Unraveling the genetic components of voluntary exercise behavior in adolescents and young adults

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CHAPTER 1

GENERAL INTRODUCTION

Humans have been physically active since the beginning of their existence to provide for themselves and their offspring. Contributing to activities such as hunting and gathering was not so much a choice as it was essential for the survival of the group. Although there might be individual differences in how they spent their evenings; relaxing by the fire, dancing, or chewing on mind-altering substances, in the morning every individual had to pick up their daily, physically demanding activities. As centuries passed, humans invented many tricks and tools to make their lives easier and less labor intensive. In addition, more spare time became available to focus on other interests beyond mere survival and pursue other activities (i.e. hobbies) in order to fuel feelings of enjoyment. These developments made being physically active not a requisite for survival of the group, but an individual choice.

Nowadays, large individual differences are observed in the population at large regarding the amount of time spent on physical activity. These individual differences are not without consequence. In industrial countries physical *in*activity is an important contributor to non-communicable diseases (Lee et al., 2012), while moderate to vigorous intensity physical activity has been shown to have a large protective effect on mortality (Samitz et al., 2011). 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)). In view of the obvious advantage of a physically active lifestyle, the question arises why some individuals choose to regularly engage in physical activity, while others do not, consequently referred to as 'couch potatoes'.

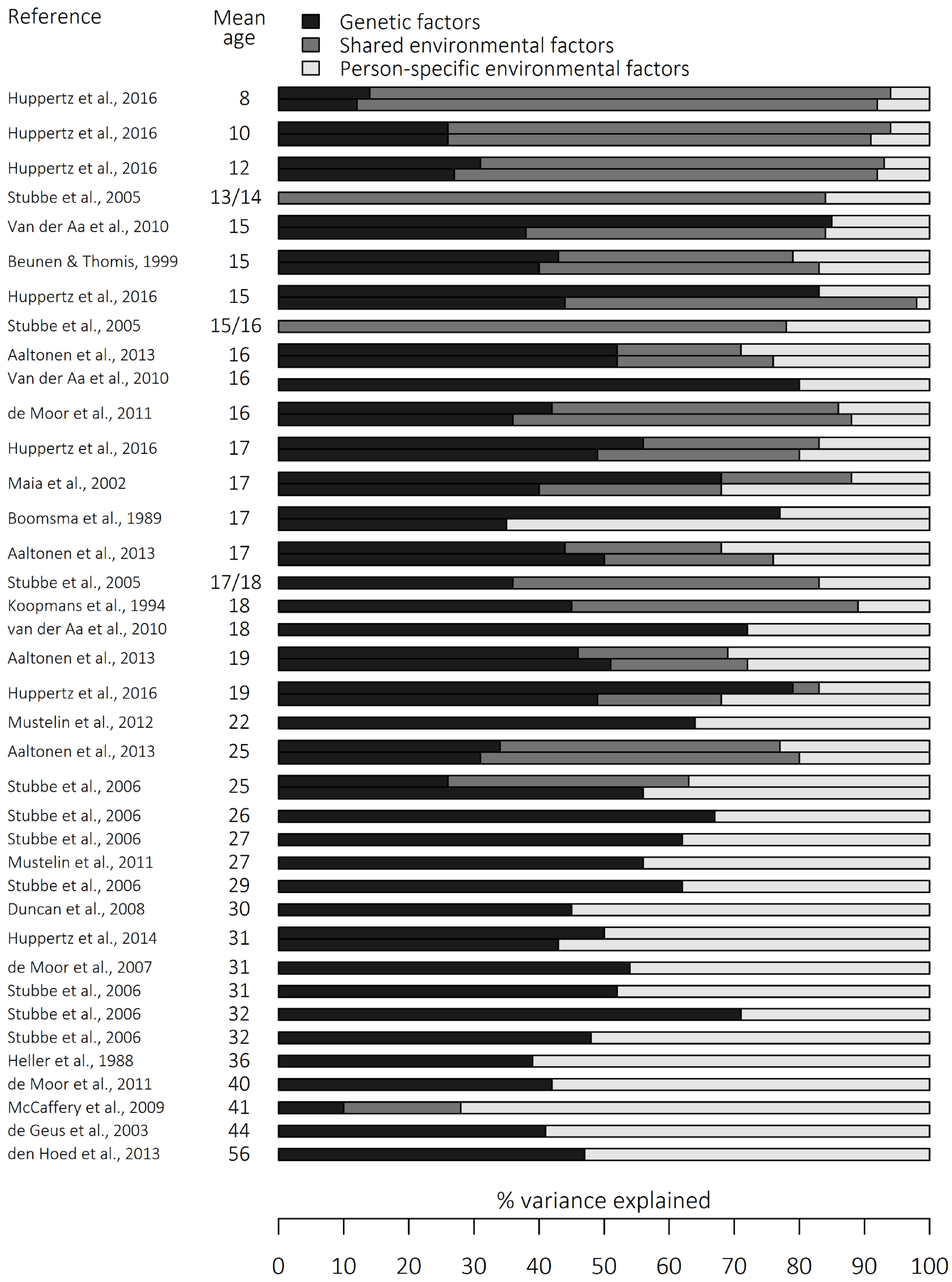
Correlates and determinants of a physically active lifestyle have been studied intensively over the past three decades as mapping the determinants of health behaviors is crucial for defining targets of intervention. Over 30 years ago, Dishman and colleagues stated that *'one barrier to developing effective methods to encourage physical activity (…) is the lack of knowledge of the determinants of regular physical activity'* (Dishman et al., 1985). In the following years, researchers have identified numerous potential determinants in cross-sectional or longitudinal studies that to a greater or lesser extent contribute to the maintenance of physical activity. Although physical activity encompasses a broad domain of activities at work, at home and during transportation, the emphasis of many studies has been on voluntary exercise behavior in leisure time. Exercise behavior is rapidly becoming the major source of moderate-to-vigorous activity in many industrialized countries. A large body of studies has addressed various environmental and social factors as determinants of exercise behavior, for example low socioeconomic status, high job strain, health beliefs, access to sport facilities, and support by peers and family (Bergstrom et al., 1996; Dishman et al., 1985; Drenowatz et al., 2010; Haase et al., 2004; Matson-Koffman et al., 2005; Payne et al., 2005; Sallis et al., 2000; Varo et al., 2003). However, when environmental circumstances are identical for a specific population, individuals still differ in exercise status. Starting in the 1980s, twin and family studies have provided evidence that a substantial part of the variation in exercise behavior is determined by genetic predisposition.

TWIN STUDIES

Twin and family studies have been paramount in understanding the genetic architecture of complex traits (Polderman et al., 2015). Children often resemble their parents regarding exercise status (de Moor et al., 2011; Seabra et al., 2014). To separate genetic effects (the heritability) from other factors that are shared by family members (i.e. upbringing, neighborhood), the classical twin design exploits the known differences in genetic similarity in identical and non-identical twins (or siblings). Genetically identical twins or monozygotic (MZ) twins are the result of the division of a single fertilized egg during an early stage in embryonic development, and non-identical twins or dizygotic (DZ) twins result from two separate fertilized eggs. Consequently, MZ twins are genetically identical and the observed difference between the twins is due to person-specific environmental factors: experiences that one of the twins has and the co-twin does not. Dizygotic twins share on average 50% of their genetic make-up. Consequently, the observed differences between the twins are a result of genetic differences and person-specific environmental factors. If MZ-resemblance for the trait of interest is higher than DZ-resemblance, it constitutes evidence for genetic influences on the trait (the classical twin model).

Figure 1.1 shows the relative importance of genetic factors on exercise behavior (measured using surveys) across the lifespan. These heritability estimates vary widely (from 0% up to 85%). A large part of this variation is due to the age of the subjects; the genetic architecture of exercise behavior is different over age. Up to 14 years of age, the heritability estimates are moderate (Huppertz et al., 2016; Stubbe et al., 2005). The notion that environmental factors play a greater role in childhood than in adolescence can be explained by the important role of the parents; they provide children with the opportunity to become active by means of transportation to exercise activities, give exercise activities priority over other leisure time activities, and provide motivation and encouragement to exercise (Huppertz et al., 2016; Stubbe et al., 2005). After the age of 14, an increase is observed in heritability estimates, with consistently moderate to high estimates at the ages of 16 and 17 (Aaltonen et al., 2013; Boomsma et al., 1989; de Moor et al., 2011; Huppertz et al., 2016; Maia et al., 2002; Stubbe et al., 2005; van der Aa et al., 2010), continuing into young adulthood (Aaltonen et al., 2013; de Geus et al., 2003; de Moor et al., 2007; den Hoed et al., 2013; Duncan et al., 2008; Heller et al., 1988; Huppertz et al., 2014b; Huppertz et al., 2016; Koopmans et al., 1994; McCaffery et al., 2009; Mustelin et al., 2011; Mustelin et al., 2012; Stubbe et al., 2006; van der Aa et al., 2010). To provide a comprehensive overview of current literature, **Chapter 2** reviews published studies on the heritability of exercise behavior (and physical activity) and shows in a meta-analysis in different age groups the sample size weighted heritability estimate for exercise behavior.

Figure 1.1 Summary of previous published studies on the relative influence of genetic factors, shared environmental influences and person-specific environmental influences on voluntary exercise behavior in across the lifespan. When two bars per studies are displayed, the first bar represents the results for males; the second bar represents the results for females.


Reference
Mean age
Genetic factors
Shared environmental factors
Person-specific environmental factors
Huppertz et al., 2016 8
Huppertz et al., 2016 10
Huppertz et al., 2016 12
Stubbe et al., 2005 13/14
Van der Aa et al., 2010 15
Beunen & Thomis, 1999 15
Huppertz et al., 2016 15
Stubbe et al., 2005 15/16
Aaltonen et al., 2013 16
Van der Aa et al., 2010 16
de Moor et al., 2011 16
Huppertz et al., 2016 17
Maia et al., 2002 17
Boomsma et al., 1989 17
Aaltonen et al., 2013 17
Stubbe et al., 2005 17/18
Koopmans et al., 1994 18
van der Aa et al., 2010 18
Aaltonen et al., 2013 19
Huppertz et al., 2016 19
Mustelin et al., 2012 22
Aaltonen et al., 2013 25
Stubbe et al., 2006 25
Stubbe et al., 2006 26
Stubbe et al., 2006 27
Mustelin et al., 2011 27
Stubbe et al., 2006 29
Duncan et al., 2008 30
Huppertz et al., 2014 31
de Moor et al., 2007 31
Stubbe et al., 2006 31
Stubbe et al., 2006 32
Stubbe et al., 2006 32
Heller et al., 1988 36
de Moor et al., 2011 40
McCaffery et al., 2009 41
de Geus et al., 2003 44
den Hoed et al., 2013 56
% variance explained
0 10 20 30 40 50 60 70 80 90 100

A MODEL TO EXPLAIN DIFFERENCES IN VOLUNTARY EXERCISE BEHAVIOR

In order to identify the mechanisms that give rise to the heritability of exercise behavior, De Geus & de Moor (2008) proposed a model in which the maintenance of exercise behavior is, based on the principles of instrumental conditioning, determined by the positive reinforcement or feelings of punishment (Figure 1.2). This model focuses on the genetic modulation of acute affective responses to exercise and longer-term effects on self-esteem through genetic effects on exercise ability.

The aim of this thesis is to put this model to use in an effort to explain the heritability of exercise behavior in adolescents and young adults. The likelihood of engaging in or maintaining exercise behavior might increase by the presence of genetic variants that amplify the feelings of pleasure, performance, or sense of accomplishment.

To this end, a laboratory study was set up. Over 200 adolescent twin pairs and their siblings were selected from the Netherlands Twin Register (van Beijsterveldt et al., 2013) and invited to participate. The experimental design included assessment of their exercise ability (aerobic fitness and muscle strength) and the affective response to various types of exercise on a treadmill and cycle ergometer. At the end of the session a maximal exercise test was performed. Details on the experimental protocol can be found in **Chapter 3**.

ZOOMING IN ON THE MODEL

In accordance with the Hedonic theory, which suggests that individuals repeat behavior regularly when it makes them feel good; a positive affective response to exercise will make a person more likely to repeat this activity, whereas repeated negative affective responses will lead to discontinuation of the behavior. Individuals for whom the net rewarding effects are dominant will repeat the behavior and become regular lifetime exercisers, whereas individuals that experience aversive effects of exercise might drop out of an exercise program (upper part Figure 1.2). 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. In contrast to the persistent general belief that exercise is enjoyable for everyone, strong individual differences are found in the affective responses during and after exercise. Some individuals report an increase in pleasure or no change and others report reduced pleasure (Ekkekakis et al., 2005; Ekkekakis et al., 2011; Van Landluyt et al., 2000; Welch et al., 2007). De Geus & de Moor (2008) have hypothesized that these individual differences in part reflect differences in genetic sensitivity to the psychological effects of exercise. In **Chapter 4** the heritability of the affective responses during and after an exercise bout was estimated for the first time.

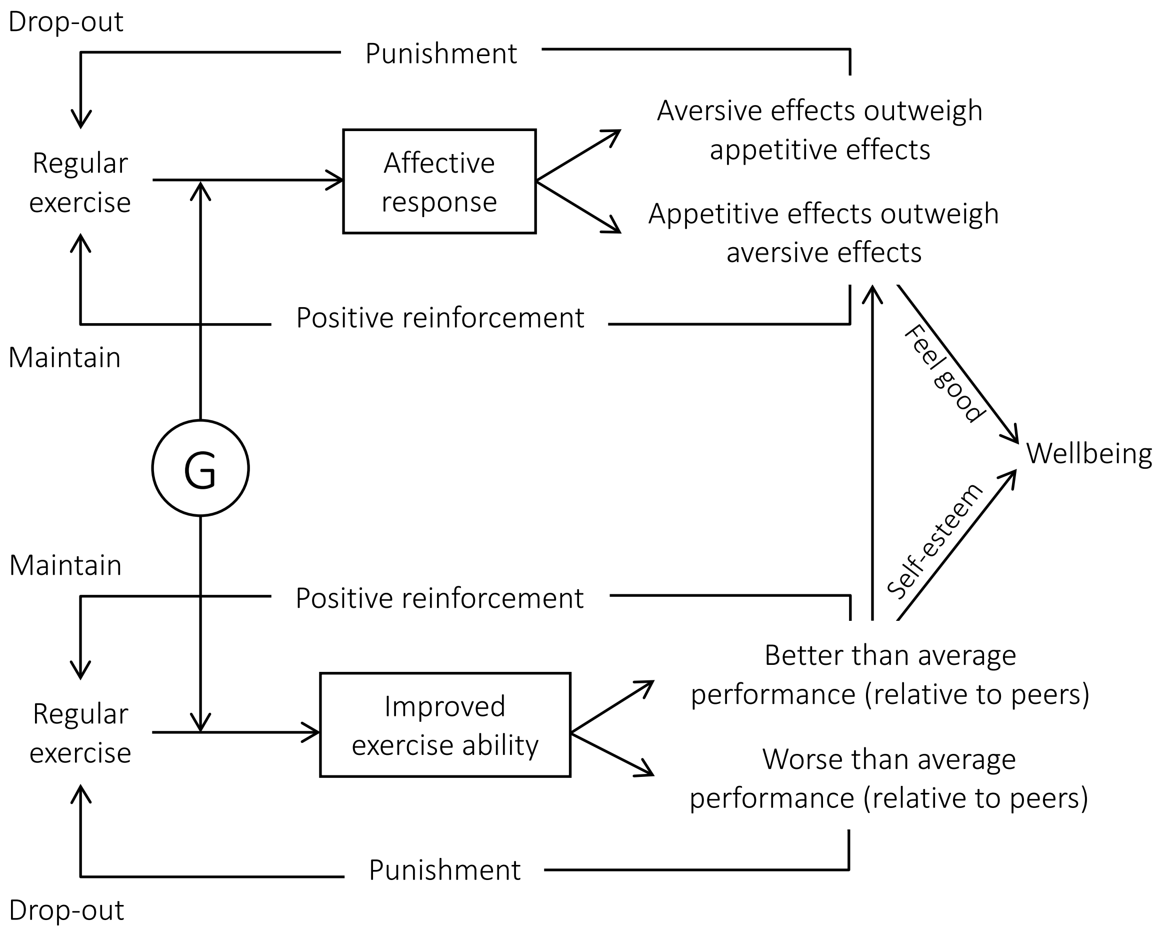


Figure 1.2 Model on the heritability of exercise behavior (de Geus & de Moor, 2008). G = Genes.

A second contributor to the net appetitive effects of exercise might be the improvement of exercise ability induced by regular exercise (lower part Figure 1.2). These improvements will not be the same for everyone and depend on trainability. This may impact on the appetitive effect of regular exercise. When an individual finds himself outperforming others, or gaining more rapidly than peers when exposed to comparable training regimes, this will lead to feelings of competence. Lower levels of performance and trainability might lead to disappointment or shame (particularly when the exercise is performed in a competitive context). This may be a strong factor in adolescence, when the sensitivity to one's own relative ranking among peers may be largest. Evidence for genetic influences on exercise ability and trainability is provided by many studies, for example the HERITAGE study (Bouchard et al., 1995). This and other studies provided evidence for genetic influences on cardiorespiratory fitness, muscle strength, balance, and flexibility. However, heritability estimates vary across samples and estimates for adolescents are not always available. To replicate and expand the literature on the genetic architecture of physical fitness components, we estimated the heritability of muscle strength measures (vertical jump and handgrip strength), balance, and flexibility in a large sample of adolescent twins and their siblings in **Chapter 5**. These estimates were incorporated in a meta-analysis on the heritability of muscle strength, flexibility and balance. In addition, **Chapter 6** reports on the heritability of $\dot{V}O_{2max}$ in adolescents and to arrive at a robust estimate for the heritability of $\dot{V}O_{2max}$ in children to young adults, a sample size weighted meta-analysis was performed on all extant twin and sibling studies in adolescents and young adults.

Regular exercise is argued to be effective in reducing anxious and depressive symptoms and several meta-analyses indicate that exercise has an antidepressant effect in clinical populations. However, it is difficult to rule out that these findings can be explained by underlying (genetic) factors influencing both exercise behavior at one time point and influence symptoms of anxiety and depression at a later time point (a phenomenon also known as genetic pleiotropy). Earlier, Bartels et al. (2008) and De Moor et al. (2011) showed that in population-based twin studies the nature of the association between exercise and anxious-depressive symptoms is best explained by correlated genetic effects on these two traits. **Chapter 7** shows that the model by De Moor & De Geus (2008) accommodates this genetic correlation while still allowing exercise to causally increase wellbeing in specific subgroups of the population.

EXPANDING THE MODEL

The sports psychology literature has provided us with other factors that are also robustly correlated with regular exercise behavior, such as personality (Allender et al., 2006; de Moor et al., 2006; Hoyt et al., 2009; Rhodes & Smith, 2006) and perceived benefits and barriers (Allender et al., 2006; Hagger et al., 2002; Rhodes et al., 2009). Personality might influence the complex balance of appetitive and aversive effects induced by exercising. Regular exercisers score lower on neuroticism and higher on extraversion, conscientiousness, and sensation seeking. Furthermore, a positive attitude towards exercise and, consequently, the likelihood of maintaining exercise behavior increases when an individual perceives that the benefits of exercise outweigh the disadvantages. As these factors are proven to be heritable as well, they might all contribute to the heritability of voluntary exercise behavior in adolescents and young adults. **Chapter 8** incorporates these factors in the model of De Geus & de Moor (2008).

Finally, **Chapter 9** provides a summary of the main findings. In addition, we discuss these findings in a broader context. Attention to innate characteristics and biological mechanisms in the research on determinants of exercise behavior will provide new insights into how to best shape interventions. The results could allow for more stratified or personalized approaches that exploit genetic variation influencing exercise behavior in interventional strategies.