin, L. (1990). An experiential perspective on the motivational features of exercise and lifestyle. *Canadian Journal of Sport Science, 15*, 51–58.

Gauvin, L., Rejeski, W. J., & Reboussin, B. A. (2000). Contributions of acute bouts of vigorous physical activity to explaining diurnal variations in feeling states in active, middle-aged women. *Health Psychology, 19*, 365–375.

Gauvin, L., & Spence, J. C. (1996). Physical activity and psychological well-being: knowledge base, current issues, and caveats. *Nutrition Review, 54*, S53–S65.

de Geus, E. J. C., Boomsma, D. I., & Snieder, H. (2003). Genetic correlation of exercise with heart rate and respiratory sinus arrhythmia. *Medicine and Science in Sports and Exercise, 35*, 1287–1295.

de Geus, E. J. C., van Doornen, L. J., & Orlebeke, J. F. (1993). Regular exercise and aerobic fitness in relation to psychological make-up and physiological stress reactivity. *Psychosomatic Medicine, 55*, 347–363.

de Geus, E. J. C., van Doornen, L. J., de Visser, D. C., & Orlebeke, J. F. (1990). Existing and training induced differences in aerobic fitness: their relationship to physiological response patterns during different types of stress. *Psychophysiology, 27*, 457–478.

de Geus, E. J. C., Karsdorp, R., Boer, B., deRegt, G., Orlebeke, J. F., & Vandoornen, L. J. P. (1996). Effect of aerobic fitness training on heart rate variability and cardiac baroreflex sensitivity. *Homeostasis in Health and Disease, 37*, 28–51.

Haase, A., Steptoe, A., Sallis, J. F., & Wardle, J. (2004). Leisure-time physical activity in university students from 23 countries: associations with health beliefs, risk awareness, and national economic development. *Preventive Medicine, 39*, 182–190.

Hagberg, J. M., Ferrell, R. E., Dengel, D. R., & Wilund, K. R. (1999). Exercise training-induced blood pressure and plasma lipid improvements in hypertensives may be genotype dependent. *Hypertension, 34*, 18–23.

Hagberg, J. M., Park, J. J., & Brown, M. D. (2000). The role of exercise training in the treatment of hypertension – an update. *Sports Medicine, 30*, 193–206.

Halliwill, J. R. (2001). Mechanisms and clinical implications of post-exercise hypotension in humans. *Exercise Sport Science Reviews, 29*, 65–70.

Hamer, M., Jones, J., & Boutcher, S. H. (2006). Acute exercise reduces vascular reactivity to mental challenge in offspring of hypertensive families. *Journal of Hypertension, 24*, 315–320.

Hamer, M., Taylor, A., & Steptoe, A. (2006). The effect of acute aerobic exercise on stress related blood pressure responses: a systematic review and meta-analysis. *Biological Psychology, 71*, 183–190.

Heller, R. F., O'Connell, D. L., Roberts, D. C., Allen, J. R., Knapp, J. C., Steele, P. L., et al. (1988). Lifestyle factors in monozygotic and dizygotic twins. *Genetic Epidemiology, 5*, 311–321.

Herholz, K., Buskies, W., Rist, M., Pawlik, G., Hollmann, W., & Heiss, W. D. (1987). Regional cerebral blood flow in man at rest and during exercise. *Journal of Neurology, 234*, 9–13.

Hernelahti, M., Kujala, U. M., & Kaprio, J. (2004). Stability and change of volume and intensity of physical activity as predictors of hypertension. *Scandinavian Journal of Public Health, 32*, 303–309.

Hernelahti, M., Kujala, U. M., Kaprio, J., & Sarna, S. (2002). Long-term vigorous training in young adulthood and later physical activity as predictors of hypertension in middle-aged and older men. *International Journal of Sports Medicine, 23*, 178–182.

Hernelahti, M., Levalahti, E., Simonen, R. L., Kaprio, J., Kujala, U. M., Uusitalo-Koskinen, A. L. T., et al. (2004). Relative roles of heredity and physical activity in adolescence and adulthood on blood pressure. *Journal of Applied Physiology, 97*, 1046–1052.

Hernelahti, M., Tikkanen, H. O., Karjalainen, J., & Kujala, U. M. (2005). Muscle fiber-type distribution as a predictor of blood pressure – a 19-year follow-up study. *Hypertension, 45*, 1019–1023.

Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: exercise effects on brain and cognition. *Nature Reviews Neuroscience, 9*, 58–65.

Hoffman, M. D., & Hoffman, D. R. (2008). Exercisers achieve greater acute exercise-induced mood enhancement than nonexercisers. *Archives of Physical Medicine in Rehabilitation, 89*, 358–363.

Kaplan, G. A., Lazarus, N. B., Cohen, R. D., & Leu, D. J. (1991). Psychosocial factors in the natural history of physical activity. *American Journal of Preventive Medicine, 7*, 12–17.

Kaplan, G. A., Strawbridge, W. J., Cohen, R. D., & Hungerford, L. R. (1996). Natural history of leisure-time physical activity and its correlates: Associations with

mortality from all causes and cardiovascular disease over 28 years. *American Journal of Epidemiology, 144*, 793–797.
Kilpelainen, T. O., Lakka, T. A., Laaksonen, D. E., Laukkanen, O., Lindstroem, J., Eriksson, J. G., et al. (2007). Physical activity modifies the effect of SNPs in the SLC2A2 (GLUT2) and ABCC8 (SUR1) genes on the risk of developing type 2 diabetes. *Physiological Genomics, 31*, 264–272.
King, A. C., Blair, S. N., Bild, D. E., Dishman, R. K., Dubbert, P. M., Marcus, B. H., et al. (1992). Determinants of physical activity and interventions in adults. *Medicine and Science in Sports and Exercise, 24*, S221–S236.
King, A. C., Taylor, C. B., Haskell, W. L., & Debusk, R. F. (1989). Influence of regular aerobic exercise on psychological health: a randomized, controlled trial of healthy middle-aged adults. *Health Psychology, 8*, 305–324.
Koopmans, J. R., van Doornen, L. J. P., & Boomsma, D. I. (1994). Smoking and sports participation. In U. Goldbourt, & U. de Faire (Eds.), *Genetic factors in coronary heart disease*. Dordrecht: Kluwer Academic Publisher.
Kujala, U. M., Kaprio, J., & Koskenvuo, M. (2002). Modifiable risk factors as predictors of all-cause mortality: the roles of genetics and childhood environment. *American Journal of Epidemiology, 156*, 985–993.
Kupper, N., Willemsen, G., Posthuma, D., de Boer, D., Boomsma, D. I., & de Geus, E. J. (2005). A genetic analysis of ambulatory cardiorespiratory coupling. *Psychophysiology, 42*, 202–212.
Lakka, T. A., Lakka, H. M., Rankinen, T., Leon, A. S., Rao, D. C., Skinner, J. S., et al. (2005). Effect of exercise training on plasma levels of C-reactive protein in healthy adults: the HERITAGE Family Study. *European Heart Journal, 26*, 2018–2025.
Lauderdale, D. S., Fabsitz, R., Meyer, J. M., Sholinsky, P., Ramakrishnan, V., & Goldberg, J. (1997). Familial determinants of moderate and intense physical activity: a twin study. *Medicine and Science in Sports and Exercise, 29*, 1062–1068.
Loimaala, A., Huikuri, H., Oja, P., Pasanen, M., & Vuori, I. (2000). Controlled 5-mo aerobic training improves heart rate but not heart rate variability or baroreflex sensitivity. *Journal of Applied Physiology, 89*, 1825–1829.
van Loon, A. J., Tijhuis, M., Surtees, P. G., & Ormel, J. (2000). Lifestyle risk factors for cancer: the relationship with psychosocial work environment. *International Journal of Epidemiology, 29*, 785–792.
Loos, R. J. F., Rankinen, T., Tremblay, A., Perusse, L., Chagnon, Y., & Bouchard, C. (2005). Melanocortin-4 receptor gene and physical activity in the Quebec Family Study. *International Journal of Obesity, 29*, 420–428.
Lorentzon, M., Lorentzon, R., Lerner, U. H., & Nordstrom, P. (2001). Calcium sensing receptor gene polymorphism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. *European Journal of Endocrinology, 144*, 257–261.
Maia, J. A. R., Thomis, M., & Beunen, G. (2002). Genetic factors in physical activity levels – a twin study. *American Journal of Preventive Medicine, 23*, 87–91.
Martin, N., Boomsma, D., & Machin, G. (1997). A twin-pronged attack on complex traits. *Nature Genetics, 17*, 387–392.
Matson-Koffman, D. M., Brownstein, J. N., Neiner, J. A., & Greaney, M. L. (2005). A site-specific literature review of policy and environmental interventions that promote physical activity and nutrition for cardiovascular health: what works? *American Journal of Health Promotion, 19*, 167–193.
Mujika, I., & Padilla, S. (2000). Detraining: loss of training-induced physiological and performance adaptations. Part I short term insufficient training stimulus. *Sports Medicine, 30*, 79–87.
Mujika, I., & Padilla, S. (2001). Cardiorespiratory and metabolic characteristics of detraining in humans. *Medicine and Science in Sports and Exercise, 33*, 413–421.
Munafo, M. R., Brown, S. M., & Hariri, A. R. (2008). Serotonin transporter (5-HTTLPR) genotype and amygdala activation: a meta-analysis. *Biological Psychiatry, 63*, 852–857.
North, T. C., McCullagh, P., & Tran, Z. V. (1990). Effect of exercise on depression. *Exercise and Sport Sciences Reviews, 18*, 379–415.
Orleans, C. T., Kraft, M. K., Marx, J. F., & McGinnis, J. M. (2003). Why are some neighborhoods active and others not? Charting a new course for research on the policy and environmental determinants of physical activity. *Annals of Behavioral Medicine, 25*, 77–79.
Payne, N., Jones, F., & Harris, P. R. (2005). The impact of job strain on the predictive validity of the theory of planned behaviour: an investigation of exercise and healthy eating. *British Journal of Health Psychology, 10*, 115–131.
Perusse, L., Rice, T., Province, M. A., Gagnon, J., Leon, A. S., Skinner, J. S., et al. (2000). Familial aggregation of amount and distribution of subcutaneous fat and their responses to exercise training in the HERITAGE family study. *Obesity Research, 8*, 140–150.
Perusse, L., Tremblay, A., LeBlanc, C., & Bouchard, C. (1989). Genetic and environmental-influences on level of habitual physical-activity and exercise participation. *American Journal of Epidemiology, 129*, 1012–1022.
Phares, D. A., Halverstadt, A. A., Shuldiner, A. R., Ferrell, R. E., Douglass, L. W., Ryan, A. S., et al. (2004). Association between body fat response to exercise training and multilocus ADR genotypes. *Obesity Research, 12*, 807–815.
Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2000). *Behavioral genetics* (4th ed.). New York: Worth.
Purcell, S. (2002). Variance components models for gene–environment interaction in twin analysis. *Twin Research, 5*, 554–571.
Purcell, S., & Sham, P. (2002). Variance components models for gene–environment interaction in quantitative trait locus linkage analysis. *Twin Research, 5*, 572–576.
Rice, T., An, P., Gagnon, J., Leon, A. S., Skinner, J. S., Wilmore, J. H., et al. (2002). Heritability of HR and BP response to exercise training in the HERITAGE Family Study. *Medicine and Science in Sports and Exercise, 34*, 972–979.
Rice, T., Despres, J. P., Perusse, L., Hong, Y. L., Province, M. A., Bergeron, J., et al. (2002). Familial aggregation of blood lipid response to exercise training in the health, risk factors, exercise training, and genetics (HERITAGE) family study. *Circulation, 105*, 1904–1908.
Salmen, T., Heikkinen, A. M., Mahonen, A., Kroger, H., Komulainen, M., Pallonen, H., et al. (2003). Relation of aromatase gene polymorphism and hormone replacement therapy to serum estradiol levels, bone mineral density, and fracture risk in early postmenopausal women. *Annals of Medicine, 35*, 282–288.
Samani, N. J., Erdmann, J., Hall, A. S., Hengstenberg, C., Mangino, M., Mayer, B., et al. (2007). Genome-wide association analysis of coronary artery disease. *The New England Journal of Medicine, 357*, 443–453.
Seabra, A. F., Mendonca, D. M., Goring, H. H. H., Thomis, M. A., & Maia, J. A. (2008). Genetic and environmental factors in familial clustering in physical activity. *European Journal of Epidemiology, 23*, 205–211.
Seefeldt, V., Malina, R. M., & Clark, M. A. (2002). Factors affecting levels of physical activity in adults. *Sports Medicine, 32*, 143–168.
Sherwood, N. E., & Jeffery, R. W. (2000). The behavioral determinants of exercise: implications for physical activity interventions. *Annual Review of Nutrition, 20*, 21–44.
Shi, X. R., Stevens, G. H. J., Foresman, B. H., Stern, S. A., & Raven, P. B. (1995). Autonomic nervous-system control of the heart – endurance exercise training. *Medicine and Science in Sports and Exercise, 27*, 1406–1413.
Simonen, R. L., Perusse, L., Rankinen, T., Rice, T., Rao, D. C., & Bouchard, C. (2002). Familial aggregation of physical activity levels in the Quebec family study. *Medicine and Science in Sports and Exercise, 34*, 1137–1142.
Simonen, R. L., Rankinen, T., Perusse, L., Leon, A. S., Skinner, J. S., Wilmore, J. H., et al. (2003). A dopamine D2 receptor gene polymorphism and physical activity in two family studies. *Physiology & Behavior, 78*, 751–757.
Simonen, R. L., Rankinen, T., Perusse, L., Rice, T., Rao, D. C., Chagnon, Y., et al. (2003). Genome-wide linkage scan for physical activity levels in the Quebec family study. *Medicine and Science in Sports and Exercise, 35*, 1355–1359.
Smith, J. C., O'Connor, P. J., Crabbe, J. B., & Dishman, R. K. (2002). Emotional responsiveness after low- and moderate-intensity exercise and seated rest. *Medicine and Science in Sports and Exercise, 34*, 1158–1167.
Sonstroem, R. J., & Morgan, W. P. (1989). Exercise and self-esteem: rationale and model. *Medicine and Science in Sports and Exercise, 21*, 329–337.
Spangenburg, E. E., & Booth, F. W. (2003). Molecular regulation of individual skeletal muscle fibre types. *Acta Physiologica Scandinavia, 178*, 413–424.
Steptoe, A., Edwards, S., Moses, J., & Mathews, A. (1989). The effects of exercise training on mood and perceived coping ability in anxious adults from the general population. *Journal of Psychosomatic Research, 33*, 537–547.
Steptoe, A., Kimbell, J., & Basford, P. (1998). Exercise and the experience and appraisal of daily stressors: a naturalistic study. *Journal of Behavioral Medicine, 21*, 363–374.
Stubbe, J. H., Boomsma, D. I., & de Geus, E. J. C. (2005). Sports participation during adolescence: a shift from environmental to genetic factors. *Medicine and Science in Sports and Exercise, 37*, 563–570.
Stubbe, J. H., Boomsma, D. I., Vink, J. M., Cornes, B. K., Martin, N. G., Skytthe, A., et al. (2006). Genetic influences on exercise participation: a comparative study in adult twin samples from seven countries. *PLoS ONE, 1*, e22.
Stubbe, J. H., De Moor, M. H. M., Boomsma, D., & de Geus, E. J. (2006). The association between exercise participation and well-being: a co-twin study. *Preventive Medicine*.
Stubbe, J. H., & de Geus, E. J. Genetics of exercise behavior. In Y. -K. Kim (Ed.), *Handbook of behavior genetics*. Berlin: Springer Verlag, in press.
Svedenhag, J., Martinsson, A., Ekblom, B., & Hjemdahl, P. (1991). Altered cardiovascular responsiveness to adrenoceptor agonists in endurance-trained men. *Journal of Applied Physiology, 70*, 531–538.
Teran-Garcia, M., Rankinen, T., Rice, T., Leon, A. S., Rao, D. C., Skinner, J. S., et al. (2007). Variations in the four and a half LIM domains 1 gene (FHL1) are associated with fasting insulin and insulin sensitivity responses to regular exercise. *Diabetologia, 50*, 1858–1866.
Teran-Garcia, M., Santoro, N., Rankinen, T., Bergeron, J., Rice, T., Leon, A. S., et al. (2005). Hepatic lipase gene variant -514C > T is associated with lipoprotein and insulin sensitivity response to regular exercise – the HERITAGE Family Study. *Diabetes, 54*, 2251–2255.
The Wellcome Trust Case Control Consortium. (2007). Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature, 447*, 661–678.
Thor, P., Floras, J. S., Hoffmann, P., & Seals, D. R. (1990). Endorphins and exercise: physiological mechanisms and clinical implications. *Medicine and Science in Sports and Exercise, 22*, 417–428.
Tzormpatzakis, N., & Sleap, M. (2007). Participation in physical activity and exercise in Greece: a systematic literature review. *International Journal of Public Health, 52*, 360–371.
Varo, J. J., Martinez-Gonzalez, M. A., Irala-Estevez, J., Kearney, J., Gibney, M., & Martinez, J. A. (2003). Distribution and determinants of sedentary lifestyles in the European Union. *International Journal of Epidemiology, 32*, 138–146.
Williams, A. G., Rayson, M. P., Jubb, M., World, M., Woods, D. R., Hayward, M., et al. (2000). Physiology – the ACE gene and muscle performance. *Nature, 403*, 614.
Williamson, J. W., McColl, R., & Mathews, D. (2003). Evidence for central command activation of the human insular cortex during exercise. *Journal of Applied Physiology, 94*, 1726–1734.
Williamson, J. W., McColl, R., & Mathews, D. (2004). Changes in regional cerebral blood flow distribution during postexercise hypotension in humans. *Journal of Applied Physiology, 96*, 719–724.

Williamson, J. W., McColl, R., Mathews, D., Ginsburg, M., & Mitchell, J. H. (1999). Activation of the insular cortex is affected by the intensity of exercise. *Journal of Applied Physiology, 87*, 1213–1219.

Winnicki, M., Accurso, V., Hoffmann, M., Pawlowski, R., Dorigatti, F., Santonastaso, M., et al. (2004). Physical activity and angiotensin-converting enzyme gene polymorphism in mild hypertensives. *American Journal of Medical Genetics, 125A*, 38–44.

Woods, D. R., Humphries, S. E., & Montgomery, H. E. (2000). The ACE I/D polymorphism and human physical performance. *Trends in Endocrinology and Metabolism, 11*, 416–420.

Yamamoto, K., Miyachi, M., Saitoh, T., Yoshioka, A., & Onodera, S. (2001). Effects of endurance training on resting and post-exercise cardiac autonomic control. *Medicine and Science in Sports and Exercise, 33*, 1496–1502.