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2017

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Publisher's PDF, also known as Version of record

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citation for published version (APA)

Schutte, N. M. (2017). *Unraveling the genetic components of voluntary exercise behavior in adolescents and young adults*. [PhD-Thesis - Research and graduation internal, Vrije Universiteit Amsterdam].

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CHAPTER 9

SUMMARY &

SYNTHESIS

It is not without reason that public health authorities worldwide have launched interventions aimed at physical activity during work/school time and transportation to work and school, and at physical activity in leisure time (e.g. the Global Recommendations on Physical Activity for Health by the World Health Organization (2010), the EU Physical Activity Guidelines by the EU Working Group *Sport and Health* (2008), and the Physical Activity Guidelines for Americans by the U.S. Department of Health and Human Services (2008)). Moderate to vigorous intensity exercise has been shown to have large protective effect on mortality (Samitz et al., 2011). Yet, in spite of these well-motivated attempts, large individual differences remain to be observed in physical activity habits, including the important component of regular exercise behavior in leisure time.

In the knowledge that many twin and family studies have provided evidence that a substantial part of the variation in exercise behavior is determined by genetic predisposition (particularly in late-adolescence and young adulthood as shown in Figure 1.1), the main aim of this thesis was to identify the mechanisms that give rise to this heritability of exercise behavior.

The heritability of adolescent exercise behavior

Chapter 2 provides an overview of published studies on the quantitative genetics and molecular genetic findings for physical activity and exercise behavior. Up to 12 years of age, heritability estimates are low to moderate, whereas in (late-)adolescence, heritability estimates of voluntary exercise behavior are moderate to high. The results from the meta-analyses in three different age groups confirm increasing influence of genetic factors with age on exercise behavior: meta-analytic heritability estimates of 20% (7 to 12 years), 35% (13 to 15 years), and 53% (16 to 18 years) were reported. This changing genetic architecture of voluntary exercise behavior across the life span has been described before (Huppertz et al., 2016; Stubbe et al., 2005; Stubbe & de Geus, 2009). The notion that shared environmental factors play a greater role in childhood than adolescence can be explained by the important role of the parents; they provide the children with the opportunity to become active, by means of transportation to exercise activities, give exercise activities the priority over other leisure time activities and motivation and encouragement to exercise. During adolescence, this parental meddling becomes less prominent, and the influence of genetic factors becomes more important (Huppertz et al., 2016). In spite of the evidence for this increasing

contribution of heritable factors to exercise behavior from twin and family studies, efforts to identify the actual genes contributing to this heritability are limited. The model by De Geus & De Moor (2008) (introduced in the first chapter of this thesis) provided us with testable hypotheses regarding the nature of the genetic factors affecting regular voluntary exercise behavior. In this model it is argued that likelihood of engaging in or maintaining exercise behavior might be increased by the presence of genetic variants that amplify the feelings of pleasure, sense of accomplishment and performance.

A delicate balance: affective response to exercise

The model by De Geus & de Moor (2008) is based on the principles of instrumental conditioning, determined by the positive reinforcement or feelings of punishment. Exercise induced positive affective responses ('feel good' experiences during or shortly after an exercise bout) may be an important contributor to appetitive effects of exercise. Previous studies showed a robust association between a more favorable affective response during exercise and the intention to engage in voluntary exercise (Kwan & Bryan, 2010; Ruby et al., 2011) and greater actual participation in (voluntary) moderate to vigorous exercise (Dunton & Vaughan, 2008; Rhodes & Kates, 2015; Schneider & Graham, 2009; Williams et al., 2008; Williams et al., 2012). Short-term aversive effects may arise during exercise at higher intensities, most strikingly above the level where the supply of energy through oxygen must be supplemented by anaerobic metabolism. Blood lactate begins to accumulate above resting levels because lactate clearance is no longer able to keep up with lactate production and large individual variation in affective responses is seen (Ekkekakis et al., 2005; Ekkekakis et al., 2011; Van Landuyt et al., 2000; Welch et al., 2007). In Chapter 4, we tested the role of exercise induced affective responses in the motivation to exercise, by estimating the heritability of the affective responses during and after exercise and the overlap with the genetic factors influencing regular voluntary exercise behavior. Genetic factors explained 12% to 37% of the individual differences in the affective responses during and after (sub)maximal exercise tests in the cycle ergometer and treadmill. Without exception, more positive affective responses were associated with higher amounts of regular exercise activity ($.15 < r < .21$) and this association was accounted for by an overlap in genetic factors influencing affective responding and exercise behavior.

Other studies that directly test the association between genetic variants and exercise-induced affective responses are scarce. Bryan et al. (2007) showed mediating effects of a single nucleotide polymorphism (SNP) in the brain-derived neurotrophic factor (*BDNF*) gene (G/A at nucleotide 196; Rs6265) on the association between exercise and positive mood, heart rate, and perceived exertion in a sample of healthy exercisers. Karoly et al. (2012) found two SNPs (rs8044769 and rs3751812) in the fat mass and obesity-associated protein gene (*FTO*) gene to be related to positive affect change during exercise (Karoly et al., 2012). Furthermore, a phylogenetically old mechanism that could influence the net balance of positive and negative affective responses during and after a bout of exercise could be an innate drive to be physical active (Swallow et al., 1998). The fulfillment of this ‘activity drive’ could be intrinsically rewarding, just as relieving hunger or thirst. Mouse lines that were selectively bred for voluntary-wheel running behavior have shed some light on this motivation to exercise. Behavioral pharmacological but also brain imaging studies in these mice by the laboratory of Garland showed that selection for increased voluntary wheel running altered dopamine signaling (Rhodes et al., 2005). Recently, it was shown that the facilitation of dopamine signaling is modulated by glutamate and GABA (Saul et al., 2016), neuromodulators that play a role in brain reward circuitry (Kelley & Berridge, 2002) and the neurotransmitter serotonin (Claghorn et al., 2016; Saul et al., 2016), which is also involved in the brain’s rewarding system (Kelley & Berridge, 2002).

Tipping the balance: personality and perceived benefits & barriers

Even more complex factors may influence the balance between aversive and appetitive effects of exercise in humans. A substantial body of evidence confirms personality to be a robust correlate of regular exercise behavior. Regular exercisers score lower on neuroticism and higher on extraversion, conscientiousness, and sensation seeking (de Moor et al., 2006; Rhodes & Smith, 2006; Wilkinson et al., 2013; Wilson & Dishman, 2015). In Chapter 8, we replicate the association of extraversion with voluntary exercise behavior, and show a significant genetic correlation between these traits. Extraverts are argued to be less aroused than introverts, whereas introverts have a higher level of activation to start with. Therefore, introverts might be easily overstimulated and less attracted to social situations and, consequently, exercise activities. The association with exercise behavior might be particularly

prominent in adolescence, when most exercise activities are performed in teams with friends and peers.

In the above, we assume that the genetic correlation between extraversion and exercise behavior results from the causal effects of (heritable) extraversion on exercise behavior. In doing so, we implicitly rule out reverse causality with (heritable) exercise behavior increasing extraversion. Initial support for a causal effect of extraversion on exercise (and not the reverse) comes from twin studies modeling the longitudinal trajectories of both extraversion and exercise behavior over a prolonged time period (De Moor & de Geus, *in press*). Further support could be generated by studies using candidate genes for extraversion to predict exercise behavior, using what is known as the Mendelian randomization approach (Davey Smith & Hemani, 2014). Mendelian randomization entails the utilization of common genetic variants that have a well-characterized biological function to study the effect of a suspected environmental exposure on a disease risk or trait (in this case, exercise behavior). Under the causal hypothesis that extraversion is a determinant of exercise behavior, genetic variants influencing extraversion should also be associated with exercise behavior. Provided sufficient power, failure to find this genetic influence would act to falsify a causal effect of extraversion.

Biological theories suggest that extraversion is linked to the mesolimbic dopamine system as this mechanism is related to individual differences in the functioning of the reward system (Depue & Collins, 1999) and several studies show an association of extraversion with genes involved in the dopaminergic system (Golimbet et al., 2007; Reuter & Hennig, 2005; Smillie et al., 2010). Following the Mendelian Randomization logic these genes should be associated with exercise behavior if extraversion is a causal agent. Simonen et al. (2003) indeed reported an association of a single nucleotide polymorphism (SNP) in the *DRD2* gene with physical activity in families of the Quebec Family Study and HERITAGE Family Study. However, both Jozkow et al. (2013) and Huppertz et al. (2014a) failed to replicate this association. These mixed results could doubt the role of dopaminergic signaling in voluntary exercise behavior. However, as shown by Saul et al. (2016) in mice, the total dopaminergic pathway is complex and part of a large neurobiological framework. For instance, the neurobiology of dopaminergic reward seeking might be linked to another reward system, the endocannabinoid system, which has long been implicated in exercise (Raichlen et al., 2012; Sparling et al., 2003). In addition, we now know that the single genetic variants influencing

complex traits have a very small effect size and that they may not be picked up by samples comprised of ‘only’ thousands of subjects (Flint, 2013).

Both these problems may be addressed by the more optimal strategy to find genes related to extraversion: a meta-analysis of genome wide association studies (GWAMA) with a large cumulative sample size (Flint, 2013; Visscher et al., 2012). A recent GWAMA for extraversion resulted in only one significant ‘hit’: a non-coding RNA site (LOC101928162) with unknown function (van den Berg et al., 2016). A clear prediction from our work, following the Mendelian Randomization logic is that this hit should also predict voluntary exercise behavior. As indicated, much larger samples than the one employed here are needed to test this as the effect size of this single variant is very modest. To increase power, a polygenic risk score for extraversion – for which GWA meta-analytic summary statistics are available in the public domain (de Moor et al., 2012) – could further be used to predict voluntary exercise behavior. Under the causal hypothesis that extraversion is a *causal driver* of regular exercise behavior this prediction should be significant. However, finding a significant effect would not rule out a genetic pleiotropic effect: in this case multiple genetic variants influence exercise, but independently also extraversion.

Extraversion may also act through more complex routes, e.g. in attitude formation on exercise behavior. Courneya and Hellsten (1998) showed that extraversion was correlated to exercise motives, such as improvement of fitness and health, social contacts, and sheer enjoyment (Courneya & Hellsten, 1998). In Table 8.3 in Chapter 8, the path coefficients between extraversion and perceived benefits ($a_{3,1}$) and ‘lack of skills, support and/or resources’ ($a_{4,1}$), ‘lack of energy’ ($a_{6,1}$), and ‘lack of enjoyment’ ($a_{7,1}$) were significant ($p < .05$), suggesting that a significant amount of this association is explained by genetic factors. The perceived benefits and barriers of exercise behavior form another set of psychological factors that could influence the net affective response to exercise behavior. Individuals who have come to believe that the (long-term) advantages of exercising outweigh the (short-term) disadvantages are more likely to adopt and maintain exercise activities (Becker, 1974). In line with this, many studies reported robust associations between perceived benefits and exercise behavior whereas perceived barriers are as robustly associated with less engagement in exercise behavior (Allender et al., 2006; Hagger et al., 2002; Rhodes & Smith, 2006; Trost et al., 2002). Perceived benefits of exercise behavior are amongst others fitness and health,

social contacts, and enjoyment, whereas lack of opportunity and support, feelings of embarrassment, the lack of energy, or time constraints are part of the perceived barriers of exercise behavior.

Huppertz et al. (2014b) demonstrated moderate to high heritability estimates for the perceived benefits and barriers in adult twins and siblings, with the highest estimates for ‘lack of enjoyment’ (44% to 47%) and ‘lack of skills, support and resources’ (including items such as ‘I do not have anybody to exercise with’ and ‘I do not have the required materials for exercising’, 45% to 48%). Aaltonen et al. (2016) reported comparable heritability estimates for motives for engaging in physical activity in leisure time in adult twins, ranking ‘Enjoyment’ (33% to 53%) and affiliation (‘be with friends and/or do activity with others’, 35% to 39%) as the motive dimensions with the highest heritability. Both studies also report perceived barriers or motive dimensions related to ‘to be fitter and/or look better than others’ or the other side of the spectrum ‘embarrassment’ to be substantial heritable (27 to 49%). Moreover, Huppertz et al. (2014b) revealed that perceived benefits and barriers of exercise may have a causal effect on exercise behavior even in the presence of pleiotropic genetic effects independently influencing exercise motives and barriers and exercise behavior. In Chapter 8, we replicated the heritability estimates for perceived benefits and barriers and showed that they have a substantial genetic overlap with exercise behavior.

Tipping the balance further: exercise ability

Being good at exercise and performing better than others will lead to feelings of competence, whereas lower levels of performance might lead to disappointment or shame. Perceptions of differences in ability will therefore greatly contribute to the affective response to exercise. This might be especially during (late-)adolescence, when the influence of role models in health behaviors is large (DuBois & Silverthorn, 2005; Yancey et al., 2011). Exercise performance level may be influenced by skills specific to a sport, although a number of general fitness characteristics including strength and endurance, are strong predictors of performance across a variety of sports and exercise activities (McArdle, 2009). Chapter 5 and 6 show that both adolescent muscle strength, as well as flexibility, balance and endurance capacity (quantified by $\dot{V}O_{2max}$) are influenced by innate factors. When including the heritability estimates for these traits in meta-analyses, genetic factors explained most of the

variance in vertical jump (62%; $N = 874$), handgrip strength (63%; $N = 4516$) and flexibility (50%; $N = 1130$), $\dot{V}O_{2max}$ (in mL/min 59%; $N = 1088$ and in mL/min/kg 72%; $N = 1004$) in children, adolescents and young adults (age < 30y). However, in our sample we cannot currently determine the exact contribution of the two different components that make up the heritability of physical fitness: genetic factors that contribute to baseline (untrained) physical fitness levels and those related to the extent of the training-induced gains in physical fitness (i.e. genetic factors contributing to 'trainability').

Substantial individual differences exist in trainability, i.e. individuals differ to a great extent in their response to a standardized training protocol. This is in part due to genetic variation. Bouchard demonstrated this effect in families in the HERITAGE Study (Bouchard et al., 1995), by submitting more than 200 families to a 20 week exercise program. Large individual differences in trainability were seen for several performance phenotypes; the training-induced changes in $\dot{V}O_{2max}$, several skeletal muscle phenotypes, resting heart rate, resting blood pressure, and other risk markers for cardiovascular diseases could for a large part be explained by genetics (An et al., 2003; Bouchard et al., 1999; Hong et al., 2000; Perusse et al., 2000; Rice et al., 2002; Rico-Sanz et al., 2003). In our study we could not separately compute heritability for basal ability and trainability as our study used a mixture of sedentary subjects and moderately and vigorous exercisers. Physical fitness in the former will mostly reflect genetics of baseline exercise ability whereas fitness in the two latter groups will reflect a mixture of the genetics of baseline exercise ability and trainability.

So far, identifying the genes involved in either basal exercise ability or trainability has proven difficult (Pitsiladis et al., 2016). Candidate genes studies of muscle strength have focused on insulin-like growth factor- and myostatin-related genes and genes involved in inflammatory factors. Linkage analyses revealed several additional regions of interest in the genome, although individual genes could not be identified as yet (see Thomis and Aerssens, 2012 for a review). One of the most studied polymorphisms is the R577X variation in the *ACTN3* gene. This gene seems to influence the performance of fast skeletal muscle fibers and *ACTN3* XX homozygotes may have modestly lower skeletal muscle strength in comparison with R-allele carriers (Yang et al., 2003). For maximal oxygen uptake, only one GWA study has been conducted to date by Bouchard et al. (2011b). Strikingly, in spite of the small sample size, this study revealed that 16 SNPs accounted for 45% of the variance in gains in $\dot{V}O_{2max}$ after

exposure to a standardized 20-weeks exercise program in a sample of 473 sedentary adults (Bouchard et al., 2011b). No GWA studies have yet been performed on $\dot{V}O_{2max}$ in the untrained or baseline state (before training). It is challenging to collect enough data to be well-powered for gene finding studies as measuring maximal oxygen uptake involves laboratory equipment and a significant amount of time (especially in training studies). This might explain the lack of (well-replicated) findings in this field.

Exercise ability should not only be defined in terms of peak performance capacity but also in terms of being able to withstand potential injuries. A downside of being a fervent exerciser is the increased risk of sports injuries. Of importance is the nature of the injury and the duration of the treatment and discomfort (pain) as well as lost sporting time, school, and working time, and healthcare costs. Environmental risk factors for sports injuries are for example training using incorrect or below-standard sportswear, unmatched opponents in competitive exercise activities, and nutrition (Shanmugam & Maffulli, 2008). However, there is growing evidence that genetic factors are implicated in the susceptibility for sports injuries (Collins & Raleigh, 2009). Especially the *COL1A1* gene, that encodes for the protein type 1 collagen, which is a major component of tendons and ligaments. A SNP upstream of this gene is associated with a decreased risk for acute soft tissue ruptures (Collins et al., 2010). Although the data on sports injuries was not included in this thesis, it might be an interesting addition to ‘exercise ability’ in the model when explaining the heritability of voluntary exercise behavior.

Expanding the model of De Geus & de Moor (2008)

In Chapter 8, we aimed to establish the prospective contribution of personality, perceived benefits and barriers, exercise-induced affective response, and subjective and objective exercise ability to the heritability of voluntary exercise behavior in a sample of adolescents and young adult twins. We hypothesized that the genetic factors contributing to these determinants correlate with the genetic factors that are responsible for the individual variation seen in exercise behavior in adolescents and young adults. We showed that eleven determinants have genetic overlap with exercise behavior. These determinants included the ‘extraversion’ dimension of personality, calmness measured by the Activation-Deactivation checklist after a submaximal exercise test, perceived benefits of exercise and perceived barriers to exercise, and subjective and objective exercise ability. When including these

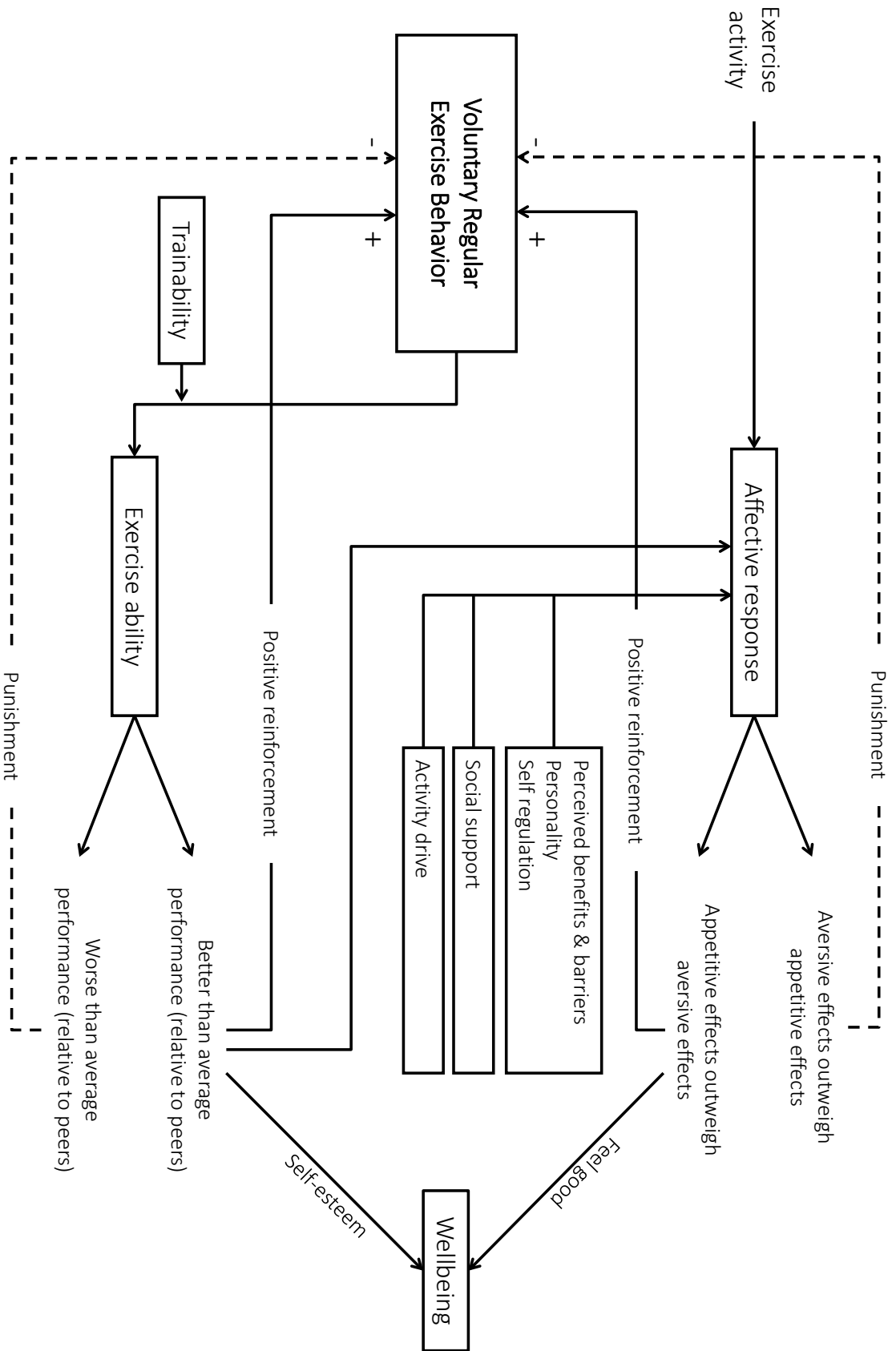


Figure 9.1 An updated model on the heritability of exercise behavior.

determinants in a covariance decomposition model, we showed that all of the covariance of these determinants with exercise behavior at follow-up is due to genetic factors.

These findings allow us to expand the model by De Geus & de Moor (2008). Figure 9.1 shows the expanded model based on the new work in this thesis. The upper part of the extended model consists of the core concept of instrumental conditioning (Hall, 1976) that remains central as it was in the original model. When people engage in regular exercise activities, they are exposed to a combination of acute (during the exercise bout and shortly after) aversive and appetitive effects. The net balance of these effects determines whether the activity will be experienced as rewarding or punishing, and this will strongly contribute to the adoption and maintenance of regular exercise behavior. We add six modulators of the affective response: personality, perceived benefits and barriers, self-regulation, social support, activity drive, and subjective exercise ability. A role for three of these, personality, perceived benefits and barriers and subjective exercise ability, were directly supported by the work in this thesis (Chapter 8).

Self-regulation is the ability to regulate one's emotions, thoughts, and behavior in the face of acute temptations and impulses. It is necessary for regulating one's behavior in order to achieve specific longer term goals (Baumeister et al., 2007). A large body of literature shows that self-regulation, or the related concepts of self-motivation and self-efficacy are correlates of regular exercise behavior (Dishman et al., 2005; MacAuley et al., 1998; Nigg, 2001). According to the model depicted in Figure 9.1, these concepts do so in part by influencing the perception of acute aversive effects. Being able to endure the temporary discomforts of exercise in view of a future reward (e.g. fitness, losing weight, winning the game) or long-term goal (health) is a core characteristic of self-regulation. In addition, the feeling of accomplishment of this self-discipline might tip the balance between aversive and appetite effects even during exercise. The concept of self-regulation is also argued to be shaped by genetic variants (Posner & Rothbart, 2009). Furthermore, including the innate 'activity drive' (Rowland, 1998) in the model, as the fulfillment of which is intrinsically rewarding, is based on a large literature of animal studies. Studies with spontaneous wheel-running inbred mice-strains and selective breeding in mice for high voluntary wheel-running activity resulted in numerous genomic regions that were associated with physical activity in mice (Kelly et al., 2010; Lightfoot et al., 2008; Nehrenberg et al., 2010). This suggests a biological mechanism

that propels the motivation to exercise. Finally, social support is a known factor to be of relevance in any behavioral intervention and exercise is no exception (Dishman et al., 1985; Sallis et al., 2000). As reviewed in Chapter 2, we find that in childhood common environmental factors that are shared by siblings of the same family play a much larger role in exercise behavior than genetic factors and this may largely reflect a positive effect of social support by parents and siblings. In part this effect can be purely instrumental; the parents need to enable the children to partake in sports and exercise activities by providing them sportswear, gear, and arranging transportation. However, family social support can also have a component of encouragement which can act to increase the acute appetitive effects of exercise for the child.

A new factor in the model is the importance of subjective exercise ability, measured as the relative ranking of one exercise performance and skills against peers. Although linked to actual exercise ability, it is possible that this subjective ability is even more important than objective ability in modulating the affective response to exercise. In Chapter 8 we demonstrate for the first time that subjective exercise ability, as expected from the underlying objective exercise ability, is a heritable trait (66%) and genetically associated with exercise behavior. Moreover, it may also explain the genetic association between exercise behavior and mental wellbeing that we reported in Chapter 7. People's beliefs about their capabilities to produce designated levels of exercise performance lead to feelings of competence and mastery. The subjective perception of exercise ability may therefore be an important determinant of exercise-induced increases in self-esteem. Together with the often reported 'feel good' in those exercisers that are characterized by a favorable balance of appetitive and aversive acute psychological effects, self-esteem can cause the increased wellbeing reported by exercisers.

Many potential and complex interactions between all components of the model have currently been left out. For instance, subjective exercise ability, although based on objective exercise ability, could be influenced by personality and social support. The latter may be particularly relevant in younger children who may find it easier to believe their parents about their performance, in spite of evidence to the contrary, based their actual performance. The biology of the activity drive may overlap with that of the extraverted personality and perceived barriers like 'lack of time' may be a function of self-regulatory capacities. While

appreciating these complexities, with the exception of social support, all elements in the model have been shown to be heritable. In keeping with the original model, they remain to be considered part of the intermediate pathways between the genomic level and the behavioral level, and meaningful explanatory variables for the high heritability of regular voluntary exercise behavior.

Remaining tasks

Throughout this thesis, we trustingly labeled the studied traits ‘determinants’, yet reverse causality cannot simply be ruled out. As previously discussed in relation to extraversion, genetic correlation may arise because the genetic variants influencing exercise behavior could become part of the heritability of the so-called determinant if regular exercise itself affects the determinant. Furthermore, a third scenario is that the same genetic variants independently influence the determinant and the tendency to become a regular exerciser. Mixtures of these three causal scenarios may be at play as well, e.g. there may be bidirectional causality in the presence of pleiotropy. Training studies could help resolve causality, but might suffer from selection bias, as they are typically conducted in sedentary individuals (regular exercisers would not show meaningful changes). Twin studies can resolve causality in unselected population-based samples if the sample size is sufficiently large to detect environmental correlations (de Moor et al., 2008), but might be a challenging undertaking for the relatively involved experimental protocol used here. Below 5000 twin pairs, the power to detect a significant environmental correlation between affective responses and exercise behavior is poor (Stubbe & de Geus, 2009). Mendelian Randomization would be a very good alternative strategy to resolve causality as this technique detects causal effects in an unbiased manner (Davey Smith & Hemani, 2014; Lawlor et al., 2008). Fortunately, for some of our determinants, global genome-wide association analyses initiatives exist and a robust (and replicated) set of genetic variants influencing our intended determinants will become available in time.

Future exploration of the genetic mechanisms underlying exercise behavior should also more prominently model possible gene-environment interplay. The effect of an environmental exposure on an individual may depend on his or her genotype. Vice versa the effects of a specific genetic variant may be dependent on the environment. The effect of genetic variants

can be amplified during or after being exposed to specific environmental factors. New previously ‘dormant’ genetic variants may become expressed due to exposure to environmental factors, whereas ‘active’ genetic variants may become suppressed by them. These (heritable) changes in gene expression are also known as epigenetics. Classic twin studies typically assume the gene-environment (GxE) interaction to be negligible, as the design (estimating A, C, and E) cannot discriminate between the main effects of genes and their interaction. When applying the classical twin model, interactions between genetic factors and the shared environment will result in an overestimation of the main effects of genes, whereas interactions between genetic factors and the unique environment will result in an underestimation of the main effects of genes. Fortunately, when (multiple) measures of environmental factors are collected GxE interaction terms can be included in heritability modelling, thereby improving the accuracy of the heritability estimate (Purcell, 2002). Gene-environment interaction can also be incorporated in candidate gene studies (Dick et al., 2015) and even in GWA studies (Thomas, 2010; Winham & Biernacka, 2013).

Implications for intervention on exercise behavior

9 To encourage adolescents and young adults to adopt a physically active lifestyle, the innate individual differences can be used as a starting point. Acknowledgement of the existence of heritable individual differences in the determinants of exercise behavior can suggest that it may be harder to engage some people in exercise than others, but that in no way means that we should stop trying. As opposed to general beliefs regarding the heritability of behavior, heritable traits can still be worthy targets for intervention (Plomin & Haworth, 2010). Many intervention studies for many traits have shown that genetic influences on the variance in a trait do not hamper attempts to favorably change the mean population level of the trait. Even if genetic factors are still a main cause of remaining variation around the increased post-intervention mean.

Understanding the genetic pathways that lead to differences in voluntary exercise behavior may help identify specific biological and psychological determinants that would be solid targets for intervention. Individuals may experience rather different ‘gains’ when exercising. Favorable genetic profiles may for instance cause a larger sensitivity to the rewarding or a smaller sensitivity to the punishing effects of broad classes of activities, including exercise. For

some individuals, 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. For others, the aversive effects of exercise, at least in the forms that they tried so far, may greatly overwhelm the rewarding effects, may elicit feelings of punishment and cause the individual to drop-out. The latter individuals might benefit more from an individualized exercise intervention, in which the appetitive aspects for that specific individual should be emphasized and the aversive aspects reduced as much as possible. To optimize the appetitive aspects of exercising that are specific to that individual and generating realistic person-specific goals, different genotypes may require entirely different exercise programs.

Final remarks

The large individual differences in regular voluntary exercise behavior in late-adolescents and young adults are for a large part due to genetic factors. This thesis aimed to unravel the genetic components of this healthy behavior by studying its genetic association with known correlates and determinants. Increased understanding of the individual differences in voluntary exercise behavior is a necessary step to innovate and invigorate public health programs aimed at exercise behavior change. Focusing on the population *variation* and increasing the appetitive aspects of exercising that are specific to an individual by generating realistic person-specific goals will, in the end, increase overall exercise behavior in adolescents and young adults.