

Matthijs Daniël van der Zee

Molecular and behavioral genetic investigation of voluntary exercise behaviors



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OF VOLUNTARY EXERCISE BEHAVIORS**

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CHAPTER

Introduction

Throughout our evolutionary history, humans lived in a physically demanding environment. Hunting, gathering and the constant threat of predators caused genes in humans to be specifically selected to cope with this environment causing most of our biological systems to function optimally in high physically active environments (Booth et al., 2008). Since the industrial era many technological advancements for both home- and work-environments have continuously decreased the necessity of physical activity. This has had the benefit of reducing physical hardships on workers, and substantially reducing the amount of disabilities caused by heavy labor demanding jobs. Unfortunately, however, these beneficial aspects are mirrored by detrimental effects. Nowadays, physical activity is considered a well-established major contributor to both physical and mental health (Bauman et al., 2016; Berlin & Colditz, 1990; de Geus, 2020; Ekelund et al., 2015; Fishman et al., 2016; Garber et al., 2011; Janssen & Leblanc, 2010; Lee et al., 2012; Morris et al., 1980; Samitz et al., 2011; Zhu et al., 2016) with an estimated economic burden of \$53.8 billion worldwide (Ding et al., 2016). Despite many public health recommendations (Haskell et al., 2007; Kohl et al., 2012; "Physical Activity Guidelines for Americans," ; World Health Organization, 2013) and calls for worldwide governmental policy changes (Kohl et al., 2012), a large proportion of the population still does not engage in enough physical activity for optimal health-benefits, regardless of which guidelines are used (Ekelund et al., 2016; Hallal et al., 2012; Lee et al., 2012; World Health Organization, 2014). Moreover, it has recently been suggested that the population of high-income countries spends the majority of awake time being physically inactive (Hansen et al., 2012; Matthews et al., 2008).

The broadly defined physical activity has proven difficult to measure reliably through self-report (Prince et al., 2008). More reliable objective alternatives, such as accelerometers, on the other hand are

less viable options for large-scale population-based studies. An important component of physical activity, for both research and public health in general, is voluntary regular exercise behavior, such as jogging, swimming or going to a gym. Measuring voluntary regular exercise through self-report has proven to be more reliable than overall physical activity (de Moor et al., 2008; Haase et al., 2004; Stubbe et al., 2006; Stubbe et al., 2007). Additionally, voluntary regular exercise behavior has been shown to be a highly stable trait (van der Zee, van der Mee, et al., 2019). On top of that, whilst overall physical activity can be highly dependent on environmental factors that may be difficult to change (e.g. physical labor, walkability, and the distance from home to work), there is less dependence of regular exercise behavior on these factors, thus making regular exercise behavior a more feasible target for behavioral intervention.

In order to develop (more) effective interventions more knowledge of the determinants of the behavior are required (Dishman et al., 1985). These determinants can have different sources. For instance, many studies have assessed environmental determinants such as access to facilities (Matson-Koffman et al., 2005), socio-economic status (Haase et al., 2004; Varo et al., 2003), job strain (Payne et al., 2005), or social support (Sherwood & Jeffery, 2000). Apart from, and in addition to the environment, determinants of exercise behavior can also be genetic, either influencing exercise behavior directly such as through endurance capacity (de Geus, 2020; de Geus & de Moor, 2008; Schutte et al., 2019), or indirectly through intrapersonal traits such as personality (H. J. Eysenck et al., 1982) or subjective benefits and barriers to exercise (Schutte et al., 2019). Another possible biological determinant would be epigenetic effects (non-permanent changes to DNA that can alter gene expression), which, similar to genetic effects, can influence exercise behaviour directly or indirectly. Unlike genetic effects, the causal direction between epigenetic changes and exercise

behaviour is more complex, as epigenetic change can causally influence exercise behaviour (either directly or indirectly), but exercise behaviour may also induce epigenetic changes (either directly or indirectly).

With a growing number of scientific studies into the contribution of genetic factors to variation in regular exercise behavior it has become increasingly clear that genetic factors are an important determinant for this behavior (Bartels et al., 2012; de Geus et al., 2003; de Moor, Stubbe, et al., 2007; den Hoed et al., 2013; Huppertz et al., 2012; Mustelin et al., 2009; Stubbe et al., 2006; van der Zee et al., 2020). Despite this large contribution of genetic factors to the variance in regular exercise behavior, finding molecular genetic variants that have a significant effect has proven to be a difficult endeavor. Some genetic variants have been identified through candidate gene studies (Berentzen et al., 2008; Cole et al., 2010; Fuentes et al., 2002; Gielen et al., 2014; Hubáček et al., 2011; Huppertz, Bartels, Groen-Blokhuis, et al., 2014; Jozkow et al., 2013; Kostrzewa et al., 2015; Loos et al., 2005; Lorentzon et al., 2001; Mäestu et al., 2013; Murakami et al., 2011; Richert et al., 2007; Simonen, Rankinen, Pérusse, et al., 2003; Stefan et al., 2002; van der Mee et al., 2017; Wilkinson et al., 2013; Winnicki et al., 2004) but only a handful of these have been independently replicated, and only a small number of genome-wide association studies have been performed (de Moor et al., 2009; Doherty et al., 2018; Kim et al., 2014; Klimentidis et al., 2018; Lin et al., 2018), with even fewer producing significant results. In this thesis several methods will be described and applied to further our understanding of the genetic etiology of voluntary regular exercise behavior.

Voluntary regular exercise behavior in the Netherland Twin Register

The Netherlands Twin Register (NTR) is an ongoing research initiative where twins, their relatives, and their partners volunteer to complete extensive surveys every two to three years. A detailed description of methods and procedures used for data collection in the NTR is provided elsewhere (Ligthart et al., 2019). Throughout the years the same questions on regular exercise behavior were included in most of these surveys, which has led to a total of 162,286 observations of voluntary regular exercise behavior by 78,525 unique individuals. To assess voluntary regular exercise behavior participants were first asked whether they regularly exercise ('yes' or 'no'), if affirmative they were asked a number of follow up questions. They were asked to list all exercise activities they regularly did, and per activity they were asked (1) for how many years they have been doing so, (2) how many months a year (on average) they do this activity, (3) the weekly frequency, and (4) the average duration of each exercise bout. The definition of voluntary regular exercise behavior adhered to throughout this thesis does not include the following activities: non-physical sports such as chess, seasonal activities such as skiing during a winter holiday (i.e. any activity that is performed less than 6 months a year), irregular activities performed less than once a week, non-voluntary activities such as physical education, biking as a form of transportation, and any activity as a result of physical labor. Throughout my thesis these activities were treated the same as no exercise.

The most common way to summarize this information into a single variable is by first assigning each exercise activity the age-appropriate Metabolic Equivalent of Task (MET) score (Ainsworth et al., 2011; Ridley et al., 2008). This MET value is the ratio of energy expenditure rate during an exercise activity compared to sitting at rest (1 MET). An activity with a higher MET score indicates greater rate of

energy expenditure. Then by multiplying this MET score with the weekly frequency and average duration per exercise activity a single value of MET-minutes (or MET-hours) per week is obtained per activity. Finally these values are summed across all activities performed by an individual to obtain a single total MET-minutes per week (METmin/wk) value for that individual.

This total value, however, is still a broad definition of exercise behavior, as it includes all activities, which as described previously may yield less reliable results compared to a more homogenous and narrow definition, especially in genetic association studies (N. Cai et al., 2020). Ideally, instead of taking the total value, we would study each different type of exercise as a separate outcome. However, doing so would dilute any sample size too much, as even the most endorsed activities only occur in about a quarter of the regular exercisers at best. Alternatively, exercise can be separated into several different dimensions. One of these dimensions is team-based exercise, which includes the activities where a group of individuals have to cooperate towards common objectives; the other end of this dimension is solitary exercise where the activity is performed by a single exerciser. Another is competitive exercise, which includes activities where an exerciser or a group of exercisers compete against another exerciser or group of exercisers for victory. Lastly externally paced exercise includes activities where the rate of performing that activity is determined by external factors (such as other exercisers in basketball, or a changing environment in windsurfing), whereas internally paced exercise includes activities where the rate of performing the exercise is solely determined by the exerciser.

In **Chapter 2** of this thesis I leveraged the unique dataset provided by the NTR to assess the longitudinal stability of total exercise, and the exercise domains separately. This chapter also includes a more detailed description of the definitions of exercise and

its domains in the NTR, as well as extensive descriptive statistics of total exercise and the exercise domains. Furthermore, the exercise domains were also used in later chapters where different genetically informed designs were used.

Twin-, family and extended family-study designs

Exercise behavior, like many other behavioral traits 'runs in the family'. Within any given family the odds of an individual being an exerciser increases if other family members are also exercisers. This resemblance can, as alluded to earlier, be due to environmental factors (sometimes referred to as 'nurture') or genetic factors (sometimes referred to as 'nature'). By analyzing monozygotic (MZ) and dizygotic (DZ) twins we can disentangle the relative influence of environmental and genetic variation on a given trait. In the classical twin model we leverage the knowledge that MZ twins share (close to) all their inherited genetic variants, whereas dizygotic twins share half of their inherited genotypes on average (Falconer & Mackay, 1996; Plomin et al., 2013). In the classical twin model the relative impact of three of four possible sources of variance can be estimated. First, additive genetic factors (A) that represent the sum of linear effects of genetic variants that influence a given trait. Second, unique environmental factors (E) that represent environmental factors unique to any single individual, such as different lifestyles, or life events, and includes measurement error. Third shared environmental factors (C) which represent environmental factors shared within a family, such as parenting, socio-economic status, and in the case of twins the prenatal environment. Lastly, non-additive genetic factors (D), which represent non-linear effects of genetic variants, such as dominance effects, or interaction effects (Plomin et al., 2013). Since MZ twins share all factors included in A, all factors in C, and all factors in D, any difference between MZ twins can only be ascribed to unique environmental factors. However, since

DZ twins only share half of the factors included in A on average, if MZ resemblance is higher when compared to DZ resemblance, this is indicative of additive genetic factors being a determinant for the trait.

Due to the limited number of available correlations and covariances in a classical twin study, only three of these four factors can be tested simultaneously. But this issue can be overcome by including multiple different family-members. Parents of twins for example, share half of their additive genetic factors with their offspring, as well as their shared environment, but none of their non-additive genetic factors. Biological aunts and uncles share a quarter of their additive-genetic factors with their nieces and nephews, but none of their shared environmental factors. Including such extended pedigree-data with more variation in shared A, C, D, and E factors makes it possible to take all four factors into account simultaneously (Keller et al., 2009).

In **Chapters 3 and 4** of this thesis I describe twin and family-models in more detail and how these designs can elucidate the genetic effects of voluntary regular exercise behavior. Additionally **Chapter 3** of this thesis provides an overview and meta-analysis of twin-studies on voluntary regular exercise behavior, as well as other related physical activity phenotypes such as moderate-to-vigorous physical activity. **Chapter 4** of this thesis not only describes twin-studies, but also includes an overview of family-studies on regular exercise behavior. In **Chapter 5**, I present the results of our extended-family study on regular exercise behavior, and the six exercise domains. In **Chapter 5** I also explore the various sources of spousal resemblance in exercise behavior.

Genome-wide association studies (GWAS)

As mentioned previously, finding genetic variants related to exercise behavior has proven to be challenging. A reason for this might

well be that, like many other complex behavioral traits, genetic variants contributing to exercise behavior are likely widespread across the genome, all with very small effect sizes (Buniello et al., 2019). Moreover, the pathways through which these variants affect exercise behavior may also vary wildly. Some may affect exercise through the brain, some may affect exercise through pathways related to muscle- or bone-development, others through metabolism, or blood-composition. Some genetic variants have been identified through candidate-gene studies (Berentzen et al., 2008; Cole et al., 2010; Fuentes et al., 2002; Gielen et al., 2014; Hubáček et al., 2011; Huppertz, Bartels, Groen-Blokhuis, et al., 2014; Jozkow et al., 2013; Kostrzewa et al., 2015; Loos et al., 2005; Lorentzon et al., 2001; Mäestu et al., 2013; Murakami et al., 2011; Richert et al., 2007; Simonen, Rankinen, Pérusse, et al., 2003; Stefan et al., 2002; van der Mee et al., 2017; Wilkinson et al., 2013; Winnicki et al., 2004), where exercise behavior is tested for association with one (or a few) genetic variants. Unfortunately, replication for these variants that show significant association is minimal. A better alternative to detect the many genetic variants likely influencing exercise compared to these candidate-gene approach would be a genome-wide association study (GWAS). In a GWAS millions of single nucleotide polymorphisms (SNPs) spread across the human genome are tested for their effect on a given trait simultaneously (Claussnitzer et al., 2020; Visscher et al., 2012; Visscher et al., 2017). By testing a wide range of SNPs known to vary between humans, GWAS studies are free from selection of genetic variants based on previous knowledge, and often yield results related to genes that would not have been selected based on prior knowledge. The downside of GWAS is that stringent statistical corrections are applied due to the millions of tests performed simultaneously. Due to these corrections, and the expected small effect sizes of individual variants, the sample sizes required for a GWAS are much larger than conventional studies.

Two GWASs have been published before the beginning of my PhD project (de Moor et al., 2009; Kim et al., 2014), both of which did not yield results that withstand the scrutiny of the multiple testing correction (p -value below 5×10^{-8}). During the creation of my thesis three more GWAS studies have been published, one of which did not yield significant results (Lin et al., 2018), whereas the other two produced the first genome-wide significant genetic variants for exercise behavior (Hara et al., 2018; Klimentidis et al., 2018).

In **Chapter 6** of this thesis I present the results of a GWAS on total volume of exercise behavior, and the six exercise domains described earlier. This chapter also includes a more detailed description of previously published GWAS and candidate-gene studies.

Post-GWAS: Polygenic Scores and Mendelian Randomization

The results of GWA studies can in turn be used for a number of different methods, the most common of which is the polygenic score (PGS), sometimes also referred to as polygenic risk score (L. E. Duncan et al., 2019; Slunecka et al., 2021). The results of a GWAS include effect-sizes, often as regression coefficients, for each genetic variant, related to a specific allele of that genetic variant. These estimates indicate a predicted change in the outcome trait per copy of the associated allele an individual has. In other words, a positive estimate results in a predicted increase in volume of exercise behavior for each copy of the associated allele an individual has. By multiplying the estimates from a GWAS by the number of effect alleles per variant, and summing these estimates for all variants a polygenic score is obtained for each individual, which represents the sum of the predicted genetic effects on that individual's exercise behavior. It is important to note that when these scores are intended to be used for any kind of prediction the

sample used for the GWAS should be a different sample than the sample in which the PGS is generated in order to prevent bias.

By leveraging the information provided by genetic information from GWAS and PGS, Mendelian Randomization (MR) can be used to test causality in an observational epidemiological setting (Davey Smith & Ebrahim, 2003). Briefly, MR is based on Mendel's second law (Bateson & Mendel, 2013), the law of random assortment, which states that the inheritance for one trait is independent of the inheritance of another trait. Because of this, if a subject is genetically more liable for trait A, and trait A causes trait B, in an epidemiological study the group with higher susceptibility for trait A will also have an increase in trait B. Note this does assume that at the very least trait A has some genetic basis, and if a genetic proxy is used for trait A it needs to explain a significant portion of the variance in the trait, put otherwise it must be a strong genetic instrument. For most complex behavioral traits, influenced by many genes of small effect, only a PGS may qualify as a strong instrument. However, one of the key assumptions of MR is that of no pleiotropy, i.e. genes that cause trait A exclusively influence trait B through their causal effect on trait A. This assumption is not likely to hold for polygenic scores (Solovieff et al., 2013; Visscher & Yang, 2016). By using twin-data in conjunction with MR this assumption can be relaxed and pleiotropy directly estimated (Minică et al., 2018), also controlling for assortment (i.e. choosing a partner based on their similar exercise behavior) and dynastic effects (i.e. direct effects of parental genotype on the offspring phenotype) (Minică et al., 2020).

In **Chapter 7** of this thesis I use Mendelian Randomization with a PGS, in conjunction with a number of other methods to assess possible causal effects of the 'Big Five' personality dimensions (Digman, 1990) on voluntary exercise behavior, both total volume and the two main dimensions of competitive team-based exercise activities and non-competitive solitary exercise activities.

Finally, in **Chapter 8** the main results and conclusions of the chapters contained in this thesis are summarized. Also in this chapter I will discuss my perspective on the future development of genetic etiology of regular exercise behavior and possible implications.



CHAPTER

Tracking of Voluntary Exercise Behaviour over the Lifespan

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Abstract

Background

The aim of many physical activity interventions is to develop life-long habits of regular exercise and sports activities in leisure time. Previous studies that assessed tracking (i.e., the stability of a trait or behavior over the lifespan) of leisure time exercise behavior across various parts of the life span have treated it as a uniform construct by summing all types of leisure time exercise activities into a single summary score for the total volume of exercise. This study provides new insight by additionally determining tracking across leisure time exercise activities in six different domains: (1) team-based versus solitary activities, (2) competitive versus non-competitive activities, and (3) externally paced versus internally paced activities. We also assessed which of the domains of exercise activities best predicted total volume of exercise at follow-up.

Methods

A large dataset ($N = 43,889$) from the Netherlands Twin Register (NTR) was used to analyze the tracking of exercise behavior over time. Using this dataset, we were able to examine tracking as a function of baseline age (8 to 80 years) and tracking duration (2 to 22-year follow-up), taking into account sex differences, using generalized estimating equations.

Results

Two-year tracking coefficients are moderate to high for total volume of exercise across ages at baseline, ranging from .38 to .77 with a median of .57. Tracking coefficients tend to decrease as the distance to follow-up increases, down to a median of .38 for the 22-year tracking coefficients. The patterns of tracking were largely domain-

independent and were largely similar for solitary, competitive, non-competitive, externally and internally paced activities. With the exception of team-based activities, tracking was seen to increase as a function of baseline age. Cross-domain tracking did not favor any specific domain of exercise activity as the best predictor for total volume of exercise behavior and this was true at all baseline ages.

Conclusion

We conclude that exercise behavior is moderately to highly stable across the life span. In particular in adulthood, where the tracking of exercise mimics that of a classical behavioral trait like personality. This stability reinforces existing evidence that exercise habits are hard to change, but at the same time suggests that successful intervention leading to the adoption of exercise habits will tend to last.

Background

In our evolutionary history, the physically demanding environment caused genes in humans to be specifically selected to cope with high levels of physical activity. This resulted in human physiology in which most systems (e.g. metabolic and cardio-vascular) do not function optimally unless regularly engaged by sufficient physical activity (Booth et al., 2008). However, technological advancements, made since the industrial era, have continually decreased the necessity of physical activity, both in work- and home-environments. This has drastically reduced physical hardships of workers as well as the amount of disabilities caused by jobs that demand heavy labor, but unfortunately these beneficial aspects of lower levels of physical activity are mirrored by detrimental effects on the risk for chronic non-communicable diseases. Physical inactivity is considered a well-established risk factor for cardiovascular disease and cancer (Aune et al., 2015; Kyu et al., 2016) as well as for chronic psychiatric disorders (Schuch et al., 2016). The importance of intervention on physical activity has been stressed for many decades (Lewis et al., 2017; Morris et al., 1980).

Such interventions can be aimed at increasing total physical activity including means of transportation and work-related physical activity, or they can specifically target leisure time physical activity. A disadvantage of targeting total physical activity is that it can be highly dependent upon factors that are outside of a person's immediate control, such as the type of employment, and the mode of travel to and from work allowed by the distance between home and work locations. Workplace based exercise facilities are offered by some but not by all employers, and not all allow this to be done in office hours. From a public health perspective, increasing voluntary physical activity during leisure time may be a more viable target for behavioral intervention. Such interventions might be well served by building on the natural

tendency to participate in sports and exercise activities that is still evident in many people. Such tendencies are actively nursed by physical education classes in primary and secondary education and by public health policies supporting sports and exercise in youngsters by co-financing sports clubs and facilities. However, the extent to which this leads to the development of life-long habits of regular exercise behavior in leisure time remains to be established. This is unfortunate because the physiological and psychological benefits of regular physical activity do not seem to last if such activity is discontinued (Telama et al., 1996; Twisk et al., 2002).

A number of 'tracking' studies have been performed to identify patterns in the development of leisure time physical activity over the lifespan. Tracking is typically defined as the tendency of individuals to maintain their rank or position within a group over time (Telama, 2009) and tracking coefficients of sufficient magnitude allow a reliable prediction of future exercise behavior from the current behavior. Not surprisingly, most research on tracking of leisure time exercise behavior has been focused on tracking from childhood to adolescence (Aarnio et al., 2002; Francis et al., 2013; Pahkala et al., 2013; R. Tammelin et al., 2014), or on tracking in the transition from childhood/adolescence to adulthood (Kjønniksen et al., 2008; Parsons et al., 2006; Richards et al., 2007; T. Tammelin et al., 2003; Telama et al., 1996; Telama et al., 2005); although some studies have also looked at tracking in middle-aged and older cohorts (Anderssen et al., 1996; Barnett et al., 2008; Fortier et al., 2001; Parsons et al., 2006; Picavet et al., 2011; Tudor-Locke et al., 2008). A number of replicated results can be extracted from these studies (Malina, 2001; Telama, 2009). First, tracking of leisure time physical activity decreases with the duration of follow-up with tracking coefficients from baseline to follow-up of 0.37 to 0.71 on shorter intervals of three to nine years, but lower tracking when time intervals are longer than nine years, as low as 0.07 in some

cases of 31-year follow-ups (Parsons et al., 2006). Second, tracking from childhood to adolescence or from adolescence to adulthood is lower than the tracking across the longer phase of adulthood itself. Third, in keeping with the first two findings, lowest tracking is found from childhood to adulthood. Fourth, tracking seems to be influenced by sex, with lower coefficients found in women than in men (Telama, 2009).

A major shortcoming of all these previous studies is that they have treated leisure time exercise behavior as a uniform construct by summing all exercise and sports activities that the person engages in into a summary score (McMurray et al., 2003; Parsons et al., 2006) that either reflects the time spent on exercising, or an estimation of the total energy expended in exercise. The latter is done by multiplying frequency, duration, and an estimate of the intensity of the exercise activities usually expressed as a multiple of the basal metabolic rate (i.e., in MET hours weekly). Although the use of such a summary score is very valuable, it cannot detect more detailed patterns in the tracking of different types of exercise behavior. Ideally tracking coefficients would be analyzed for each sport or exercise activity individually (fitness, soccer, jogging, tennis, karate, etc.) but doing so would significantly reduce the number of available subjects per cell even in very large databases. Therefore, as a compromise, exercise activities could be divided into domains based on three dimensions (1) a team-based or individual nature, (2) a competitive or non-competitive nature, and (3) an externally paced or an internally paced nature. The third of these dimensions is based on the nature of the skills required in the exercise activities (Galligan, 2000; van der Mee et al., 2017). These domains were chosen because exercise behavior in these different domains of exercise behavior is likely to be differently sensitive to the many transitions and life-changing events experienced during the course of life. Their contribution to the overall volume of exercise and

sports behavior may likewise differ across time. Team-based exercise behavior for example is expected to track less well into adulthood when compared to solitary activities (Sallis et al., 1996; Telama et al., 2006), likewise participation in competitive exercise is expected to decline (da Silva, 1980). We believe personality and cognitive flexibility to be the major determinants of a preference for internally, or externally paced exercise (van der Mee et al., 2017) and thus, given the stability of personality, produce larger tracking in these domains. A better understanding of the development of life-long habits of regular exercise behavior in these various domains, and particularly the identification of 'vulnerable periods' with lowered tracking is directly needed. Supporting such a favorable development still proves a major challenge in many societies.

Using a large nationwide dataset (longitudinal $N = 43,889$), available at the Netherlands Twin Register (NTR), our aim is to assess the shortcomings mentioned above, allowing us to add significantly to the existing knowledge of the longitudinal tracking of exercise behavior in various domains. The NTR dataset spans a wide age range and includes children, adolescents and adults (8-82 years) in which exercise behavior has been assessed longitudinally in a very similar manner in biennial NTR survey waves. This unique resource allows us to analyze tracking-coefficients of up to a 22-year follow-up, to assess this long-term tracking with starting baseline ages in childhood, adolescence or adulthood, and to split all analyses by sex to compare tracking coefficients in males and females. Importantly, the information provided by the subjects allowed us to compute the tracking coefficients across total MET-minutes weekly but also separately for MET-minutes in the domains of team vs individual, competitive vs non-competitive, and externally paced vs internally paced exercise activities. We expected to find significant stability for the leisure time exercise behaviors in all domains with higher tracking

coefficients across shorter time spans, lower values in females than in males, and a gradual increase in tracking from childhood to adulthood.

Methods

Participants

The NTR is an ongoing research initiative that includes twins and their relatives. Subjects (both adults and children) are assessed every two to three years using extensive surveys. Subjects aged 14 and older fill out self-report surveys, and parents of children under 14 are asked to fill out surveys on the behavior of their children. In all cases the parent-rating of the mother is preferred and if this rating is not available, rating of the father is used (inter-rater correlations ranged from .74 to .85 depending on the age of the subject). Methods and procedures used for data collection in the NTR are described elsewhere (van Beijsterveldt et al., 2013; Willemsen et al., 2013). Subjects were included only if any measure of voluntary exercise behavior was available in at least two surveys (N = 43,889).

Voluntary Exercise Behavior

Overall physical activity has proven to be difficult to measure reliably through self-report (Prince et al., 2008), but the more salient regular exercise activities voluntarily done in leisure time are much more reliably recalled (de Moor et al., 2008; Stubbe et al., 2006). The current study focusses on voluntary regular exercise behavior in leisure time, collected by virtually the same survey methods in large numbers of twins, their parents, siblings, spouses and the children of twins and siblings (van Beijsterveldt et al., 2013; Willemsen et al., 2013). To assess the volume of voluntary exercise behavior we ask whether the participant exercised regularly in their leisure time ('Yes' or 'No'). If the participants (or their parental informant) responded affirmative, they were asked to indicate all of the exercise activities done regularly.

For each exercise activity reported, they noted the number of months per year, weekly frequency and average duration in minutes of the activity. Depending on the age of the participants (≤ 16 vs > 16) Ainsworth's Compendium of Physical Activity (Ainsworth et al., 2011) or the adaptation for children by Ridley et al. (2008) was used to assign a Metabolic equivalent of task (MET) value to each exercise activity, reflecting its energy expenditure as a multiple of the basal energy expenditure (approximately 1 kcal/kg/hour) in an average subject engaged in that activity. For each participant, a total weekly MET value (METmin) was computed across all exercise activities by summing the products of the number of minutes spent weekly on each exercise activity and its MET value. Activities were only considered if that participant had engaged in them for at least three months during the past year, thereby excluding short-lived, non-regular activities, such as outdoor skiing in winter or beach sports in summer holidays. For children and adolescents, exercise during obligatory physical education classes at school was not included in the weekly MET value for voluntary exercise behavior.

Six additional variables were computed based on the specific type of exercise and sports activities. The first was the total volume spent on competitive exercise activities, i.e., activities where an individual, or team, has to compete against another individual, or team, for victory. If a subject's only voluntary exercise behavior was spent in non-competitive sports (e.g., cardio, muscle training) this was counted as zero METmin (as was done for all non-exercisers). Conversely all METmin spent on non-competitive activities were also summed into a second variable for total volume spent on non-competitive exercise activities. The third variable was the sum of all METmin spent on team-related activities, in which exercisers work together to achieve a common goal. Conversely, all of the METmin spent on solitary exercise (e.g., horse sports, aiming based sports or fighting sports) was summed

to a fourth variable. The fifth and sixth variable were based on the exercise being either externally paced (exercise activities where the environment controls the rate of performing the activity) or internally paced (exercise activities where the performer controls the rate at which the activity is performed).

Statistical Analyses

Sex-differences, age effects, age-by-sex interaction, and the quadratic age effect on exercise behavior were analyzed in a cross-sectional dataset containing the last non-missing observation of each subject. These effects were fitted using generalized equation estimation (GEE) models, in order to control for the nested (family) structure of the data. In the GEE model the correlation structure was set to be exchangeable as suggested for family data by previous work (Minică et al., 2015).

Because surveys were generally sent out every two years, ages were transformed to always be even for the tracking analyses. Distance from age at baseline to age at follow-up were therefore always multiples of 2 years, the longest follow-up duration being 22 years. The tracking of exercise behavior was computed for every combination of baseline age and follow-up duration (i.e. 2-year, 4-year, 6-year, ..., 20-year, 22-year) where at least 50 complete combinations were available. GEE models were used to correct for family structure that was present in the NTR, as mentioned earlier. A GEE model was fitted with family as a random factor, and exercise at follow-up as dependent variable. Before the GEE slope-estimates were estimated, MET-scores at baseline and follow-up were normalized. This normalization allows us to consider the slope-estimates as tracking-coefficients, enabling a comparison of our results to results from previous publications where a correlation was used. The standardized slope estimates were plotted

in a heatmap that represents tracking as a function of the age at baseline and the follow-up duration.

To analyze the changes in exercise tracking across the lifespan, N-weighted linear regression was performed, regressing the tracking-coefficient on age at baseline for each follow-up duration. This regression was repeated for team-based, individual, competitive, non-competitive, and externally paced or internally paced MET-scores for all subjects together, as well as separately for males and females. To analyze the effects of sex on the tracking-coefficients this linear regression was also run including sex as a predictor in this regression, as well as an interaction effect between sex and age. Because this analysis is repeated over seven exercise domains a p -value threshold of .05/7 (0.007) will be considered for statistical significance.

Results

Means and standard deviations for METmin scores in 2-year age-bins are presented in an additional table (see Supplementary Table 2.1), for the entire sample and graphically displayed separately for males and females in Figure 2.1. An increase is seen from age 8 to age 16 for total METmin after which a rapid decline sets in that gradually slows down in mid adulthood. The major source of this biphasic pattern is participation in competitive, team-based, and often externally paced activities that is characteristic of Dutch children and adolescents and includes the most endorsed sports soccer and field hockey (Ministry of Sports Wellbeing and Health, 2016). In particular team participation drops sharply after age 16-18, reaching low levels (< 40 METmin weekly) after age 50. A contrasting pattern is seen for solitary non-competitive and internally paced activities which gradually increase to a peak level in early adulthood staying reasonably constant till age 50, after which they also decline. The most endorsed solitary exercise activities were running and weight/muscle training in fitness centers.

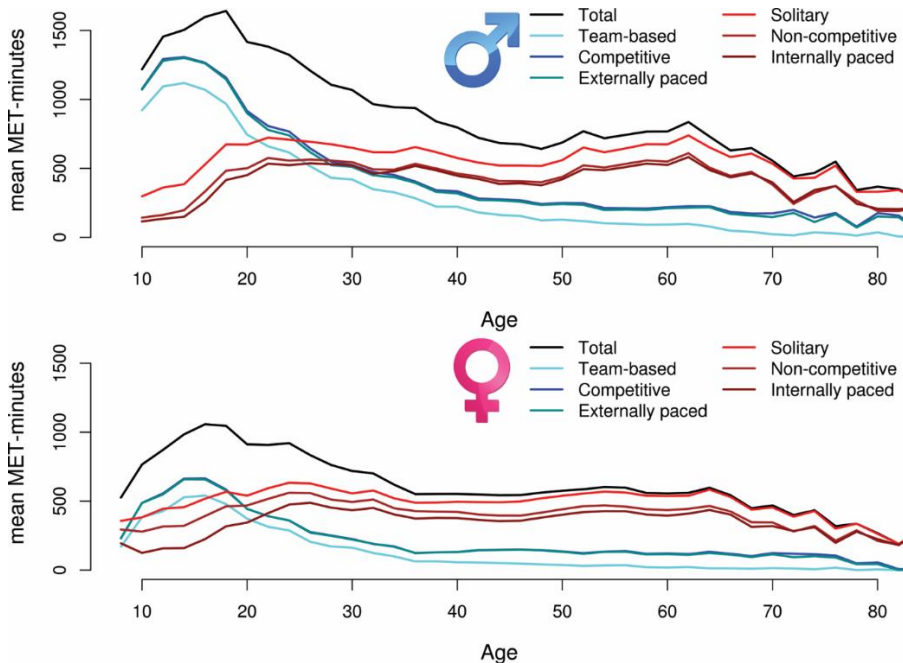


Figure 2.1. Mean volume of exercise in males (top panel), and females (bottom panel) over time, total volume and volume of exercise in all three dimensions (competitive & non-competitive, team & solitary, and externally & internally paced).

Formal testing of the effects of age and sex on METmin in a GEE model revealed significant linear decrease ($\beta = -26.8$, $p < 10^{-90}$) of exercise over age, a significant quadratic effect ($\beta = 0.04$, $p = 0.0006$), as well as a significant ($p < 10^{-90}$) effect of sex with males showing higher levels of exercise. Additionally, the GEE model revealed a significant ($p = 5.31 \times 10^{-65}$) interaction effect between age and sex demonstrating that the decrease of exercise over time is less pronounced in females when compared to males. The age and sex effects are consistent across total volume, competitive METmin, team-based METmin and externally paced METmin. For solitary, and non-competitive METmin females had higher values than males ($p < 10^{-90}$, and $p = 2.55 \times 10^{-31}$ respectively), while for internally paced METmin the effect of sex was not significant ($p =$

0.86). For solitary ($\beta = 19.22, p < 10^{-90}$), non-competitive ($\beta = 22.67, p < 10^{-90}$), and internally paced ($\beta = 22.78, p < 10^{-90}$) METmin a positive linear effect of age is observed, a negative quadratic effect ($p < 10^{-90}$ in all cases), and a negative age-by-sex interaction term in these domains ($p_{\text{solitary}} = 1.73 \times 10^{-22}$, $p_{\text{non-competitive}} = 4.12 \times 10^{-39}$, $p_{\text{internally paced}} = 1.98 \times 10^{-11}$) shows that the increase in exercise over time is less pronounced in females compared to males.

Correlations at various ages (8 to 80) of exercise activities in the various domains are presented in Figure 2.2. It is clear that internally paced, non-competitive, and solitary exercise correlate highly at all ages, and that competitive and externally paced exercise also correlate highly at all ages. For team-based exercise a more complex pattern is seen. It correlates highly with externally paced and competitive exercise in childhood and adolescence, but this correlation decreases strongly in adulthood. In parallel, the correlation of externally paced and competitive exercise with solitary exercise increases across adulthood.

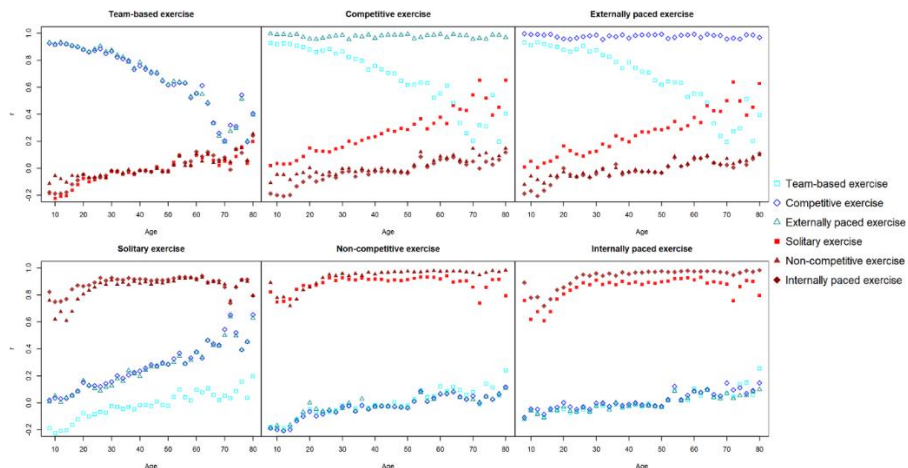


Figure 2.2. Correlations (r) between exercise domains as a function of age.

Tracking

All available tracking coefficients split by males and females for total METmin are displayed in the heatmap in Figure 2.3 and tracking coefficients for the various domains are displayed in an additional Figure (see Supplementary Figure 2.1). Insets show the sample size for each of the heatmap entries (all coefficients were based on $N > 50$). A summary of 2-, 8-, 14-, and 20-year tracking coefficients of all domains is provided in an additional table (see Supplementary Table 2.2).

Two-year tracking coefficients are moderate to high for total METmin across all ages, ranging from .38 to .77 with a median of .57. Tracking coefficients tend to decrease as the distance to follow-up increases, ranging from a median of .57 at 2-year tracking down to a median of .38 for 22-year tracking coefficients. A similar pattern of decreased tracking with increased follow-up duration is seen for all other exercise domains (see Supplementary Figure 2.1).

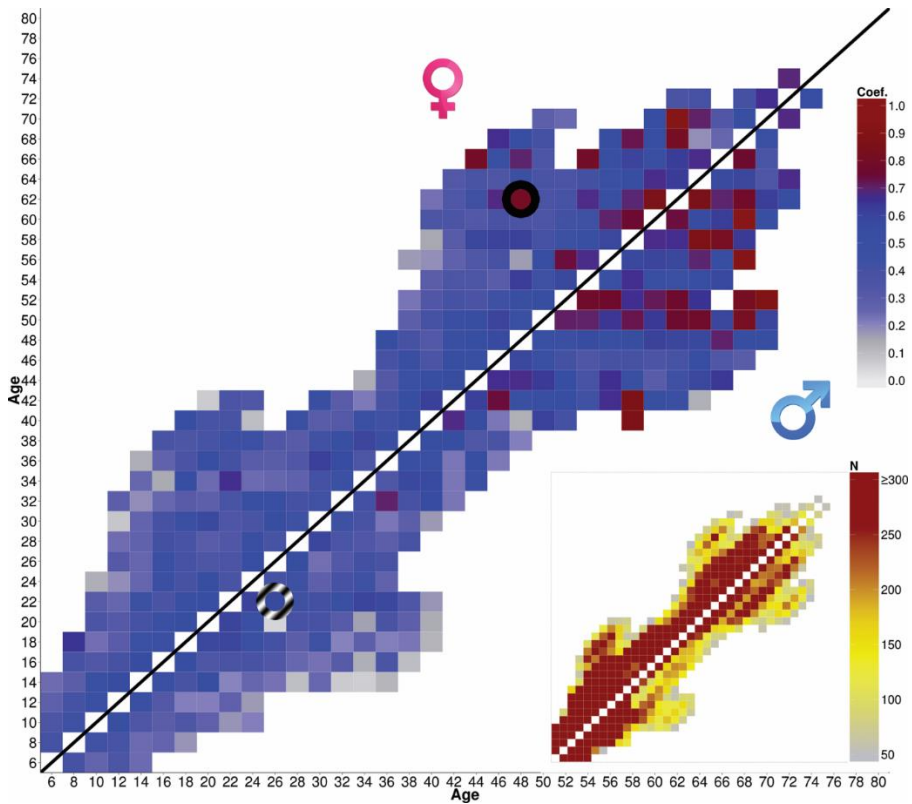


Figure 2.3. Tracking coefficient heatmap of total volume of exercise. The inset in the bottom right corner represents sample size (N) in each cell, cut off at $N=300$ for visual purposes. Colors in the main panel represent the value of the tracking coefficient (grey to blue to red from low to high), colors in the inset represent number of samples (grey to yellow to red from low to high). To demonstrate; the cell in the full circle represents the tracking coefficient (0.81) of age 48 at baseline, and age 62 at follow-up in females. The cell in the striped circle represents the tracking coefficient (0.57) of age 22 at baseline, and age 26 at follow-up in males.

Changes in exercise tracking across the life span

The tracking of exercise as expressed by total METmin shows a clear increase with age at baseline regardless of distance to follow-up. Figure 2.4 fits regression lines to the tracking-coefficients for follow-up durations 2, 8, 14 and 20 years as a function of the age at

baseline. The increase in tracking across the life span held for all other exercise subdomains (for plots see Supplementary Figures 2.2-2.6) with the single exception of team-based METmin where tracking coefficients often decrease with age (see Figure 2.4).

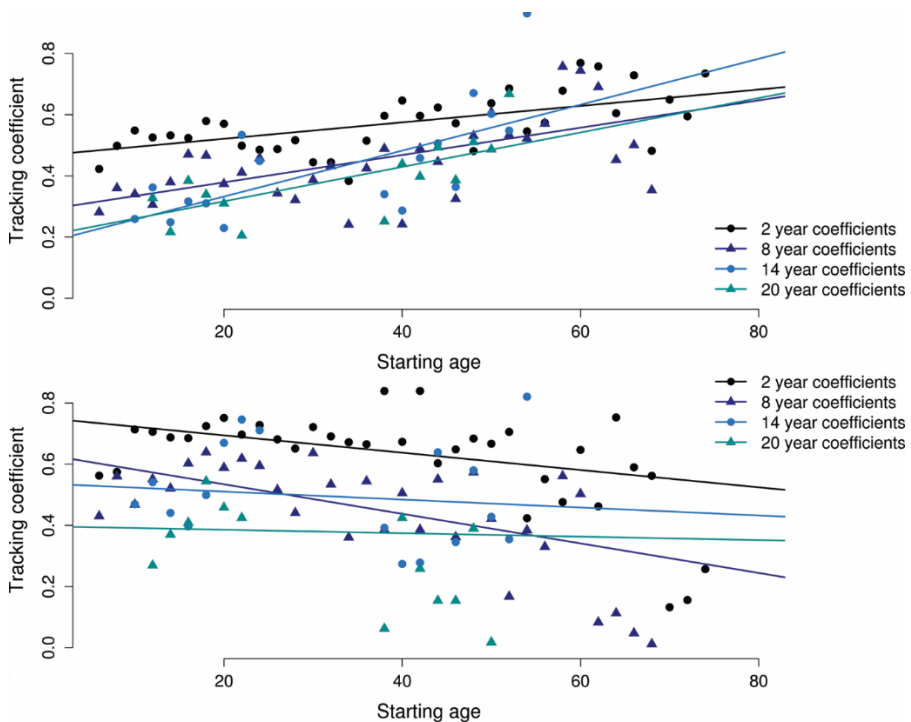


Figure 2.4. Tracking coefficients for total volume of exercise behavior (top panel), and team-based exercise (bottom panel) as a function of age at baseline.

It is important to observe that, regardless of which type of exercise is analyzed, there is no noticeable change in the patterns of tracking coefficients when the informant changes, that is when we change from parent-rated to self-rated voluntary exercise behavior (from 12 to 14 years) with the same instrument.

Sex differences in tracking

To assess sex-differences in the tracking-coefficients the previous linear regression model was expanded to include an effect of sex, and the interaction of sex and age. Significant main effects of sex were present in total METmin and competitive METmin where tracking was slightly higher in females compared to males. In total METmin, as well as solitary, non-competitive and internally paced METmin the interaction was also significant, suggesting that in these domains the increase of the tracking coefficient over time is less pronounced in females compared to males.

Cross-domain tracking

In an exploratory analysis we tested whether team-based, individual, competitive, non-competitive, externally paced or internally paced activities were the best predictor of the total volume of exercise at follow-up. For this, the above analyses were repeated with METmin in any of the domains at baseline, and the total amount of MET-minutes spent exercising at follow-up in the GEE models described earlier.

Heatmaps of tracking coefficients of any exercise domain at baseline are displayed in an additional figure (see Supplementary Figure 2.7), and the summary of 2-, 8-, 14-, and 20-year tracking coefficients of all domains is included in an additional table (see Supplementary Table 2.2). Overall, the cross-domain tracking coefficients were lower than the within-domain tracking coefficients. For team-based the median two-year tracking coefficients was 0.24, compared a median of 0.67 for within-domain tracking coefficients. For competitive, and non-competitive exercise the median two-year cross-domain coefficients were 0.35 and 0.41 compared to 0.67 and 0.50 within-domain respectively. For externally paced and internally paced exercise the median two-year cross-domain coefficients were 0.35 and 0.41 compared to 0.66 and 0.52 within-domain respectively.

Only for solitary based exercise were the median two-year cross-domain tracking coefficients (0.49) very comparable to that of within-domain tracking (0.52). The magnitude of between-domain tracking decreased as the distance to follow-up increased, just as was seen for within-domain tracking. This led to a decrease in the differences between within-domain and between domain tracking, because the 'surviving' exercise activity had become the main source of the total volume of exercise behavior. For team-based exercise, the median 22-year cross-domain tracking coefficient was 0.21 compared to 0.27 in within-domain coefficients. For solitary based exercise the median 22-year between-domain tracking coefficient was 0.17 compared to 0.21 within-domain. For competitive and non-competitive the median 22-year cross-domain coefficients were 0.24 and 0.19 compared to 0.28 and 0.20 within-domain respectively. For externally paced and internally paced exercise the median 22-year cross-domain tracking coefficients were 0.24 and 0.21 compared to 0.27 and 0.29 within-domain respectively

Similar to what was done for the within-domain coefficients, linear regression of the tracking coefficients on age at baseline was performed across different follow-up durations. Regressions for 2-, 8-, 14-, and 20-year coefficients for each domain are given in additional figures (see Supplementary Figures 2.8-2.13). These slopes show the pattern that was already obvious from Figure 2.1: the total volume of exercise behavior in METmin is best predicted by previous levels of competitive, team-based activities in childhood and adolescence, but much better by non-competitive, solitary, and internally paced exercise after age 30.

Discussion

The aim of this paper was to examine tracking of voluntary exercise behavior in leisure time over the entire lifespan. Exercise

activities were clustered in different domains reflecting the nature of the activity to be (1) competitive or non-competitive, (2) team or solitary, and (3) externally or internally paced. The prevalence of engaging in voluntary exercise behavior, especially competitive, team-based, and externally paced sports increases during childhood, to reach its peak during mid-adolescence, around age 16. After mid-adolescence the total volume of exercise behavior starts a decelerating downward trend which is largely explained by the decline in participation in competitive, team-based sports. The participation in non-competitive, solitary sports increases from childhood to late adolescence to remain relatively stable between 18 and 64 years (51% to 60% exercisers). After the age of 64 the participation in non-competitive solitary sports starts to decline as well, causing the total participation in regular exercise to drop down to 23.1% at age 82, at which point 100% of the exercise activities engaged in are solitary.

The results of the analysis of tracking-coefficients suggest that tracking of voluntary exercise behavior is moderate to high (.38 to .57) regardless of the exact domain of exercise activities analyzed. In concordance with the expectations from the extant literature, as briefly reviewed in the introduction, tracking coefficients decreased with increased duration to follow-up and were generally lower from childhood or adolescence into early adulthood compared to tracking across early to late adulthood. In deviation of the latter, the tracking coefficients of team-based exercise decreases with age. These findings are in line with previous findings (Sallis et al., 1996; Telama et al., 2006). Contrary to our expectation, competitive exercise did not demonstrate a decline in tracking as substantial as the decline observed in team-based exercise. Given the strong decrease in team sports after adolescence it becomes increasingly difficult to form teams of similar skill and motivation, and (2) may cause some teams to

fall apart and exercisers to quit due to a lack of likeminded team-members.

In spite of decreased tracking of team sports, our results show that the tracking coefficients of competitive and externally paced exercise increase, and that their correlation to solitary exercise also increases over time. This suggests that subjects switch from a team-based, externally paced, competitive exercise (such as football or field-hockey) to a solitary, externally paced competitive exercise (such as tennis or squash) later in life. In accordance with previous reports, we observed higher tracking coefficients in males for total volume of exercise, however our results suggest that when baseline age, and an age-sex interaction are taken into account it appears that in total volume, as well as solitary, non-competitive and internally paced exercise the effect of sex is dependent on age at baseline.

We show that long-term tracking from childhood to adulthood for leisure time exercise activities in all domains, albeit significant, is at most modest. This may not be surprising because this period contains some of the major transitional phases and life-changing events that can impact on the time available for leisure exercise, including entering high school, leaving home, taking up a job, and starting a family. Yet, the idea that childhood and adolescence should be specifically targeted to ensure life-long exercise habits is widespread, and motivates physical education classes in primary and secondary education and national, regional, and local policies to enable and encourage sports and exercise in youngsters. Telama (2009) formulated a number of mechanisms that could underlie tracking from childhood to adulthood, the carry-over value hypothesis, the ability and readiness hypothesis, the habit formation hypothesis, and the self-selection hypothesis.

The carry-over value hypothesis suggests that early adoption of specific exercise/motor skills acquired in childhood will lead adults

to participate in that same exercise. Splitting the analyses over the domains and comparing the results of within-domain tracking coefficients with cross-domain tracking coefficients across the lifespan allows us to address this hypothesis. The carry-over value would predict higher within-domain tracking compared to cross-domain tracking. The ability and readiness hypothesis suggests that subjects with high level of exercise in youth will also be among the higher exercisers in adulthood, regardless of the type of sport. The ability and readiness hypothesis would predict high tracking coefficients from any domain at baseline to total exercise at follow-up. In our data, the ability and carry-over value hypothesis finds stronger support than the ability and readiness hypothesis. Within-domain coefficients were higher than cross-domain tracking coefficients. However, some evidence for the ability and readiness hypothesis is found in late adulthood where the tracking coefficients of individual exercise at baseline and total exercise at follow-up approach those of within-domain total exercise. We caution that this may be a result of (nearly) all exercisers partaking in individual exercise at this stage of life.

The habit formation hypothesis suggests that simply repeating a behavior many times (independent of skill level) will form a habit. This hypothesis would, more strongly than the carry-over value hypothesis, predict higher within-domain than cross-domain tracking across the entire life span. Our results only partly support the habit formation hypothesis, because substantial exchange between exercise activities across the different domains is seen, although in late adulthood tracking of domain-specific exercise is very high. It may be that habits are more easily formed at later ages due to circumstances allowing for easier habit formation such as a steady job, whereas in childhood, adolescence and young adulthood skill level is more important and

there are many other factors impacting on exercise choice (puberty, education, career change, etc.).

Finally, the self-selection hypothesis states that subjects with a genetic predisposition for high exercise ability and/or exercise motivation will more often partake in exercise (Lightfoot et al., 2018). Using the twin-family structure of part of the data presented here, we have previously provided evidence for this hypothesis by showing substantial heritability of voluntary exercise behavior across the life span (de Moor et al., 2011; Huppertz et al., 2016). However, heritability has been established only for total volume of exercise. For exercise activities in the team-based/solitary, competitive/non-competitive and external/internal paced domains the self-selection hypothesis has not been addressed although a candidate gene study provides some indication of possible different genetic architectures for these domains (van der Mee et al., 2017).

A limitation of this study is the use of self-report which may suffer from both recall and social desirability biases. Self-report of participation in sports and leisure time exercise behavior has shown to be more reliable than self-report on other leisure time physical activities (Telama, 2009). Whether leisure time exercise behavior could be better quantified by using objective methods like accelerometers is not an easy question. When the focus is on energy expenditure in leisure time, more reliable estimates will likely derive from accelerometers than from self-report. Accelerometer-derived activity counts can, however, not be used to discriminate between competitive and non-competitive or team-based versus solitary activities, at least not without additional self-report on the content of the activities. Accelerometry, typically with a 7-day recording time, may also miss sports activities performed with a frequency that is less than weekly. So far, direct comparison between objective and recall methods have not revealed clear differences in tracking coefficients for leisure time

physical activity (Telama, 2009) and self-reported leisure time physical activity robustly predicted objectively measured moderate to vigorous activity across a 25 year follow-up period (Waller et al., 2018). Without discrediting recall and social desirability bias, the use of self-report instead of objective measurements may not be overly problematic for these specific behaviors.

Conclusions

In conclusion, voluntary exercise behavior in leisure time decreases over age, although this depends on sex, and the type of exercise. Team-based competitive exercise activities appear more prone to decay than solitary, non-competitive activities. Tracking coefficients show voluntary exercise behavior to be a moderate to highly stable behavioral tendency, although this too depends on the age and domain of exercise. Comparing domains over the lifespan non-competitive and internally paced exercise proved to be the most stable domains, in particular in late adulthood. Stability decreases as the distance to follow-up increases, resulting in less carry-over from exercise at young ages to late adulthood. Team-based exercise in particular appears to be a poor predictor of the total volume of exercise behavior in late adulthood. The varying results we found for age-effects, sex-effects, and the longitudinal tracking between the exercise domains substantiates the need to examine voluntary exercise behavior as a function of age and sex, and split the activities across the various domains in favor of using a single score summarizing across all domains. For exercise interventionists, our results signal that the glass is half full. The substantial stability of this important health behavior reinforces the existing evidence that exercise habits are hard to change, but at the same time suggests that any successful intervention that leads to the adoption of exercise habits stands a good chance to last.



CHAPTER

Is Physical Activity Regulated by Genetics? Evidence From Studies in Humans

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Introduction

Physical activity (PA) is a broad concept containing a variety of different human behaviors that share the common denominator of expected beneficial effects on mental and somatic health (World Health Organization, 2013). Typically daily physical activities take up about 30% of total energy expenditure and reflect a mixture of obligatory activities related to transportation, work, or household chores and self-chosen physical active behaviors including sports and exercise activities in leisure time. Objective measurements of daily PA in studies conducted in Europe and the US have confirmed the existence of large individual differences in activity levels (Hagströmer et al., 2010; Hansen et al., 2012). These differences are observed in men and women alike, and persist after stratifying for age which is known to have a strong effect on average PA level (Rowland, 2016).

To increase the success of intervention on this important health behavior, much research has been devoted to the causes of the individual differences seen in PA in the general population. In this chapter, we focus on the role played by genetic factors. Broadly, the genetic research on PA phenotypes can be classified into (a) twin studies that partition the observed variance in PA phenotypes into environmental and genetic components based on well-established biometric models of human inheritance (Plomin et al., 2013), and (b) gene-finding studies that use either candidate gene based approaches based on the known biological role of proteins (e.g. in neurotransmission) or agnostic whole-genome searches using genome-wide microsatellite (linkage) or SNP markers to detect genomic loci harboring variants associated with PA. We will summarize the current evidence from each of these types of studies to address the question of whether PA is regulated by genetics.

Twin studies

Physical active behaviors appear to 'run in the family', for example, the chance of one family member being a regular exerciser increases the chance of all other family members to be, or to become, an exerciser. Familial aggregation of PA can be investigated by computing correlations among relatives such as siblings, parents and their offspring. However, siblings among each other, and parents and their offspring, share not just half of their genes, they also share a household, socio-economic status, the neighborhood, and various other aspects of belonging to the same family or living in the same neighborhood (the so-called shared environment), including parenting behaviors, family functioning, shared peers, etc.

Twin studies can separate the two mechanisms of familial aggregation by comparing the resemblance in monozygotic (MZ) or identical twins to the resemblance in dizygotic (DZ) or fraternal twins (Plomin et al., 2013). When twins are reared together the amount of this sharing of the family environment is the same for MZ and DZ twins. The important difference between MZ and DZ twins is that the former share most, if not all, of their genotypes, whereas the latter share on average only half of the genotypes segregating in that family. If the resemblance in PA within MZ pairs is larger than that in DZ pairs, this suggests that additive genetic factors (A) influence PA. If MZ resemblance is more than double as large it suggests the influence of non-additive (D) genetic factors. Additive genetic factors represent the sum of all linear effects of the genetic loci that influence the trait of interest. Non-additive factors include dominance and epistatic interaction effects. If, however, the resemblance in PA in DZ twins is more than half as large as it is in MZ twins, this points to shared environmental factors (C) as the cause of twin resemblance. Furthermore, the extent to which MZ twins do not resemble each other is ascribed to the unique environmental factors (E). These include all

person-specific experiences like differential jobs or lifestyles, accidents or other life events, and in childhood, differential treatment by the parents, going to different schools and having non-shared friends and peers. Measurement error will also be subsumed by the unique environmental factor.

We have previously reviewed all twin and family studies on the heritability of total PA and regular sports and exercise behaviors in childhood or adolescent samples (Schutte et al., 2018). In younger children, the shared environmental factors (C) explain the largest part of the variation in physical activity. However, the importance of these shared environmental factors decreases in adolescence and young adulthood, where genetic effects become the dominant factor explaining individual differences in both total PA and regular sports and exercise behaviors. A sample size weighted meta-analysis showed PA heritability estimates of 20% (95% CI: 13, 27) in children, 35% (95% CI: 17, 52) in early adolescents, and 53% (95% CI: 47, 59) in late-adolescents. This increase in heritability ran in parallel to a gradual decrease in the importance of shared environmental factors, which are the main cause of individual differences in physical activity and exercise behavior in young childhood, but then gradually become overwhelmed, by the importance of genetic factors during adolescence. Using longitudinal follow-up of twins from childhood to adolescence, we show that the increase in heritability, at least for voluntary exercise behaviors, was due to a strong increase in the genetic variance in the course of adolescence that was not paired to a similar increase in environmental variance (Huppertz et al., 2016). Whether the trend of increasing heritability is continued or curbed in young, middle or late adulthood remains to be established.

Sufficient studies in adult twins (> 18 years of age) have now accrued to allow a similar meta-analytic approach and to arrive at solid estimates of additive genetic and shared environmental variance for

PA phenotypes in adulthood. We searched publications in the English language on human subjects in PubMed and Web-of-Science from January 1980 to December 2017 using the keywords ('Physical Activity' OR Exercise OR Sports OR Lifestyle) AND (Genetic OR Genes OR Linkage OR QTL OR Twin OR Family OR Familial OR Heritability) AND "Humans"[MeSH terms]. From the 850 putative papers, title and abstract analysis was used to select only those publications reporting MZ and DZ/sib correlations (in at least 30 complete pairs) and/or estimates of (non-)additive genetic, shared and/or unique environmental variance components. Reference sections of selected papers were used to identify additional papers missed by these search terms. We then removed samples reporting on twins with a mean age lower than 18. Next, we removed partly overlapping datasets from the same twin cohorts. When the same phenotype was used in largely the same age group, we only used the study reporting the largest dataset, which typically would be the most recent study. A final set of 27 adult twin studies (Aaltonen et al., 2010, 2013; Carlsson et al., 2006; de Geus et al., 2003; de Moor, Posthuma, et al., 2007; de Moor, Stubbe, et al., 2007; de Moor et al., 2011; den Hoed et al., 2013; G. E. Duncan et al., 2015; Eriksson et al., 2006; Frederiksen & Christensen, 2003; Gielen et al., 2014; Heller et al., 1988; Huppertz et al., 2017; Huppertz et al., 2016; Huppertz, Bartels, Jansen, et al., 2014; Joosen et al., 2005; Karvinen et al., 2015; Kujala et al., 2002; McCaffery et al., 2009; Mustelin et al., 2012; Mustelin et al., 2011; Nelson et al., 2006; Simonen et al., 2004; Spinath et al., 2002; Stubbe et al., 2005; Vink et al., 2011) were selected by the above search criteria.

Physical activity phenotypes

In the final set of 27 adult twin studies, we encountered a large variation in measurement instruments and PA measures used. By far the largest common denominator was the use of survey-based

methods using subjective PA reporting on self or family members. In large population-based twin registries, surveys are often considered the only feasible strategy. However, subjective reporting of PA is vulnerable to distortion due to recall error and reporting biases (Hagstromer et al., 2010). It is particularly difficult to estimate both the duration and frequency of physical activities that are light to moderate in intensity, including common activities like walking and standing, or household activities (Bassett Jr et al., 2000). For total PA and light to moderate PA, objective measurement strategies using indirect calorimetry, the double labeled water method or movement sensors (Westerterp, 2013) are therefore superior.

When the focus is not on the detection of total PA, but when people are asked to report moderate to vigorous PA, specifically when confined to structured activities in leisure time, self-reporting seems to fare much better (Craig et al., 2003). The cognitive salience of such intensive physical activities is higher than light to moderate intense activities occurring as part of daily routine. Reliability of self-reporting further increases when a restriction is made to the reporting of regular exercise and sports behaviors in leisure time. In our own research, for instance, we have shown a high short-term test-retest reliability (de Moor & de Geus, 2012; Stubbe et al., 2007) as well as substantial tracking over longer periods of time for the weekly volume of voluntary exercise behavior (Huppertz et al., 2016).

Our meta-analysis was organized into the main domains of PA that we encountered in the literature: Total Physical Activity (TPA), Moderate to Vigorous Physical Activity (MVPA, including separate measures for moderate or vigorous PA where applicable), Leisure Time Physical Activity (LTPA), and Voluntary Exercise Behavior (VEB). The first two categories (TPA and MVPA) cover activities that are only partly under the individual's control, whereas the latter two (LTPA and VEB) cover PA that is largely voluntary in nature. We excluded PA measures

that deliberately excluded sports and exercise activities (e.g., Baecke's non-exercise related PA index), measures exclusively reporting on PA in the occupational setting (e.g. Baecke's Work/School index), and measures of daily activities of low intensity (e.g. accelerometer derived time spent in low LPA).

To convert the measured PA behaviors into an actual summary metric for use in the genetic analyses, again a breadth of different strategies has been used. Most studies adopt an estimation of the total energy expenditure by PA as their focus. Estimation of energy expenditure is usually based on published compendia (Ainsworth et al., 2011) that convert each activity into equivalents of the resting energy expenditure (1 MET, approximately 1 kcal/kg/hour). For VEB, most studies use a strategy akin to what we do in the Netherlands Twin Register, where we use an open format that allows reporting all sports and exercise activities that are performed for at least three months a year and then record duration, frequency and intensity of each reported activity. Typically, activities are censored that do not reach a minimal threshold of intensity like fishing or chess. Exercise related to swimming, sailing, or skiing that are restricted to the annual holidays is discarded. Physical Education classes are also discarded as they are poorly standardized and the activities are not voluntary. Energy expenditure in all leisure time VEB is then summed across all valid exercise activities in a weekly METHour score by taking the sum of the products of their weekly frequency, average duration, and MET score.

Another major difference across studies is the type of scale used to quantify PA. Continuous interval scales seem most optimal in terms of statistical power but quite often either ordinal categories (e.g., tertiles of METHours weekly; frequency of LTPA as once per month, once per week, every day) or even nominal dichotomies (YES/NO regular exerciser; YES/NO adheres to PA guidelines) were used. This use of dichotomies and categories is mostly inspired by the frequency

distribution of some of the LTPA and VEB phenotypes. For instance, moderate to vigorous PA in leisure time is very skewed. Likewise, many individuals do not engage in voluntary exercise behavior (zero score) and even in those who do the amount of exercise can still show a skewed distribution. Often no transformation is available that converts such mixed distributions to a normal distribution. For these phenotypes, therefore, the use of ordinal categories or a dichotomy can be meaningful. A liability threshold model can then be used in the genetic analysis to recapture the normal distribution of the latent 'liability to be a (vigorous) exerciser'.

Meta-analyses

To assess heritability and influence of common environmental factors in the four PA categories mentioned previously meta-analysis on A and C estimates was conducted across twin studies. Within the 27 study database, the A, C estimates and their standard errors were often reported separately for males and females. However, if the A, C estimates were reported only for males and females combined, we assigned the same estimates to the male and female part of the sample, adjusting the N to reflect the number of male or female twins. Most studies used age and sex as covariates, but additional covariates were sometimes used too, including socioeconomic status, body-mass index, or fitness. When multiple estimates were generated for different covariate compositions, we opted to use the estimates only correcting for age and sex effects on mean PA level. In these studies, structural equation based variance decomposition modeling was by far the most used analytic strategy. Unless stated otherwise, the results from the most parsimonious structural equation model were used in the meta-analysis. This model was most often an AE or ACE model. If the AE model was used, C was set to zero. No studies reported a model with non-additivity (D).

For each of the four PA phenotypes, the estimates for A, C were computed in a sample-size weighted meta-analysis across all available studies for males and females separately. Inverse variance weighting was not possible because not all studies provided either standard errors of the estimates or 95% confidence intervals from which the standard errors could be approximated. Forest plots in Figure 3.1 and Figure 3.2 present the characteristics and the A and C estimates per study, and the meta-analytic results per PA phenotype. Study characteristics are: country, whether males and females were combined in A and C estimation, whether PA measurement was through surveys (SUBJ) or experimental (OBJ), type of scale used (Dichotomy, CATegorical, or CONTinuous), mean age, and sex-specific sample size. The estimates for A and C are listed in the Forest plots as a function of mean sample age.

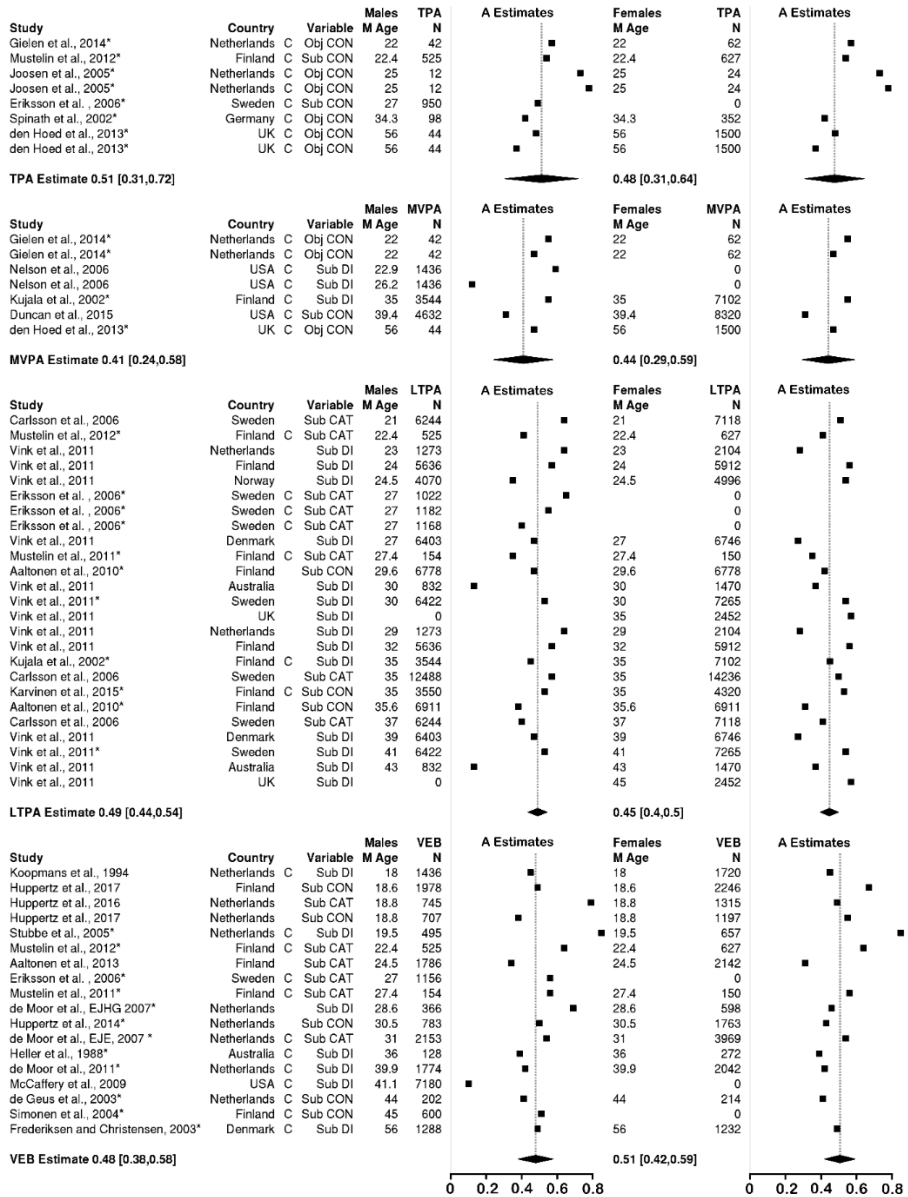


Figure 3.1. Study-specific and meta-analytic estimates of heritability (A) of total physical activity (TPA), Moderate to vigorous activity (MVPA), Leisure Time Physical activity (LTPA), and voluntary exercise behavior (VEB), for males and females. Estimates include results from subjective (Sub), and objective (Obj), continuous (CON), categorical (CAT), and dichotomous (DI) variables. *, Studies where an AE model was fitted. C; Estimates from a combined male and female sample.

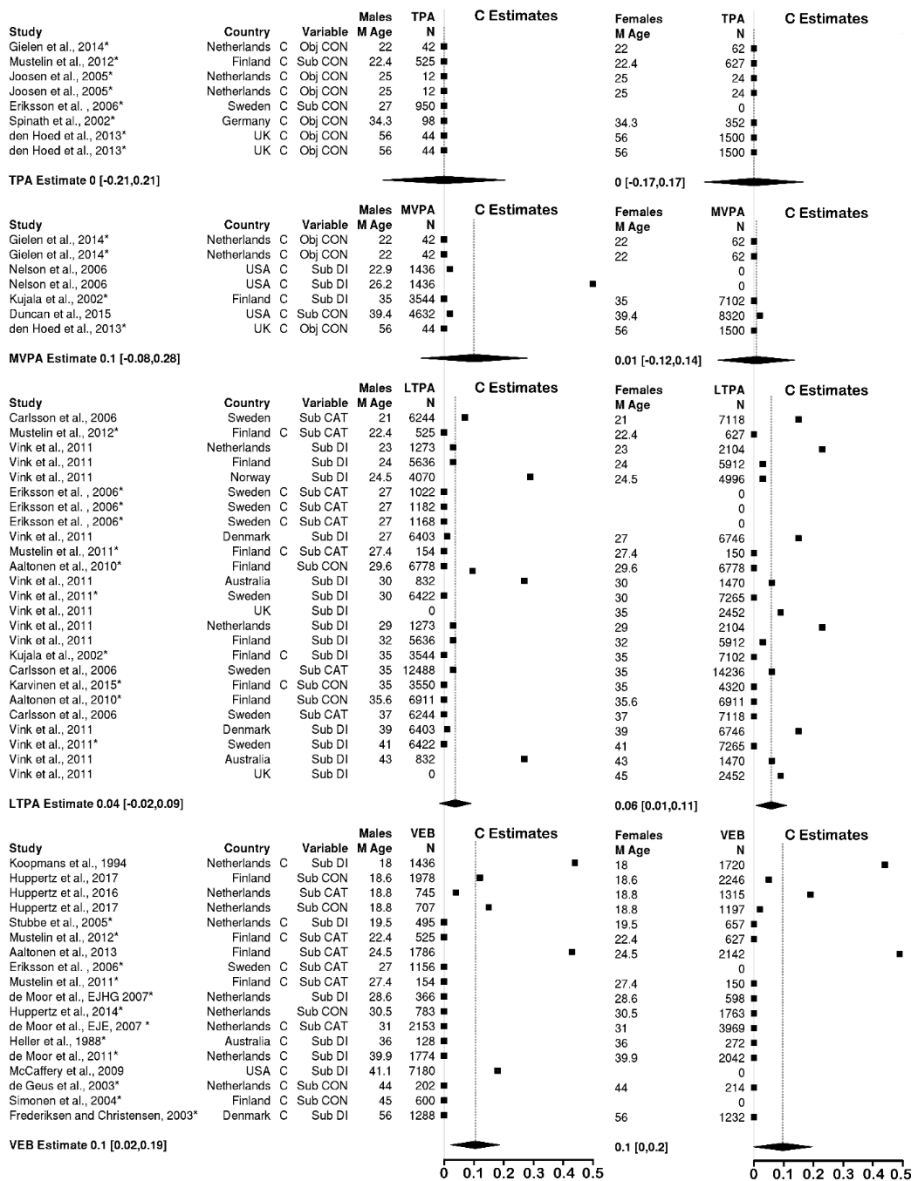


Figure 3.2. Study-specific and meta-analytic estimates of shared environmental contribution (C) to the variance in total physical activity (TPA), Moderate to vigorous activity (MVPA), Leisure Time Physical activity (LTPA), and voluntary exercise behavior (VEB), for males and females. Estimates include results from subjective (Sub), and objective (Obj), continuous (CON), categorical (CAT), and dichotomous (DI) variables. *; Studies where an AE model was fitted. C; Estimates from a combined male and female sample.

Results for Total Physical Activity

For the meta-analysis of TPA (see Figure 3.1 and Figure 3.2) a total of 6 studies using 8 phenotypes was available, most using an objective measure to quantify PA, and all combining males and females. The meta-analytic heritability estimate was 48% for females and 51% for males. Largest heritability estimates were found by Joosen et al. (2005) who used the most reliable methods, namely the doubly labeled water method and more than 14 days of accelerometer recording, albeit in the smallest sample. The two survey methods using the Baecke questionnaire yielded results comparable to the objective methods. No evidence for common environmental effects was found.

Results for Moderate to Vigorous Physical Activity

For the meta-analysis of MVPA (see Figure 3.1 and Figure 3.2) a total of 5 studies using 7 phenotypes was available, all combining males and females. The meta-analytic heritability estimate was 44% for females and 41% for males. Comparable heritability was found for objective and subjective measures. Somewhat deviant results were found in the 26 year old Add Health study participants (Nelson et al., 2006). Using a 7-day recall questionnaire to obtain a dichotomy of MVPA frequency that indicated whether participants met national PA recommendations (> 5 bouts/wk), lower heritability was paired to the only evidence for a shared household effect on MVPA (50%).

Results for Leisure Time Physical Activity

We used 8 twin studies for the meta-analysis of LTPA (see Figure 3.1 and Figure 3.2) reporting on more than 200,000 twins from 7 countries. The meta-analytic heritability estimate was 49% for males and 45% for females with narrow confidence intervals (95% CI upper – lower \approx 10%) reflecting little heterogeneity. LTPA was only available

from self-report measures in these very large epidemiological samples. In two countries, Norway and Australia, evidence for common environmental impact on LTPA was found (~28%). Comparing sample sizes, the absence of large C in other twin studies cannot be attributed to low power.

Results for Voluntary Exercise Behavior.

VEB was also measured exclusively by survey or interview measures. A total of 15 different studies using 14 unique samples/measures yielded a meta-analytic heritability estimate of 48% for males and 51% for females (see Figure 3.1) with mild heterogeneity (95% CI upper – lower ≈ 20%). Some evidence for common environmental effects were found, mostly driven by the younger samples (~10%, see Figure 3.2) with a particularly strong C effect in the young adult Finnish twins (43% males, 49% females).

Gene-finding studies

The above meta-analyses show that genetic variants play a key role in adult PA, whether it is total daily PA as measured with objective means (e.g., accelerometers), or self-reported voluntary sports and exercise activities in leisure time. We now turn to the gene finding studies aiming to detect the actual 'PA genes'. For this, we have to use a narrative approach because not enough replication is currently available for any single locus to consider meta-analysis. The majority of gene finding studies on TPA, MVPA, LTPA, and VEB have used a candidate gene approach. The use of this approach was predicated on the expectation that individual genetic variants would be associated with complex behavioral traits at a magnitude that would be small but detectable with hundreds, or a few thousand individuals. The advent of large international consortia performing meta-analyses on genome-wide association results for many complex behavioral traits in samples

as large as hundreds of thousands of participants has found this expectation to be untenable. The risk contributed by any single variant is tiny rather than just small, with only an increase of ~0.05 standard deviation per risk allele at best, necessitating much larger sample sizes to be able to detect them (Visscher et al., 2017). Based on these types of concerns regarding candidate gene studies using small samples, we focus here mainly on the data-driven genome-wide approach in linkage and genome-wide association (GWA) studies.

Linkage

The three genome-wide linkage studies (G. Cai et al., 2006; de Moor, Posthuma, et al., 2007; Simonen, Rankinen, Perusse, et al., 2003) performed to date have only produced suggestive hits, in keeping with their modest sample sizes ($767 < N < 1120$). In the Quebec family study, Simonen, Rankinen, Perusse, et al. (2003) reported linkage for TPA (13q22-q31), MVPA (4q28.2, 7p11.2, 9q31.1, 13q22-q31), and VEB (11p15 and 15q13.3). Interestingly, the latter 15q linkage region contains the *GABRG3* gene in which a SNP (rs8036270) was found to be significantly associated with VEB in GWA study on a combined sample of 2,622 Dutch and European American middle-aged adults (de Moor et al., 2009). Significant association with *GABRG3* was replicated for LTPA in older adults in a GWA study in 10684 European and 11093 African Americans (Lin et al., 2018) although with different SNPs (*rs72707657*, *rs12438610*, *rs12902711*, *rs12595253*). The *GABRG3* gene may be involved in the aversive effects of exercise-induced fatigue because high expression levels of the *GABRG3* gene was found after a bout of exhaustive exercise (Kawai et al., 2007). However, a GWA study in 13,980 Japanese older adults did not find significant association with any SNPs in the *GABGR3* gene region and the gene also did not surface in the other two GWA studies.

In the Viva La Familia study (G. Cai et al., 2006) physical inactivity, recorded as the percentage time in sedentary activity, significantly mapped to markers *D18S1102-D18S64* in the chromosome 18q21 region where the *MC4R* gene resides. An additional suggestive linkage signal for TPA was detected in the same region. *MCR4* had been implicated in smaller scaled candidate gene studies (Cole et al., 2010; Loos et al., 2005) but it failed to replicate in any of the five GWA studies, two of which explicitly tested it as a candidate gene (i.e., with a more liberal p -value). In the Viva La Familia study a further linkage signal was found for MVPA in the region at 9q31.1, which harbors the *RN7SK* gene. A SNP (*rs7023003*) near this gene produced a suggestive ($p < 10^{-5}$) association with TPA in 8,454 Korean participants (Kim et al., 2014). However, the same *RN7SK* SNP was explicitly but unsuccessfully tested for replication in Japanese participants (Hara et al., 2018) and the gene also did not surface in the other two GWA studies.

Finally, in a sample from the Netherlands Twin Register (de Moor, Posthuma, et al., 2007), a suggestive linkage with exercise participation was found in all subjects on chromosome 19p13.3 (LOD 2.18). A SNP (*rs12462609*) in this region, located in the *CACNA1A* gene, was associated with vigorous PA in 261,055 older adult participants in the UK Biobank (Klimentidis et al., 2018), and with TPA in 8,454 older adult Koreans (Kim et al., 2014) whereas another SNP (*rs111901094*) in *GATAD2A* in the 19p13 linkage region was associated with VEB in the UKB participants (Klimentidis et al., 2018). The 19p13 region did not generate a significant or suggestive signal in the other two GWA studies (Hara et al., 2018; Lin et al., 2018).

Genome wide association

Five genome-wide association (GWA) studies (de Moor et al., 2009; Hara et al., 2018; Kim et al., 2014; Klimentidis et al., 2018; Lin et al., 2018) conducted for exercise behavior or related PA phenotypes were

available at the time of writing. The three smallest GWA studies (2632 < N < 11093) did not detect significant associations after the required stringent correction for the multiple testing burden that is inherent in the agnostic genome-wide approach (de Moor et al., 2009; Kim et al., 2014; Lin et al., 2018). However, some genes listed as receiving suggestive evidence based on more lenient thresholds ($p < 10^{-5}$) showed interest-generating patterns of replication across multiple studies. For example, a suggestive association of VEB was found in Dutch and American participants of European descent (de Moor et al., 2009) for an eQTL (*rs12612420*) that reflects the expression of the *DNAPT6* gene. This association was replicated ($p = 0.0092$) in 16026 Japanese participants (Hara et al., 2018).

Suggestive evidence for an association between VEB and the *PAPSS2* gene in Dutch and American participants (de Moor et al., 2009) was replicated in 11,903 African-American participants (Lin et al., 2018) for LTPA, although for different SNPs (*rs10887741* vs *rs1819162*). The *PAPSS2* gene has been linked to maximal exercise capacity (Rico-Sanz et al., 2004) which may be a factor influencing the motivation to engage in voluntary exercise (de Geus & de Moor, 2011). Explicit testing of an association between VEB and *PAPSS2* in 13,980 Japanese participants, however, did not produce a significant replication (Hara et al., 2018). Suggestive evidence for an association with LTPA was found for *rs116550874* at 1p36.23, and *rs3792874*, *rs3792877*, *rs3792878*, *rs79173796* at 5q31.1 ($p < 8.61 \times 10^{-7}$) in 11093 African Americans and for *rs28524846* at 14q23.3 ($p = 1.30 \times 10^{-6}$) in 10684 European Americans (Lin et al., 2018). The authors point to the *ENO1*, *SLC22A5*, *PDLIM4* genes as potential sources of the association signal at 1p36. *ENO1* encodes a glycolytic enzyme and the integral membrane protein *SLC22A5* is associated with skeletal myopathy, whereas the *PDLIM4* protein is involved in the pathway of actin cytoskeleton remodeling, bone and skeletal muscle development. The *rs28524846* SNP at 14q23 is an eQTL for *MPP5* and

ATP6V1D in nerve tissue, with the MPP5 protein known to regulate myelinating Schwann cells and *ATP6V1D* related to synaptic vesicle cycle and ATPase activity.

Encouragingly, the two largest GWA studies to date did successfully detect genome-wide significant associations with PA. In a Japanese sample (N=16016), Hara et al. (2018) identified an association ($p_{\text{meta}} = 2.2 \times 10^{-9}$) between leisure-time exercise behavior and rs10252228, a SNP located in the intergenic region between *NPSR1* and *DPY19L1* genes. Hara et al. (2018) point out that the product of the *NPSR1* and that of the *DNAPT6* gene previously found by the GWA of de Moor et al. (2009) are both involved in pulmonary function. Variants in *NPSR1* have been shown to be associated with asthma-related phenotypes, and *DNAPT6* could be involved in bronchodilator response via the down-regulation of β 2-adrenergic receptors. Impairments of pulmonary function could be a barrier to the adoption of (vigorous) PA.

In the UKB (N = 380,492), Klimentidis et al. (2018) detected genome-wide significant genetic associations with touchscreen-survey based measures of MVPA. After applying corrections for work-related PA and an indicator of socioeconomic status, associations with MVPA were found at rs429358 (*APOE*), rs169504 (*PBX2*), rs4129572 (*EXOC4*), rs3094622 (*RPP21*), rs181220614 (*ARHGEF26-AS1*), rs149943 (*ZNF165*), and rs2988004 (*PAX5*). Intriguingly, the Alzheimer disease risk allele (E4) of the *APOE* gene was associated with higher levels of MVPA. That *APOE* e4 carriers have more MVPA could be in keeping with the idea that physiological determinants of the ability to perform (intense and/or prolonged) PA lead to higher levels of PA. As noted by Klimentidis et al. (2018), *APOE* e4 carriers had a more favorable response to exercise, for instance as suggested by a study showing larger aerobic fitness in response to training (Thompson et al., 2004). This is in keeping with the theoretical notion that individuals who have

higher exercise ability and/or trainability will find it easier to adopt regular exercise as a lifestyle (de Geus & de Moor, 2008, 2011; Lightfoot et al., 2018).

From the UKB self-reports (Klimentidis et al., 2018) two dichotomous measures of more vigorous PA were defined: VPA by classifying participants as engaged in vigorous PA if they spend more than 25 minutes on activities “that make you sweat or breathe hard” for three or more days a week and VEB by classifying participants as regular vigorous exercisers if they spend more than 15 minutes on two or more days a week doing strenuous sports or other exercises. Significant genetic association for VPA was found at *rs1248860* (*CADM2*), *rs2764261* (*FOXO3*), *rs3781411* (*CTBP2*), *rs12707131* (*EXOC4*), and *rs328919* (*DPY19L1*) and for VEB at *rs62253088* (*CADM2*), *rs166840* (*AKAP10*), *rs10946808* (*HIST1H1D*), *rs75930676* (*SIPA1L1*), and *rs4865656* (*LOC642366*). In addition, accelerometer data were available in just over 91,000 participants. From up to seven days of accelerometer wear overall acceleration was obtained as a measure of TPA and the fraction of accelerations > 425 mg as a measure of VPA, yielding significant associations at *rs55657917* (*CRHR1*) and *rs185829646* (*ANKRD22*) for TPA and *rs743580* (*PML*) and *rs6433478* (*CIR1*) for VPA.

The *CADM2* gene, primarily expressed in the brain, surfaced in the UKB study as a gene influencing vigorous sports and exercise related PA. Previously this gene had been linked to risk-taking behavior and extraversion (Boutwell et al., 2017) as well as executive function (Ibrahim-Verbaas et al., 2016). This shows a remarkable parallel to results reported in the largest candidate study to date by van der Mee et al. (2017) where a polygenic dopaminergic risk score that summed the increaser alleles in *COMT* and *DAT1* for both executive function and reward sensitivity was associated with the volume of externally paced sports and exercise activities. Possibly, *CADM2*, like

these dopaminergic genes operates through a double whammy of increased reward value of exercise and increased sports skills.

Conclusions

Although the gradual rise in heritability of PA seen in adolescence is not continued in adulthood, it is clear that genetic factors remain a major contributor to individual differences in adult physical activity behaviors. In the reports on over 283,904 adult twins we find that about half of the variance in the four PA phenotypes can be explained by genetic factors (Males 48% CI 44%-52%; Females 47% CI 44%-50%). The substantial contribution of the shared environment (C) to childhood PA seems to have largely dissipated in adulthood (Males & Females 6% CI: 3%-10%). There is generally a good correspondence in estimates across individual studies even when they use samples from different countries or measures. For TPA and MVPA, objective measurement showed slightly higher genetic estimates than subjective measurement, but the differences are not striking. Major sex differences in genetic architecture of LTPA and VEB seemed to be absent; for TPA and MVPA estimates the verdict is still out as analyses were mostly based on combined male/female samples.

The extant studies using a candidate gene, linkage or whole-genome association approach have yielded a number of genes and variants worth careful monitoring in future gene finding efforts. Previously, three biological themes have emerged as a potential source for "Physical Activity Genes" from theory: (1) the brain circuitry related to motivational and affective aspects of PA, (2) the brain circuitry involved in the maintenance of energy intake/expenditure balance, and (3) the physiological determinants of the ability to perform (intense and/or prolonged) PA, ideally at an above average level (de Geus & de Moor, 2008, 2011; Lightfoot et al., 2018). Many of the variants reviewed above do seem to fit these theoretical notions, but we issue

a note of caution that this may partly reflect our deep desire (and uncanny ability) to make sense of data by 'reasoning towards' our theoretical models. Rigorous replication followed by experimental validation (in animal models) is direly needed. However, the experience from many other complex behavioral traits allows us to end upbeat: once very large samples are amassed in international meta-analytic consortia, we can confidently expect large progress in our understanding of how physical activity is regulated by genetics.



CHAPTER

Genetic Influences on Regular Exercise Behavior

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Introduction

Regular engagement in physical activity lowers the risk for morbidity and mortality through cardiovascular disease (CVD), type 2 diabetes, and cancer (Aune et al., 2015; Kyu et al., 2016; L. Liu et al., 2016; Pandey et al., 2015). Despite these well documented benefits of physical activity, a large proportion of adults worldwide does not engage in such activities on a regular basis (Troiano et al., 2008). As a consequence, a physically inactive lifestyle remains a major threat to health in modern-day society, with substantial economic costs (Ding et al., 2016). This is reflected in public health recommendations worldwide, which unanimously include encouragement to a more active lifestyle (Brown et al., 2012; "Physical Activity Guidelines for Americans," ; World Health Organization, 2013).

Correlates and determinants of a physically active lifestyle have been studied intensively over the past three decades in an attempt to define optimal targets for 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). Since then, researchers have identified, in cross-sectional or longitudinal studies, numerous potential determinants that contribute to the adoption and maintenance of physical activity. Physical activity encompasses a broad domain of activities at work, at home, during transportation, and in leisure time. In this chapter, the emphasis is on voluntary exercise activities in leisure time such as jogging, swimming, exercising at fitness clubs, and participation in recreational or competitive team and individual sports. Such voluntary exercise activities are often specifically aimed at improving skills, fitness, and health and are rapidly becoming the major source of physical activity of moderate-to-vigorous intensity in many industrialized countries.

The bulk of studies devoted to the determinants of voluntary exercise behavior have attempted to explain low exercise prevalence in terms of social and environmental barriers. These include poor access to facilities (Matson-Koffman et al., 2005), low socioeconomic status (Haase et al., 2004; Varo et al., 2003), non-Caucasian race (Hasson et al., 2017), high job strain (Payne et al., 2005), subjective "lack of time" (Sherwood & Jeffery, 2000), low belief in health benefits (Haase et al., 2004), and low social support by family, peers, or colleagues (Sherwood & Jeffery, 2000). Although these social factors are important, they explain only a small part of the individual differences in voluntary exercise behavior. In this chapter, we review the evidence from twin and family studies that genetic factors play an important role too.

Definitions of voluntary exercise behavior

Heritability estimates of behavioral phenotypes are sensitive to the exact definition of the phenotype. We will therefore first give an overview of how voluntary exercise behavior has been defined in the studies used in this review.

The four important characteristics of the studies presented in Tables 4.1 through 4.3 are that the reported exercise activities were performed regularly, voluntarily, in leisure time, and in the context of fitness or sports. We stress that this definition of voluntary exercise behavior is different from total physical activity, even when a restriction is made to leisure-time physical activity (LTPA) or more narrowly to LTPA that is of moderate-to-vigorous intensity. Such LTPA measures will encompass almost all voluntary exercise behavior but may additionally include gardening, dancing, or active transportation by walking or bicycling to school/work, none of which are considered to fall under voluntary exercise behavior in our definition. We further exclude obligatory exercise activities like physical education (PE)

classes or job-related sports and exercise (army boot camps; fireman training) and activities that are done infrequently like sailing, surfing, or skiing during a limited number of days per year. We note that our definition of voluntary exercise behavior also excludes accelerometer/step counter based physical activity, unless an ancillary diary or recall method is used. Without additional self-reporting, these activity counts cannot distinguish between voluntary exercise activities or other forms of moderate-to-vigorous activity (e.g., vacuum cleaning, bicycling, stair climbing).

Almost all studies on regular voluntary leisure-time sports and exercise activities as defined above have used self-reports, but the methods of assessment of these activities have differed across studies. Some studies used surveys, whereas others used interviews. Exercise behavior was assessed with only a single "YES/NO participation" question (Boomsma et al., 1989) or by presenting subjects with a list of specific exercise activities (Martinez-Gonzalez et al., 2001; van der Aa et al., 2010), whereas still others allowed all exercise activities to be reported in a free format (de Moor et al., 2006). The quantitative metrics for exercise behavior have differed accordingly. Some studies use a categorical scale classifying participants in a dichotomy of "regular exercisers" and non-exercisers, sometimes adding an additional level of moderate exercisers. These studies have used different thresholds for the minimum frequency and the minimum intensity of the exercise activities to separate regular exercisers from non-exercisers, making it somewhat difficult to either pool or compare the prevalence of regular exercisers across studies.

To avoid confusion by these differing thresholds and more optimally use the variation in the volume of exercise behavior among exercisers themselves, voluntary exercise behavior should preferably be expressed as the energy expenditure in exercise activities across a fixed time interval (e.g., weekly). This can be done by multiplying

frequency, estimated intensity and duration for each activity, and summing across all reported exercise activities. Unfortunately, the type, duration, frequency, and intensity of exercise activities have not always been assessed in great detail in older studies.

Prevalence of voluntary exercise behavior

In the Netherlands Twin Register, data on exercise behavior has been collected by virtually the same methods through surveys in large numbers of twins, their parents, siblings, spouses, and the children of twins and siblings (van Beijsterveldt et al., 2013; Willemssen et al., 2013). To assess the volume of voluntary exercise behavior, we ask whether the participant exercised regularly in their leisure time ("Yes" or "No"). If the participants (or their parental informant) responded affirmative, they were asked to indicate all of the exercise activities done regularly. For each exercise activity reported, they noted down the number of months per year, weekly frequency, and average duration in minutes of the activity. Depending on the age of the participants (≤ 16 vs >16), Ainsworth's Compendium of Physical Activity (Ainsworth et al., 2011) or the adaptation for children by Ridley et al. (2008) was used to assign a Metabolic equivalent of task (MET) value to each exercise activity, reflecting its energy expenditure as a multiple of the basal energy expenditure (approximately 1 kcal/kg/ hour) in an average subject engaged in that activity. For each participant, a total weekly MET value (METhr) was computed across all exercise activities by summing the products of the number of hours spent weekly on each exercise activity and its MET value. Activities were only scored if that participant had engaged in them for at least three months during the past year. For children and adolescents, exercise during obligatory PE classes at school was not included in the weekly MET value for voluntary exercise behavior. The six-months test-retest reliability of the weekly MET value was found to be .91 (Stubbe et al., 2007), and twins proved fully

comparable to non-twins with regard to this definition of exercise behavior (de Moor et al., 2006).

Up until 2016, exercise data was collected in 78,524 participants (54.4% females) with a mean age of 31.5 (SD =17.9). A total of 67.0% of these participants engaged in regular voluntary exercise activities (N = 52,603), whereas 33.0% were non-exercisers. When taking into account the frequency and intensity of the exercise activities in METs, little over half of the population (62.6%) engages in moderate to vigorous exercise activities (4 MET or more) for at least 60 minutes per week, and only 12.9% can be considered vigorous exercisers, that is, engaging in vigorous exercise activities (7 MET or more) for at least 300 minutes per week. In Table 4.1 we illustrate the effects of two of the best-known determinants, age and sex, on the prevalence of voluntary exercise behavior. We furthermore report exercise behavior separately for the twins, their singleton siblings, and, in the older age groups, for the parents and spouses.

Age		MALES					FEMALES				
		Weekly METHours					Weekly METHours				
		Mean	SD	IQR	%SED	%VIG	Mean	SD	IQR	%SED	%VIG
≤9'	N=6425	17,3	13,7	22,4	21,2%	8,9%	10,6	9,9	12,0	25,2%	2,4%
	Twins (99.92%)	17,3	13,7	22,4	21,2%	8,9%	10,6	10,0	12,0	25,1%	2,4%
10-12	N=6683	25,3	18,6	24,9	15,0%	27,2%	16,1	14,4	19,2	16,9%	11,0%
	Twins (97.71%)	25,2	18,5	24,9	15,0%	27,2%	16,1	14,4	19,2	16,9%	11,0%
	Singletons (2.29%)	26,8	24,6	21,0	18,9%	27,0%	16,7	14,9	18,5	17,7%	12,7%
12-15	N=6181	26,6	22,7	32,3	20,5%	34,3%	18,4	18,7	23,9	21,8%	17,5%
	Twins (91.98%)	26,7	22,4	32,3	20,1%	34,4%	18,4	18,8	23,5	21,7%	17,5%
	Singletons (7.99%)	24,7	25,4	34,2	24,7%	32,5%	18,6	18,2	25,1	22,3%	17,9%
15-18	N=6948	27,3	26,0	41,0	27,2%	37,3%	17,5	21,1	27,4	33,0%	18,2%
	Twins (86.07%)	27,3	25,6	41,0	26,5%	37,6%	17,6	21,5	27,5	32,8%	18,7%
	Singletons (13.46%)	27,3	28,3	42,1	31,0%	35,6%	16,5	18,4	26,4	34,6%	15,3%
	Parents/spouses (0.47%)	16,6	16,0	26,1	36,4%	18,2%	21,0	16,6	25,9	22,7%	18,2%
18-21	N=4534	23,5	25,4	36,0	30,9%	28,5%	15,5	17,7	23,4	32,7%	13,1%
	Twins (76.93%)	23,4	24,8	36,0	30,2%	28,7%	15,9	17,8	24,0	30,9%	13,9%
	Singletons (21.72%)	23,3	26,4	36,0	33,9%	26,8%	13,6	17,3	21,9	39,6%	9,6%
	Parents/spouses (1.35%)	39,3	42,6	27,0	18,8%	50,0%	17,3	18,8	23,9	26,7%	17,8%
21-25	N=4055	21,8	23,0	36,0	29,6%	25,9%	15,2	17,6	22,0	30,6%	10,8%
	Twins (73.93%)	22,2	22,7	36,0	27,8%	26,4%	15,8	17,7	22,8	29,8%	12,2%
	Singletons (21.11%)	21,3	23,4	36,0	32,8%	25,6%	14,3	18,6	19,6	31,2%	7,5%
	Parents/spouses (4.96%)	18,1	25,9	30,6	42,3%	21,1%	9,8	11,2	14,9	39,2%	3,9%
26-35	N=6101	16,6	20,0	24,8	36,2%	15,7%	10,5	14,2	15,6	40,4%	5,8%
	Twins (56.71%)	17,7	20,5	26,6	32,6%	17,0%	11,4	15,1	16,5	38,2%	6,7%
	Singletons (16.82%)	17,4	20,2	26,4	34,7%	17,0%	11,5	14,1	16,5	35,7%	6,2%
	Parents/spouses (26.47%)	14,0	18,8	22,0	44,0%	12,4%	8,1	12,0	12,0	48,4%	3,6%
36-45	N=13668	12,1	17,8	18,0	46,0%	9,0%	8,8	11,7	13,6	43,7%	3,4%
	Twins (17.28%)	15,5	19,3	22,0	32,9%	10,9%	11,1	13,6	16,0	35,0%	5,3%
	Singletons (4.78%)	15,9	22,7	24,0	36,4%	12,3%	10,3	11,9	15,8	35,6%	3,8%
	Parents/spouses (77.9%)	11,3	17,1	17,0	48,8%	8,5%	8,1	11,1	12,5	46,5%	2,8%
46-55	N=10838	11,8	18,5	17,0	49,3%	9,0%	9,4	13,0	13,8	45,3%	4,7%
	Twins (8.72%)	14,2	17,7	19,3	37,8%	12,7%	10,6	12,8	16,5	40,1%	5,7%
	Singletons (3.03%)	10,1	14,2	16,2	48,6%	5,6%	11,5	15,0	16,0	37,1%	6,3%
	Parents/spouses (88.24%)	11,7	18,6	17,0	49,9%	8,9%	9,1	12,9	13,5	46,5%	4,5%
≥56	N=7338	11,4	19,6	16,0	53,0%	9,3%	8,0	13,2	11,1	52,1%	3,7%
	Twins (16.29%)	11,4	20,3	14,4	53,8%	9,7%	8,2	12,9	11,0	53,0%	4,7%
	Singletons (4.74%)	10,2	20,2	14,6	52,1%	6,3%	9,2	15,5	12,0	52,4%	6,3%
	Parents/spouses (78.96%)	11,5	19,6	16,3	52,9%	9,4%	7,9	13,1	11,1	51,8%	3,3%

Table 4.1. Prevalence of voluntary exercise behavior in a large population-based sample (N=78,524) from the Netherlands. SED: Sedentary, VIG: Vigorous, *: Almost no siblings participate in this age range. N: Number of participants with valid data, SD: standard deviation, IQR: Inter-quantile range, vigorous exercisers are defined as subjects with a METHr score over 35 (i.e., at least five hours per week vigorous (MET=7) activity).

We find a lower volume of exercise behavior in young children (< 9) compared to older children and adolescents. This contrasts with findings for total physical activity, which is known to decrease from a highest level in early childhood to lower levels in late childhood and adolescence (Rowland, 2016). We interpret this to reflect the predominance of play in determining the total physical activity of young children (Pellegrini & Smith, 1998). In keeping with previous reports, the volume of voluntary exercise behavior in leisure time is lower in females than in males and shows a general decline after adolescence in both sexes. For example, 72.8% of the young people between 15 and 18 years old engages in some form of regular exercise and 37.3% engages in regular vigorous exercise, whereas in adults over 55 years, these numbers have dropped to 47.0% and 9.3%. Formal testing of the linear and quadratic effects of age (in years) and sex (females coded 1) and their interaction on weekly METhr in general equation estimation (GEE) models, accounting for the nested (family) structure of the data, revealed effects of sex, with males showing higher levels of exercise ($\beta = -0.53$, $SE = 0.02$, $p < 10^{-99}$) and linear decrease in exercise with age ($\beta = -0.09$, $SE = 0.004$, $p = 1.8 \times 10^{-88}$) as well as an additional quadratic age effect ($\beta = -1.03 \times 10^{-4}$, $SE = 4.84 \times 10^{-6}$, $p < 10^{-99}$). A significant interaction between age and sex ($\beta = 0.04$, $SE = 0.002$, $p = 5.91 \times 10^{-55}$) shows that the decrease in exercise after adolescence is less pronounced in females compared to males, which is in line with previous findings (de Moor et al., 2006).

To reconfirm that exercise behaviors do not differ between twins and non-twins, we selected families with same-sex twins where at least one non-twin sibling of the same sex had also participated. We then compared the voluntary exercise behavior of twins with their non-twin siblings. No differences between twins and non-twin siblings within the same family were found for either males (N families = 5141, $\beta_{MZ} = -0.02$, $SE_{MZ} = 0.06$, $p_{MZ} = 0.73$; $\beta_{DZ} = -0.02$, $SE_{DZ} = 0.06$, $p_{DZ} = 0.73$) or

females (N families = 6028, $\beta_{MZ} = 0.05$, $SE_{MZ} = 0.03$, $p_{MZ} = 0.12$; $\beta_{DZ} = 0.05$, $SE_{DZ} = 0.03$, $p_{DZ} = 0.07$).

The prevalence of regular voluntary exercise behavior in the Dutch twin families is very consistent with the prevalence of voluntary leisure-time physical activity reported by five large-scale studies (Caspersen et al., 2000; Haase et al., 2004; Martinez-Gonzalez et al., 2001; Steptoe et al., 2002; Steptoe et al., 1997). Three of these studies were conducted in 10,000–20,000 young adults (mostly students) aged 18 to 30 years old from the European Union and elsewhere (Haase et al., 2004; Steptoe et al., 2002; Steptoe et al., 1997). All three studies found comparable prevalences of leisure-time exercise: about 70% of the students exercised regularly, meaning they engaged in exercise at least one time per two weeks (e.g., sports activities, physically active pastime). The fourth study was a pan-European study (PAN) of exercise participation in more than 15,000 adults aged 15 up to more than 65 years old from 15 member states of the European Union (Martinez-Gonzalez et al., 2001). They found that 76% of the male and 71% of the female EU population participated in some kind of physical activity during leisure time. In a fifth study, physical activity levels were assessed in 43,732 men and women from the United States aged 18 years and older (Caspersen et al., 2000). The average prevalence across adulthood for any form of activity (five or more times a week and 30 minutes or more per occasion of any activity, but no intensity specified) varied between 73% for women and 79% for men. These prevalences are somewhat higher than our 67%, but this reflects the use of total leisure-time physical activity compared to our restriction to exercise and sports activities.

Overall, a clear picture arises from the six studies described above. Despite its well-documented benefits, a large group of people does not engage in voluntary exercise on a regular basis, particularly in adulthood. Across Europe and the United States, the prevalence for

a complete lack of regular voluntary exercise behavior in adults varies between 21% and 53% depending on the exact age group and the assessment methods used. What factors cause exercisers to exercise and, more importantly, what keeps non-exercisers from doing the same? The remainder of this chapter will review evidence from twin and family studies for a significant genetic contribution to voluntary exercise behavior.

Twin studies on voluntary exercise behavior

As with many other traits, voluntary exercise behavior appears to run in the family. The familial resemblance observed for exercise can represent genetic influences (“nature”) or they can represent environmental influences that are shared within a family (“nurture”). Twin studies can separate these two mechanisms by comparing the resemblance in monozygotic (MZ) or identical twins to the resemblance in dizygotic (DZ) or fraternal twins. When twins are reared together they share part of their environment and this sharing of the family environment is the same for MZ and DZ twins. The important difference between MZ and DZ twins is that the former share (close to) all of their genotypes, whereas the latter share on average only half of the genotypes segregating in that family (Falconer & Mackay, 1996; Plomin et al., 2013).

If the resemblance in voluntary exercise behavior within MZ pairs is larger than in DZ pairs, this suggests that additive genetic factors (A) influence exercise behavior. Additive genetic factors represent the sum of all linear effects of the genetic loci that influence the trait of interest. If the resemblance in voluntary exercise behavior is as large in DZ twins as it is in MZ twins, this points to shared environmental factors (C) as the cause of family resemblance (Boomsma et al., 2002). Shared environmental factors are defined as those environmental factors that are shared within a family, such as

parenting behaviors, family functioning, neighborhood or socioeconomic status. The extent to which MZ twins do not resemble each other is ascribed to the unique (or non-shared) environmental factors (E). These include all unique experiences like differential jobs or lifestyles, accidents or other life events, and in childhood, differential treatment by the parents, and nonshared friends and peers. Measurement error will also be subsumed by the unique environmental factor.

The effect of genetic and environmental factors on voluntary exercise behavior in a sample of MZ and DZ pairs can be graphically depicted in a path diagram (see Figure 4.1).

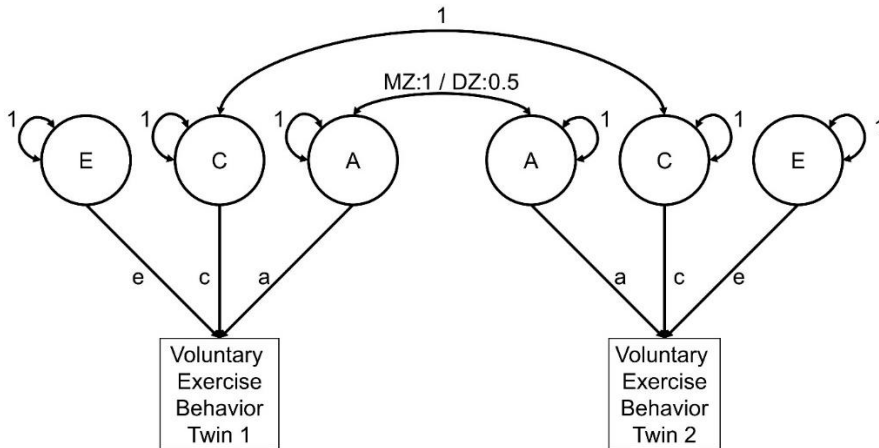


Figure 4.1. Path diagram depicting correlated latent additive genetic (A) and shared environmental (C) factors that can cause twin resemblance in voluntary exercise behavior, as well as unique environmental (E) factors that are uncorrelated in the twins. We set the correlation of the latent genetic factors for MZ twins to 1, and for DZ twins to 0.5. The correlation of shared environmental factors is set to 1 for both types of twins. The latent unique environmental factors are (per definition) uncorrelated. Unobserved latent variables have no scale: their variance is arbitrarily set to 1 (the double arrows that start and end in the latent factors). Path coefficients a , c , and e represent the factor loadings of exercise on the latent factors.

The heritability of voluntary exercise behavior is defined as the relative proportion of the total variance explained by genetic factors. In terms of the parameter estimates obtained from fitting the twin model to the data, the heritability can be expressed as $a^2/(a^2 + c^2 + e^2)$. The heritability can also be represented as a percentage by multiplying this ratio by 100. The proportions of variance ascribed to shared environmental and unique environmental factors can be computed in a similar manner and are given by, respectively, $c^2/(a^2 + c^2 + e^2)$ and $e^2/(a^2 + c^2 + e^2)$.

An overview of twin studies conducted on voluntary exercise behavior is given in Table 4.2.

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
Heller et al., 1988, Australia	adolescent and adult twins, 106 MZ pairs (36.8% male), 94 DZ pairs (26.6% male), ages 17 ~ 66 (M = 36, SD = 12)	Vigorous Exercise in the past two weeks	Males: $a^2 = 39\%$ Females: $a^2 = 39\%$
Boomsma et al., 1989, Netherlands	adolescent twins, 44 MZ pairs (36.4% male), 46 DZ pairs (32.6% male), ages 14 ~ 20 (M = 17, SD = 2)	Sports participation variable is dichotomous: "Have you been involved in sports activities during the last three months?" YES/NO	Males: $a^2 = 77\%$, $e^2 = 23\%$ Females: $a^2 = 35\%$, $e^2 = 65\%$
Koopmans et al., 1994, Netherlands	adolescent and adult twins, 578 MZ pairs (43.1% male), 1000 DZ pairs (24.1% male), ages 13 ~ 22 (M = 18, SD = 2)	Sports participation variable is dichotomous: "Do you participate in sports?" YES/NO	Males: $a^2 = 45\%$, $c^2 = 44\%$, $e^2 = 11\%$ Females: $a^2 = 45\%$, $c^2 = 44\%$, $e^2 = 11\%$
Lauderdale et al., 1997, USA	adult male Vietnam Era Twin Registry, 1006 MZ pairs, 530 DZ pairs, ages 33 ~ 51 (M = 41)	Vigorous Exercise (YES/NO): jogging > 10 miles/week	Males: $a^2 = 53\%$, $e^2 = 47\%$
		Vigorous Exercise (YES/NO): racquet sports > 5 hr/week	Males: $a^2 = 48\%$, $c^2 = 4\%$, $e^2 = 48\%$
		Vigorous Exercise (YES/NO): strenuous sports	Males: $a^2 = 30\%$, $c^2 = 17\%$, $e^2 = 53\%$
		Vigorous Exercise (YES/NO): bicycling > 50 miles/week	Males: $a^2 = 58\%$, $e^2 = 42\%$
		Vigorous Exercise (YES/NO): swimming > 2 miles/week	Males: $a^2 = 8\%$, $c^2 = 31\%$, $e^2 = 61\%$
Beunen & Thomis, 1999, Belgium	adolescent twins, 43 MZ pairs (48.8% male), 61 DZ pairs (34.4% male), M age = 15	Number of hours spent on sports each week	Males: $a^2 = 83\%$, $e^2 = 17\%$ Females: $a^2 = 44\%$, $c^2 = 54\%$, $e^2 = 02\%$
Kujala et al., 2002, Finland	adult same sex twins, 1772 MZ pairs, 3551 DZ pairs, ages 24 ~ 60	Participation in vigorous physical activity: either "alternatively walking and jogging", "jogging", or "running"	Males: $a^2 = 45\%$ Females: $a^2 = 45\%$
Frederiksen and Christensen, 2003, Denmark	elderly twins, 616 MZ pairs, 642 DZ pairs, ages 45 ~ 68	Engage in any of: jogging, gym, swimming, tennis, badminton, football, handball, aerobics, rowing, table tennis, volleyball, in leisure time	Males: $a^2 = 49\%$, $e^2 = 51\%$ Females: $a^2 = 49\%$, $e^2 = 51\%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
de Geus et al., 2003, Netherlands	adolescent twins, 69 MZ pairs (50.7% male), 88 DZ pairs (34.1% male), ages 13 ~ 22 (M = 16.7, SD = 2)	Average weekly METH spent on sports or other moderate to vigorous voluntary exercise activities (with intensity of 4 METH/wk or higher) in the last three months	Males: $a^2 = 79\%$, $e^2 = 21\%$ Females: $a^2 = 79\%$, $e^2 = 21\%$
	adult twins, 93 MZ pairs (48.4% male), 115 DZ pairs (32.2% male), ages 35 ~ 62 (M = 44, SD = 7)	Average weekly METH spent on sports or other moderate to vigorous voluntary exercise activities (with intensity of 4 METH/wk or higher) in the last three months	Males: $a^2 = 41\%$, $e^2 = 59\%$ Females: $a^2 = 41\%$, $e^2 = 59\%$
Simonen et al., 2004, Finland	adult twins, 147 MZ pairs, 153 DZ pairs, M age = 50 (SD = 8)	Weekly hours spent on leisure time exercise at ages 12 ~ 18	Males: $a^2 = 18\%$, $c^2 = 37\%$, $e^2 = 45\%$ Females: $a^2 = 18\%$, $c^2 = 37\%$, $e^2 = 45\%$
		Weekly hours spent on leisure time exercise at ages 18 ~ 70	Males: $a^2 = 51\%$, $e^2 = 49\%$ Females: $a^2 = 51\%$, $e^2 = 49\%$
Stubbe et al., 2005, Netherlands	adolescent twins NTR, 276 MZ pairs (41.7% male), 370 DZ pairs (23.5% male), ages 13 ~ 14	The METH/week score was dichotomized into YES/NO at a 4 METH/wk threshold, excluded PE	Males: $a^2 = 0\%$, $c^2 = 84\%$, $e^2 = 16\%$ Females: $a^2 = 0\%$, $c^2 = 84\%$, $e^2 = 16\%$
	adolescent twins NTR, 321 MZ pairs (42.4% male), 442 DZ pairs (25.3% male), ages 15 ~ 16	The METH/week score was dichotomized into YES/NO at a 4 METH/wk threshold, excluded PE	Males: $a^2 = 0\%$, $c^2 = 78\%$, $e^2 = 22\%$ Females: $a^2 = 0\%$, $c^2 = 78\%$, $e^2 = 22\%$
	adolescent twins NTR, 248 MZ pairs (40.3% male), 395 DZ pairs (24.3% male), ages 17 ~ 18	The METH/week score was dichotomized into YES/NO at a 4 METH/wk threshold, excluded PE	Males: $a^2 = 36\%$, $c^2 = 47\%$, $e^2 = 17\%$ Females: $a^2 = 36\%$, $c^2 = 47\%$, $e^2 = 17\%$
	adolescent twins NTR, 250 MZ pairs (36.8% male), 326 DZ pairs (25.2% male), ages 19 ~ 20	The METH/week score was dichotomized into YES/NO at a 4 METH/wk threshold, excluded PE	Males: $a^2 = 85\%$, $e^2 = 15\%$ Females: $a^2 = 85\%$, $e^2 = 15\%$
Eriksson et al., 2006, Sweden	young adult male twins, N = 1234	Leisure time sports from a modified version of the Baecke questionnaire.	Males: $a^2 = 56\%$, $e^2 = 44\%$
Stubbe et al., 2006, Australia	adult twins, 1260 MZ pairs (32.6% male), 1468	Spending at least 60 minutes each week on	Males: $a^2 = 48\%$, $e^2 = 52\%$ Females: $a^2 = 48\%$, $e^2 = 52\%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
	DZ pairs (18.3% male), ages 19 ~40 (M = 31.8)	exercise activities with intensity > 4 MET	
Stubbe et al., 2006, Denmark	adult twins, 3046 MZ pairs (43.3% male), 6410 DZ pairs (25.6% male), ages 19 ~40 (M = 31.1)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 52%$, $e^2 = 48%$ Females: $a^2 = 52%$, $e^2 = 48%$
Stubbe et al., 2006, Finland	adult twins, 2841 MZ pairs (43.8% male), 6001 DZ pairs (44.5% male), ages 19 ~40 (M = 26.9)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 62%$, $e^2 = 38%$ Females: $a^2 = 62%$, $e^2 = 38%$
Stubbe et al., 2006, Netherlands	adult twins NTR, 1266 MZ pairs (33.4% male), 1415 DZ pairs (20.8% male), ages 19 ~40 (M = 25.7)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 67%$, $e^2 = 33%$ Females: $a^2 = 67%$, $e^2 = 33%$
Stubbe et al., 2006, Norway	adult twins, 1502 MZ pairs (42.5% male), 2493 DZ pairs (21.8% male), ages 19 ~40 (M = 24.7)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 26%$, $c^2 = 37%$, $e^2 = 37%$ Females: $a^2 = 56%$, $e^2 = 44%$
Stubbe et al., 2006, Sweden	adult twins, 3598 MZ pairs (45.4% male), 5329 DZ pairs (47.3% male), ages 19 ~40 (M = 28.6)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 62%$, $e^2 = 38%$ Females: $a^2 = 62%$, $e^2 = 38%$
Stubbe et al., 2006, UK	adult female twins, 163 MZ pairs (0% male), 259 DZ pairs (0% male), ages 19 ~40 (M = 32.4)	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Females: $a^2 = 71%$, $e^2 = 29%$
de Moor, Posthuma et al., 2007, Netherlands	Adult NTR twins 156 MZ pairs (37.8% male), 326 DZ pairs (20.2% male), ages 18 ~ 50	Spending at least 60 minutes each week on exercise activities with intensity > 4 MET	Males: $a^2 = 69%$, $e^2 = 31%$ Females: $a^2 = 46%$, $e^2 = 54%$
de Moor, Stubbe et al., 2007, Netherlands	adult twins NTR, 755 MZ pairs (26.9% male), 2306 DZ pairs (15.3% male), M age = 31 (SD = 7)	Three groups based on two MET-thresholds: 0 sedentary; 0-6METH/wk moderate; 6+ METH/wk vigorous	Males: $a^2 = 54%$, $e^2 = 46%$ Females: $a^2 = 54%$, $e^2 = 46%$
McCaffery et al., 2009, USA	Vietnam Era Twin Registry, 2024 MZ pairs (100% male), 1566 DZ pairs (100% male), M ages = 41.07 (SD = 3.15)	Jog or run ≥ 10 miles/wk OR play strenuous racquet sports ≥ 5 h/wk OR ride a bicycle ≥ 50 miles/wk OR swim ≥ 2 miles/wk OR play other strenuous sports	Males: $a^2 = 10%$, $c^2 = 18%$, $e^2 = 72%$
Aaltonen et al., 2010, Finland	Baseline young adult twin data, N = 13556, ages 18 ~ 54	MET hours/day.	Males: $a^2 = 47%$, $e^2 = 53%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
			Females: $a^2 = 42\%$, $e^2 = 58\%$
	Follow-up young adult twin data, N = 13822, ages 24 ~ 60	MET hours/day.	Males: $a^2 = 38\%$, $e^2 = 62\%$ Females: $a^2 = 31\%$, $e^2 = 69\%$
	young twins NTR, 554 MZ pairs (38.1% male), 948 DZ pairs (21.2% male), ages 13 ~14 (M = 14.5, SD = 0.31)	Three groups based on two thresholds :0-5 METH/wk; 5-20 METH/wk; 20+ METH/wk	Males: $a^2 = 85\%$, $e^2 = 15\%$ Females: $a^2 = 38\%$, $c^2 = 46\%$, $e^2 = 16\%$
van der Aa et al., 2010, Netherlands	young twins NTR, 662 MZ pairs (42.6% male), 969 DZ pairs (21.7% male), ages 15 ~16 (M = 16.2, SD = 0.61)	Three groups based on two thresholds :0-5 METH/wk; 5-20 METH/wk; 20+ METH/wk	Males: $a^2 = 80\%$, $e^2 = 20\%$ Females: $a^2 = 80\%$, $e^2 = 20\%$
	young twins NTR, 488 MZ pairs (34.6% male), 747 DZ pairs (20.9% male), ages 17 ~19 (M = 18.1, SD = 0.7)	Three groups based on two thresholds :0-5 METH/wk; 5-20 METH/wk; 20+ METH/wk	Males: $a^2 = 72\%$, $e^2 = 28\%$ Females: $a^2 = 72\%$, $e^2 = 28\%$
Mustelin et al., 2011, Finland	young adult twins FinnTwin13, 59 MZ pairs, 92 DZ pairs, ages 23 ~ 31 (M = 27.4, SD = 2)	Baecke questionnaire: sport index (sports activities during leisure time)	Males: $a^2 = 56\%$ Females: $a^2 = 56\%$
	young twins NTR, 656 MZ pairs (23.3% male), 1628 DZ pairs (13.9% male), ages 13 ~18 (M = 16.4, SD = 1.1)	Spending at least 60 minutes each week on exercise activities > 4 MET	Males: $a^2 = 42\%$, $c^2 = 44\%$, $e^2 = 14\%$ Females: $a^2 = 36\%$, $c^2 = 52\%$, $e^2 = 12\%$
de Moor et al., 2011, Netherlands	adult twins NTR, 685 MZ pairs (42.6% male), 1223 DZ pairs (24.9% male), ages 30 ~65 (M = 39.9, SD = 9.4)	Spending at least 60 minutes each week on exercise activities > 4 MET	Males: $a^2 = 42\%$, $e^2 = 58\%$ Females: $a^2 = 42\%$, $e^2 = 58\%$
	(young) adult twins, N = 4604	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 22 ~ 36	Males: $a^2 = 13\%$, $c^2 = 27$, $e^2 = 60\%$ Females: $a^2 = 37\%$, $c^2 = 6\%$, $e^2 = 57\%$
Vink et al., 2011, Australia		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 37 ~ 50	Males: $a^2 = 13\%$, $c^2 = 27\%$, $e^2 = 60\%$ Females: $a^2 = 37\%$, $c^2 = 6\%$, $e^2 = 57\%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
Vink et al., 2011, Denmark	(young) adult twins, N = 26298	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 33	Males: $a^2 = 47\%$, $c^2 = 1\%$, $e^2 = 52\%$ Females: $a^2 = 27\%$, $c^2 = 15\%$, $e^2 = 58\%$
		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 34 ~ 50	Males: $a^2 = 47\%$, $c^2 = 1\%$, $e^2 = 52\%$ Females: $a^2 = 27\%$, $c^2 = 15\%$, $e^2 = 58\%$
Vink et al., 2011, Finland	(young) adult twins, N = 23095	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 27	Males: $a^2 = 57\%$, $c^2 = 3\%$, $e^2 = 40\%$ Females: $a^2 = 56\%$, $c^2 = 3\%$, $e^2 = 42\%$
		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 28 ~ 50	Males: $a^2 = 57\%$, $c^2 = 3\%$, $e^2 = 40\%$ Females: $a^2 = 56\%$, $c^2 = 3\%$, $e^2 = 42\%$
Vink et al., 2011, Netherlands	(young) adult twins, N = 6753	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 25	Males: $a^2 = 64\%$, $c^2 = 3\%$, $e^2 = 32\%$ Females: $a^2 = 28\%$, $c^2 = 23\%$, $e^2 = 48\%$
		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 26 ~ 50	Males: $a^2 = 64\%$, $c^2 = 3\%$, $e^2 = 32\%$ Females: $a^2 = 28\%$, $c^2 = 23\%$, $e^2 = 48\%$
Vink et al., 2011, Norway	young adult twins, N = 9066	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 31	Males: $a^2 = 35\%$, $c^2 = 29\%$, $e^2 = 36\%$ Females: $a^2 = 54\%$, $c^2 = 3\%$, $e^2 = 44\%$
Vink et al., 2011, Sweden	(young) adult twins, N = 27414	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 35	Males: $a^2 = 53\%$, $e^2 = 46\%$ Females: $a^2 = 54\%$, $e^2 = 46\%$
		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 36 ~ 50	Males: $a^2 = 53\%$, $e^2 = 46\%$ Females: $a^2 = 54\%$, $e^2 = 46\%$
Vink et al., 2011, UK	(young) adult female twins, N = 2451	Spending at least 60 minutes each week on exercise activities > 4 MET at ages 19 ~ 40	Females: $a^2 = 57\%$, $c^2 = 9\%$, $e^2 = 42\%$
		Spending at least 60 minutes each week on exercise activities > 4 MET at ages 41 ~ 50	Females: $a^2 = 57\%$, $c^2 = 9\%$, $e^2 = 42\%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
Mustelin et al., 2012, Finland	young adult twins FinnTwin12, 229 MZ pairs (42.4% male), 347 DZ pairs (25.4% male), ages 20 ~26 (M = 22.4, SD = 0.7)	Sport activities are scored as 1,3 or 5 according to their intensity	Males: $a^2 = 64\%$, $e^2 = 36\%$ Females: $a^2 = 64\%$, $e^2 = 36\%$
	young twins NTR, 648 MZ pairs (45.8% male), 1320 DZ pairs (26.1% male), M age = 7.45 (SD = 0.32)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 24\%$, $c^2 = 71\%$, $e^2 = 6\%$ Females: $a^2 = 22\%$, $c^2 = 67\%$, $e^2 = 11\%$
Huppertz et al., 2012, Netherlands	young twins NTR, 620 MZ pairs (45.8% male), 1141 DZ pairs (26.1% male), M age = 10.1 (SD = 0.33)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 66\%$, $c^2 = 25\%$, $e^2 = 10\%$ Females: $a^2 = 16\%$, $c^2 = 72\%$, $e^2 = 11\%$
	young twins NTR, 1540 MZ pairs (46.7% male), 2746 DZ pairs (24.3% male), M age = 12.3 (SD = 0.4)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 38\%$, $c^2 = 50\%$, $e^2 = 11\%$ Females: $a^2 = 36\%$, $c^2 = 50\%$, $e^2 = 11\%$
Aaltonen et al., 2013, Finland	adolescent twins FinnTwin16, 769 MZ pairs (38.1% male), 1743 DZ pairs (24.6% male), M age = 16.2 (SD = 0.1)	1: exercising less than once a week; 2: exercising one to three times per week; 3: exercising four or more times per week	Males: $a^2 = 52\%$, $c^2 = 19\%$, $e^2 = 29\%$ Females: $a^2 = 52\%$, $c^2 = 24\%$, $e^2 = 24\%$
	adolescent twins FinnTwin16, 724 MZ pairs (36.3% male), 1614 DZ pairs (24.7% male), M age = 17.1 (SD = 0.1)	1: exercising less than once a week; 2: exercising one to three times per week; 3: exercising four or more times per week	Males: $a^2 = 44\%$, $c^2 = 24\%$, $e^2 = 32\%$ Females: $a^2 = 50\%$, $c^2 = 26\%$, $e^2 = 24\%$
	young adult twins FinnTwin16, 715 MZ pairs (35.9% male), 1603 DZ pairs (24.2% male), M age = 18.6 (SD = 0.2)	1: exercising less than once a week; 2: exercising one to three times per week; 3: exercising four or more times per week	Males: $a^2 = 46\%$, $c^2 = 23\%$, $e^2 = 31\%$ Females: $a^2 = 51\%$, $c^2 = 21\%$, $e^2 = 28\%$
	young adult twins FinnTwin16, 613 MZ pairs (37.8% male), 1351 DZ pairs (23.2% male), M age = 24.5 (SD = 0.9)	1: exercising less than once a week; 2: exercising one to three times per week; 3: exercising four or more times per week	Males: $a^2 = 34\%$, $c^2 = 43\%$, $e^2 = 23\%$ Females: $a^2 = 31\%$, $c^2 = 49\%$, $e^2 = 20\%$
Huppertz, Bartels, Jansen et al., 2014, Netherlands	adult twins NTR, 701 MZ pairs (27% male), 572 DZ pairs (14.2% male), ages 18 ~50 (M = 30.5, SD = 7)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 50\%$, $e^2 = 50\%$ Females: $a^2 = 43\%$, $e^2 = 57\%$

Study	Sample	Exercise Behavior Phenotype	Heritability estimates
Huppertz, Bartels, Groen-Blokhuis et al., 2014, Netherlands	adult twins NTR, 701 MZ pairs (27% male), 572 DZ pairs (14.2% male), M age = 30.7 (SD = 7)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 50\%$, $e^2 = 50\%$ Females: $a^2 = 43\%$, $e^2 = 57\%$
	young twins NTR, 1262 MZ pairs (47.9% male), 2384 DZ pairs (27.1% male), M age = 7.52 (SD = 0.34)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 14\%$, $c^2 = 80\%$, $e^2 = 6\%$ Females: $a^2 = 12\%$, $c^2 = 80\%$, $e^2 = 8\%$
	young twins NTR, 1384 MZ pairs (48.3% male), 2582 DZ pairs (26.1% male), M age = 9.84 (SD = 0.43)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 26\%$, $c^2 = 69\%$, $e^2 = 7\%$ Females: $a^2 = 26\%$, $c^2 = 65\%$, $e^2 = 8\%$
Huppertz et al., 2016, Netherlands	young twins NTR, 2615 MZ pairs (46.4% male), 4589 DZ pairs (24.9% male), M age = 12.25 (SD = 0.4)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 31\%$, $c^2 = 62\%$, $e^2 = 7\%$ Females: $a^2 = 27\%$, $c^2 = 65\%$, $e^2 = 8\%$
	young twins NTR, 1451 MZ pairs (39.4% male), 2333 DZ pairs (21.4% male), M age = 14.61 (SD = 0.6)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 43\%$, $c^2 = 36\%$, $e^2 = 21\%$ Females: $a^2 = 40\%$, $c^2 = 43\%$, $e^2 = 17\%$
	young twins NTR, 959 MZ pairs (39.9% male), 1305 DZ pairs (21.2% male), M age = 16.87 (SD = 0.45)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 56\%$, $c^2 = 27\%$, $e^2 = 17\%$ Females: $a^2 = 49\%$, $c^2 = 31\%$, $e^2 = 20\%$
	young twins NTR, 458 MZ pairs (30.6% male), 572 DZ pairs (18.5% male), M age = 18.77 (SD = 0.51)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 79\%$, $c^2 = 4\%$, $e^2 = 17\%$ Females: $a^2 = 49\%$, $c^2 = 19\%$, $e^2 = 33\%$
Nederend et al., 2016, Netherlands	young twins NTR, 114 MZ pairs (50.9% male), 111 DZ pairs (32.4% male), M age = 17.1 (SD = 1.1)	The METH/week score based on the summed MET×time/wk score over all activities performed	Males: $a^2 = 80\%$, $e^2 = 20\%$ Females: $a^2 = 80\%$, $e^2 = 20\%$

Table 4.2. Twin studies on voluntary exercise behavior. NB: A number of studies reported on overlapping samples, most notably Vink et al. (2011) with Stubbe et al. (2005), and van der Aa (2010) and Huppertz et al. (2014) with Huppertz et al. (2016) although the exact exercise phenotype and age categories used differed.

Despite the slightly different measures used (i.e., Vigorous Exercise, Sports Participation, Moderate-to-Vigorous Exercise, Leisure-Time Sports, Vigorous Exercise, Exercise Participation, Sports Physical Activity) and the use of either ordinal or interval scales, these studies converge on the finding that voluntary exercise behavior is heritable across the life span. There are, however, remarkable age-related changes in the relative contribution of genetic factors to the total population variance in this behavior. The largest changes occur during childhood and adolescence (Huppertz et al., 2016; Huppertz et al., 2012; van der Aa et al., 2010). Huppertz et al. (2016) used a combination of univariate modeling on a very large cross-sectional set of Dutch twins (birth year ranged between 1986 and 2004) and a genetic simplex model on the subset of twins that had longitudinal data across multiple ages. Heritability was found to be low in seven-year-olds (14% in males and 12% in females) but gradually increased up to age 18 (79% in males and 49% in females). In contrast, the initially very high relative contribution of the shared environment to the variance in childhood exercise behavior rapidly waned when children grew into adolescence and young adulthood (from 80% to 4% in males and from 80% to 19% in females). This decrease in the shared environmental variance, which is stronger in males than in females, occurred in parallel to a large increase in the genetic variance. The genetic effects in males remained largely the same from childhood to late adolescence (although their relative importance increased), whereas in females, the contribution of novel genetic effects as a function of age was more profound.

Twin studies in Finland, Sweden, and Belgium have shown that the age-moderation of the genetic and shared environmental effects on exercise behaviors hold in these countries too (Aaltonen et al., 2013; Beunen & Thomis, 1999; Carlsson et al., 2006), and further confirmed

that shared environmental factors seem more important in young adolescent girls than in boys. The clear age moderation seen by Huppertz et al. (2016) in twins born between 1986 and 2004 was already observed by Stubbe et al. (2005) in an earlier birth study of Dutch adolescent twins born between 1971 and 1987. Taken together, these results imply that family-based interventions are useful to increase this health behavior in children, whereas individually based interventions might be better suited for adolescents.

Studies conducted in adult twins between 19 and 68 years (Aaltonen et al., 2010, 2013; Boomsma et al., 1989; de Geus et al., 2003; de Moor, Posthuma, et al., 2007; de Moor, Stubbe, et al., 2007; de Moor et al., 2011; Eriksson et al., 2006; Frederiksen & Christensen, 2003; Heller et al., 1988; Huppertz, Bartels, Jansen, et al., 2014; Koopmans et al., 1994; Kujala et al., 2002; Lauderdale et al., 1997; McCaffery et al., 2009; Mustelin et al., 2012; Mustelin et al., 2011; Nederend et al., 2016; Simonen et al., 2004; Stubbe et al., 2005; Stubbe et al., 2006; Vink et al., 2011) show that variation in exercise behavior is influenced by genetic factors, with heritability estimates ranging between 10% and 85% of the variance in exercise. Most of these studies included twins of a wide age range, for example, 19 to 40 years (Stubbe et al., 2006) or 18 to 60 years (Aaltonen et al., 2010). A large study by Vink et al. (2011) investigated in seven different countries whether the heritability of exercise behavior during adulthood (19 to 50 years) changes with age. In four of the seven countries (Denmark, Finland, Sweden, and the Netherlands), a significant decrease in heritability was observed with age (from 60–90% at age 19 to 13–40% at age 50). In the other three countries (Australia, Norway, and United Kingdom), the heritability of exercise was found to be stable during adulthood.

The results from the twin studies in Table 4.2 demonstrate convincingly that heritable factors are present at all ages. The

heritability of voluntary exercise behavior peaks during late adolescence and young adulthood.

Family studies on voluntary exercise behavior

The heritability estimates obtained from twin studies are valid only if the assumptions underlying the twin method hold. An important assumption is the equal environment assumption, which states that environmentally caused similarity in the trait or behavior of interest (i.e., voluntary exercise behavior) is the same in MZ and DZ twin pairs (Plomin et al., 2013). Only one twin study has explicitly tested the equal environment assumption for a set of relevant traits (Eriksson et al., 2006). It was tested whether twin pairs with higher contact frequency were more similar in their total physical activity, physical activity at work or in leisure-time separately, and whether this effect depended on zygosity status. No evidence for violation of the equal environment assumption was found for any of the physical activity measures. Other assumptions of the twin method include absence of assortative mating and the independence of genes and environment. If phenotypic assortative mating on exercise behavior is present, the correlation between genetic factors influencing exercise behavior is higher than the theoretical 50% in DZ twins and full siblings, which can cause underestimation of heritability and overestimation of the shared environmental effects. If there is cultural transmission, that is, the parents' exercise behavior is a part of the relevant shared environment by the twins and acts as a "role-model" for the exercise behavior of the children, then the genetic and the shared environmental effects on exercise behavior are no longer independent. Correlation of an exercise-inducing family environment with a genetic propensity to exercise will inflate estimates of C in the twin model. The presence of assortative mating and cultural transmission and how they impact heritability estimates can be tested by adding data from more types of

relatives to the twin design, such as data from parents, grandparents, spouses, and siblings. Spouse correlations inform on the presence of assortative mating. Parent offspring correlations enable testing for the effects of cultural transmission.

Table 4.3 lists the five studies that employed extended family designs to report on the familial resemblance of voluntary exercise behavior among adolescent offspring (age range 13 to 20 years) and their parents (Choh et al., 2009; de Moor et al., 2011; Koopmans et al., 1994; Seabra et al., 2008, 2014).

Study	Sample	Phenotype	Spousal, sibling and parent-offspring correlations	Estimates
Koopmans et al., 1994, Netherlands	N = 6470 Fathers: M age = 48 SD age = 5.7 Mothers: M age = 46 SD age = 5.2 Siblings: M age = 18 SD age = 2.3	Regular sports participation (YES/NO)	Spousal: 0.49 Father-son 0.37, Mother-son 0.32, Father-Daughter: 0.29, Mother-Daughter-0.30	a ² = 45% c ² = 44% e ² = 11%
Seabra et al., 2008, Portugal	N = 9500, Fathers (2375): M age = 45.4 SD = 5.8 Mothers(2375): M age = 42.9 SD = 5.5 Sons (2425): M age = 16.1 SD = 4 Daughters (2325) M age = 16 SD = 4	Baecke et al. questionnaire: sport index	Spousal: 0.29 Female siblings: 0.25, Male siblings: 0.23 Female-male siblings: 0.24 Father-son: 0.19, Mother-son: 0.15 Father-daughter: 0.18, Mother-daughter: 0.18	a ² = 25% e ² = 75%
Choh et al., 2009, USA	N = 518, aged 18 - 86 Fathers (219), Mothers(302)	Baecke et al. questionnaire: sport index	Not reported	a ² = 17% c ² = 25% e ² = 58%
de Moor et al, 2011, Netherlands	N = 3663 Fathers (1488): M age = 45.5 SD age = 4.6 Mothers (1650): M age = 45.5 SD age = 4.6 Sons (1636): M age = 16.4 SD age = 1.2 Daughters (1889): M age = 16.4 SD age = 1.2	The METH/wk score was dichotomized into YES/NO regular exercise participation at a > 4 METH/wk threshold	Spousal: 0.41, Father-son: 0.36, Mother-son: 0.18 Father-daughter: 0.21, Mother-daughter: 0.21	a ² = 64% c ² = 0% e ² = 36%

			Spousal: 0.23, Female siblings: 0.31, Male siblings: 0.29	
		From Baecke et al. questionnaire: Sports Participation	Female-male siblings: 0.23 Father-son: 0.16, Mother-son: 0.11 Father-daughter: 0.14, Mother-daughter: 0.14	a2 = 50% e2 = 50%
			Spousal: 0.12, Female siblings: 0.39, Male siblings: 0.51	
	N = 9500 Fathers (2375): M age = 45.4 SD age = 5.8 Mothers (2375): M age = 42.9 SD age = 5.5	From Baecke et al. questionnaire: Intensity of exercise	Female-male siblings: 0.18 Father-son: 0.15, Mother-son: 0.15 Father-daughter: 0.1 Mother-daughter: 0.1	a2 = 40% e2 = 60%
Seabra et al., 2014, Portugal	Sons (2425): M age = 16.1 SD age = 4 Daughters (2325): M age = 16 SD age = 4	From Baecke et al. questionnaire: Weekly amount of exercise	Spousal: 0.46 Female siblings: 0.52, Male siblings: 0.37 Female-male siblings: 0.22 Father-son: 0.14, Mother-son: 0.21 Father-daughter: 0.23, Mother-daughter: 0.23	a2 = 46% e2 = 54%
		From Baecke et al. questionnaire: Proportion of the year exercising	Spousal: 0.48 Female siblings: 0.52, Male siblings: 0.22 Female-male siblings: 0.27 Father-son: 0.22, Mother-son: 0.08 Father-daughter: 0.4, Mother-daughter: 0.4	a2 = 49% e2 = 51%

Table 4.3. Family studies on voluntary exercise behavior.

The spouse correlation for exercise behavior was significant in all these studies and ranged from 0.16 to 0.48. de Moor et al. (2011) analyzed twin-spouse pairs and demonstrated that the significant spouse correlation for exercise was best explained by phenotypic

assortment (i.e., that partners choose each other because they are similar in their exercise behavior) rather than by social homogamy (i.e., that partners similar in exercise behavior meet and marry because they come from similar social backgrounds) or social interaction processes (i.e., that partners resemble each other because they spend time together and mutually influence each other). Importantly, an extended twin-family model that took assortative mating into account led to nearly the same heritability estimates as the twin-only model.

Parent-offspring correlations have ranged from 0.13 to 0.25 and are generally somewhat lower than the full sibling correlations (0.24 to 0.31). de Moor et al. (2011) estimated in a sample of 3,525 adolescent twins and their siblings (13 to 18 years) and 3,138 parents from 1,736 families that 42% of variation in adolescent exercise behavior in boys could be explained by genetic factors, and 52% could be explained by environmental factors shared by family members of the same generation but not with the parents. In girls, 36% of the variance in exercise was explained by genetic factors and 41% by generation-specific environmental effects. Cultural transmission effects from parents to offspring were not significant in adolescence, that is, adolescents do not simply “copy” the exercise behaviors they see in their parents.

Taken together, the results of extended twin family studies suggest that heritability estimates for exercise behavior obtained from studies using only twins are not overly biased.

Gene-finding studies

The heritability of exercise behavior has been well established, but less is known about the genetic variants that are associated with this trait. Candidate gene studies in single small-sized cohort studies are now widely distrusted as a reliable source of replicable association, because most complex behavioral traits are highly polygenic, with only

a very low percentage of the variance in the trait explained by a single genetic variant. The first genome-wide association (GWA) study on voluntary exercise behavior that we conducted in 2009 was, in retrospect, also heavily underpowered (de Moor et al., 2009). It tested 1,607,535 observed and imputed SNP markers that passed stringent quality controls for their association with leisure-time exercise behavior in two independent samples comprising 1,644 Dutch and 978 American subjects. The most promising finding was in the *PAPSS2* gene (37 SNPs with pooled p-values $<1.0 \times 10^{-5}$) and in two intergenic regions on chromosomes 2q33.1 and 18p11.32. The *PAPSS2* gene encodes a protein that is involved in the sulfation of compounds such as lipids, carbohydrates, proteins, and exogenous drugs. Interestingly, the 10q23 region that harbors the *PAPSS2* gene has been linked to maximal exercise ability in a genome-wide linkage study of 453 sib pairs (Rico-Sanz et al., 2004). This is in keeping with the theoretical notion that exercise ability may be an important determinant of leisure time exercise behavior (de Geus & de Moor, 2008), which was supported by the finding that regular exercise behavior is correlated with various fitness traits, particularly maximal endurance capacity, not only phenotypically but also genetically (Schutte, Nederend, Hudziak, Bartels, et al., 2016; Schutte, Nederend, Hudziak, de Geus, et al., 2016).

More large-scale collaborative consortia are now direly needed to conduct a meta-analysis on GWA studies on voluntary exercise behavior. These could repeat the successes of similar studies for other health behaviors, like smoking and alcohol use or BMI, that have already discovered many genetic variants (L. S. Chen et al., 2012; Locke et al., 2015; Schumann et al., 2011). Detection of the genetic variants underlying voluntary exercise behavior is a route to increased future understanding of the actual biological pathways underlying the individual differences in the choice for regular exercise behavior, that

is, the biology that makes exercisers exercise but keeps non-exercisers from doing the same. Knowledge of these pathways may further help resolve causality in the well-known association of exercise with other lifestyle behaviors such as overeating and smoking, or with physical health problems like cardiovascular and metabolic disease (Kujala et al., 2002) and mental health problems, including depression (de Moor et al., 2008). More importantly, such understanding may be exploited in stratified or personalized interventions that take innate biological differences into account (de Geus & de Moor, 2008, 2011; Schutte et al., 2017). Future large-scale meta-analytic GWA efforts can therefore be expected to render important clues to improve the success of interventions on this crucial health behavior.



CHAPTER

An Extended Twin-Pedigree Study of Different Classes of Voluntary Exercise Behavior

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Abstract

We investigated the familial clustering of different classes of voluntary regular exercise behavior in extended twin-family pedigrees. In contrast to the earlier work based on twin data only, this allowed us to estimate the contributions of shared household effects (C), additive (A), and non-additive (D) genetic effects on voluntary exercise behavior. To test whether shared household effects were inflated by assortative mating we examined the causes of spousal resemblance. For adolescent and adult participants (aged 16 to 65) in the Netherlands Twin Register we constructed 19,543 pedigrees which specified all relations among nuclear family members and larger families in the register (N = 50,690 individuals). Data were available on total weekly MET minutes spent on leisure time exercise, and on total weekly MET minutes spent on exercise activities in team-based, solitary, competitive, non-competitive, externally paced and internally paced exercise. We analyzed the data in the Mendel software package (Lange et al., 2013) under multiple definitions of household sharing and used data from spouses of twins to test phenotypic assortment, social homogamy, and marital interaction as potential sources of spousal resemblance. Results confirmed the influence of genetic factors on the total volume of weekly exercise behavior throughout the life span. Broad sense heritability ranged from 34% to 41% (19-26% A, 12-21% D), and did not depend on the definition for household sharing. Engaging in team-based, competitive, externally paced activities (e.g., soccer) was ~13% more heritable than engaging in non-competitive, solitary activities (e.g., jogging). Having shared a household as siblings explained 4-8% of the variance in adult exercise behavior, whereas sharing a household by spouses yielded higher C estimates (20-24%), as it incorporates spousal resemblance. Spousal resemblance was explained by both social homogamy and marital interaction, with little evidence for phenotypic assortment. We conclude that both the

amount of voluntary exercise behavior and the preference for specific classes of exercise activities in adults is explained by additive and non-additive genetic factors and unique environmental influences that include correlated exercise behavior of spouses.

Introduction

Regular voluntary exercise activities in leisure time, such as jogging, swimming, exercising at fitness clubs, and participation in recreational or competitive team and individual sports, are rapidly becoming the major source of physical activity of moderate-to-vigorous intensity in many industrialized countries. Recent meta-analyses of twin studies revealed broad sense heritability estimates for voluntary exercise behavior in adolescence and adulthood of 48% for males and 51% for females (van der Zee & de Geus, 2019), with inconsistent evidence for an effect of shared environmental factors.

Most of the studies included in these meta-analyses had shortcomings that need to be addressed to increase our understanding of the causes of individual differences in this crucial health behavior. First, the vast majority of the studies base their conclusions on the classical twin model comparing monozygotic (MZ) and dizygotic (DZ) twin correlations. While producing robust estimates for broad sense heritability, this model cannot simultaneously estimate all four variance components potentially influencing exercise behavior: additive (A) and non-additive (D) genetic factors and shared (C) and unique (E) environmental factors. Choosing to set either non-additive or shared environmental variance components to zero can yield biased estimates, "sometimes wildly so" (page 377, Keller et al. 2009). Second, previous studies have combined all recorded voluntary exercise activities into a single summary score, lumping together rather different activities like football, jogging, hockey, weight, strength training in fitness centers, tennis, swimming, boxing etc. Preference for these activities may, however, depend on rather different dispositional traits, both in terms of personality and in the physical, cognitive and motor skill demands placed on the individual.

In the current paper we assessed the sources of variation in voluntary regular exercise behavior using an extended twin-pedigree

study design using a rich dataset from the Netherlands Twin Register (NTR). The NTR repository contains exercise data collected with virtually the same methods in twins, their parents, siblings, spouses and the children of twins and siblings. This dataset is therefore ideally suited for an extended twin family design. Such a design allows for the simultaneous estimation of additive and non-additive genetic factors and shared and unique environmental factors (Keller et al., 2009). The often-used analytical approach for this estimation is structural equation modeling (SEM) software such as Mx, OpenMx, Mplus, or LISREL (Jöreskog, 1970; Muthén et al., 2006; Neale et al., 1994). These programs offer great flexibility in model specification but are less well suited for large and irregular pedigrees where the specification of the complex multidimensional parameter space, as well as iteratively fitting the model to actual data, becomes quite challenging (Boomsma et al., 2018).

We previously used the Mendel software package (Lange et al., 2013) as an alternative approach to the analysis of data from large and complex twin-pedigrees (Boomsma et al., 2018). Mendel constructs the genetic relations among all pedigree members, e.g., MZ twin, sibling, cousins, aunt–niece, grandparent–grandchild, etc., and estimates components of genetic covariance for any pair of relatives from the weighted combination of additive and dominance effects (Weiss, 1993). Using Mendel yielded estimates of additive genetic and dominance variance components for neuroticism of 24% and 19%, respectively (Boomsma et al., 2018). These results are consistent with those produced by SEM modeling in extended twin kinships among 45,850 family members from Australia and the United States (Lake et al., 2000).

In an extended twin-pedigree study design, the presence of spouses of MZ and DZ twins further allows us to address the sources of spousal resemblance (Eaves, 1979; Heath & Eaves, 1985; van Grootheest

et al., 2008). Spousal resemblance has been reported for voluntary exercise behavior with a median spouse correlation of 0.28, varying between 0.05 and 0.49 depending on the exercise trait considered (de Moor et al., 2011; Horimoto et al., 2011; Koopmans et al., 1994; Maia et al., 2014; Pérusse et al., 1988; Pérusse et al., 1989; Seabra et al., 2008, 2014). Spousal resemblance can be caused by the preferential mating of regular exercisers with other regular exercisers. This phenotypic assortment is based on a direct preference for similar traits and behaviors in a potential mate. Two well-known alternative mechanisms can cause spousal resemblance with respect to exercise behaviors. Social homogamy refers to mate selection based on sharing the same social milieu. Exercise behaviors scale positively with socioeconomic status, which in turn scales with neighborhood safety, higher mixed land use, and more exercise facilities. All of these may increase exercise behavior, although the effect sizes are rather modest (D'Haese et al., 2014; Gidlow et al., 2006). A third cause of spousal resemblance in exercise behavior is marital interactions. In this case, the longer spouses influence each other, the more similar they become. Note this can go both ways. Non-exercising partners may cause exercisers to swap out exercise activities for other social activities. Alternatively, the regular exercise activities of the exercising partner may become contagious for the non-exercisers. A telltale sign of marital interaction is that longer relationships are associated with greater similarity in exercise behaviors of the spouses.

The causes of spousal resemblance have consequences for the interpretation of genetic and unique and shared environmental variance estimates in an extended twin design. If spousal resemblance is caused by the preferential mating of exercisers with other exercisers it will increase parent-offspring and (non MZ twin) sibling similarity. In the classical twin design, this will cause inflated estimates for shared environmental effects (Falconer & Mackay, 1996). Under social

homogamy, the genetic resemblance between parents and offspring or between siblings is not expected to increase (Eaves et al., 1989). Marital interaction does not have consequences for genetic similarity in the next generation with the caveat that the increase in exercise similarity with marriage duration can be correlated with resemblance at mating: those who are more similar to each other at the start of the relationship may be more likely to remain together (Caspi & Herbener, 1993).

To test the presence and the causes of spousal resemblance, van Grootheest et al. (2008) employed a design first coined by Reynolds et al. (2006) that is illustrated in Figure 5.1. Given data in MZ and DZ twin pairs and their spouses, this method allows one to test for the presence of phenotypic assortment, social homogamy, and marital interaction by comparing the twin-spouse correlations (r_1), co-twin spouse-correlations (r_2), spouse1-spouse2 correlations (r_3), and parent-parent correlations (r_4) in pedigrees with data for twins and their spouses. If phenotypic assortment drives spousal resemblance then the expected pattern of correlations is $r_1 > r_2 > r_3$, and –provided the trait is heritable– the resemblance between co-twin and spouse (r_2) and between the twins' spouses (r_3) should be larger in MZ twins than in DZ twins. If, on the other hand, these correlations are equal ($r_1 = r_2 = r_3$) or conform to ($r_1 = r_2 > r_3$) and the comparison of r_2 with r_3 does not differ for MZ and DZ families this suggests non-random assortment driven by social homogamy (Reynolds et al., 2000). Marital interaction would show as a larger resemblance in the older parent-of-twins couples compared to the younger twins-spouse couples, i.e., r_4 should be greater than r_1 , assuming no other generational effects.

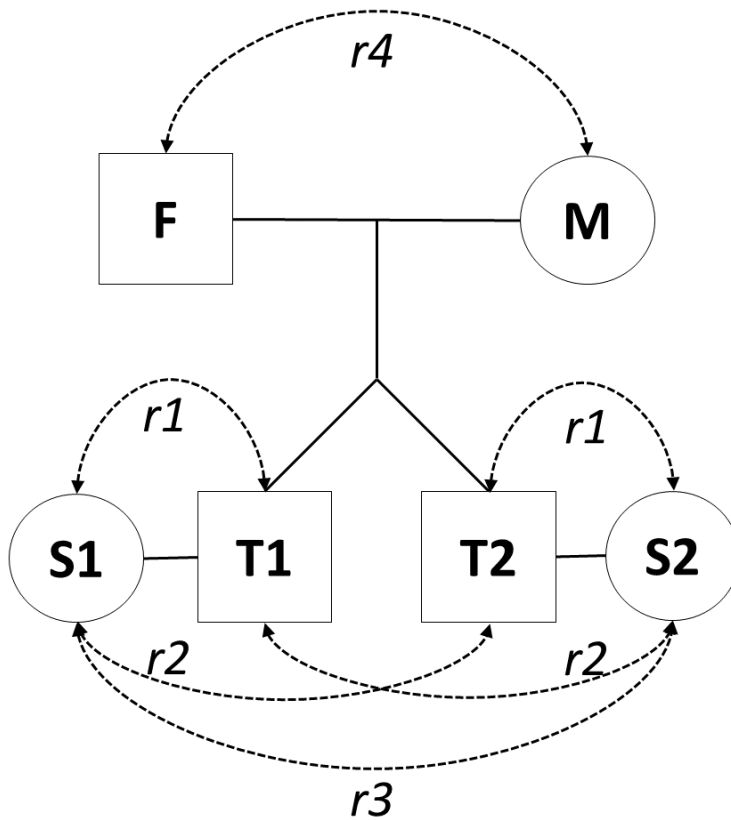


Figure 5.1. Model to analyze sources of spousal resemblance (van Grootheest et al., 2008).

In the NTR, participants list the exact type of individual sports and exercise activities they engage in, in addition to the weekly frequency and duration. Performing the analyses per exercise activity, while arguably desirable, comes with the disadvantage of reducing the number of informative pedigrees. This holds even for the activities that are most frequently endorsed (jogging, fitness, soccer, tennis, swimming). However, exercise activities can be classified in six general domains using the three axes of solitary vs team-based activities, competitive vs non-competitive activities, and activities that are internally paced vs those that are externally paced (van der Mee et al.,

2017). In competitive exercise, only activities with a competitive nature are included, i.e., a type of sport where a team or individual competes against another team or individual to win (e.g., soccer, tennis), whereas in non-competitive exercise only sports without a direct competitive nature are included (e.g., hiking, fitness). Team-based exercise reflects the volume of exercise activities spent in team-based sports, where multiple individuals work together to achieve a shared objective (e.g., field hockey, aerobic dance classes). Solitary exercise includes only the exercise or sports activities performed individually (e.g., jogging, swimming). Externally paced exercise represents the exercise behavior in activities in which the pace is determined by external factors, such as other participants or the weather conditions (e.g., judo, basketball, wind surfing). Internally paced exercise represents the volume of exercise behavior in activities in which the pace is determined by the exercisers themselves (e.g., tour cycling, inline skating, Nordic walking).

Here, we analyzed the total weekly volume of exercise (to be able to compare our results to previous findings), but also the volumes of weekly exercise behaviors specific to the six classes of exercise activity (competitive, non-competitive, team-based, solitary, externally paced, and internally paced). Based on previous twin and family studies, we expected to find a substantial broad sense heritability for the total volume of voluntary exercise behaviors, which should be mainly additive in nature. We further expected heritability of team-based, competitive and externally paced activities (field hockey, soccer) to be higher than that of solitary, non-competitive and internally paced activities (running, swimming). Enjoyment of team-based, competitive and externally paced activities (field hockey, soccer) is associated with physical fitness characteristics and cognitive and motor skills. Voluntary engagement in these activities therefore should reflect the heritability of these traits, which is known

to be high (Schutte, Nederend, Hudziak, Bartels, et al., 2016; Schutte, Nederend, Hudziak, de Geus, et al., 2016). Finally, based on previous findings using a dichotomous trait for exercise participation in a subsample of the current data (de Moor et al., 2011), we expected phenotypic assortment to play a main role in spousal resemblance.

Methods

Participants

The NTR is an ongoing national initiative focused on data-collection in twins and their extended family members. Detailed information on the longitudinal data collection procedures in the NTR can be found elsewhere (Ligthart et al., 2019). Every two to three years, extensive surveys are sent to parents of young twins, adult and adolescent twins and their parents and spouses. Almost all of these surveys included comparable questions on the type and volume of their exercise behaviors. For the present analyses, we used surveys filled out by participants in the age range of 16 to 65 years. Participants may have filled out surveys in multiple waves. For our present purposes, we selected one, if several data at waves were available. Specifically, we selected the wave in which the largest number of family members filled out the survey. For family members who did not participate in the chosen wave, we used the survey closest in time. If the family members differed greatly with respect to survey, we selected the last survey each member filled out. Finally, we only included participants who had at least one other participating family member (in any wave). Spouses of twins here count as family members. Throughout, we use 'spouse' to indicate the "partner with whom you share a lasting and stable relationship (like a marriage)", which was the wording used in the surveys.

The number of nuclear families with exercise data and with at least two family members was 19,543, and the total number of

participants with valid exercise data was 50,690. Table 5.1 describes the composition of these NTR pedigrees and their age characteristics. A more complex pedigree structure in some families was available than these nuclear family relationships. For instance, there was information on 18 grandparents of twins. There were 7 large (≥ 20 family members) pedigrees. The Mendel software fully exploits these complex family structures, providing extra sources of information, for the estimation of A, D, and C beyond that provided by parents, twins and siblings.

	<i>N</i>	<i>M_{age}</i>	<i>SD_{age}</i>
<i>Families^b</i>	19,543	-	-
<i>Individuals</i>	50,690	38.63	13.65
<i>MZ males</i>	2,560	27.26	12.41
<i>MZ females</i>	5,201	29.88	13.63
<i>DZ males from DZ male pairs</i>	1,680	24.86	11.14
<i>DZ females from DZ female pairs</i>	2,976	27.20	12.00
<i>DZ individuals from opposite-sex pairs</i>	4,293	25.03	10.40
<i>Fathers</i>	12,674	48.21	7.41
<i>Mothers</i>	15,653	45.89	7.70
<i>Brothers</i>	5,268	26.72	11.75
<i>Sisters</i>	7,982	28.34	12.51
<i>Spouse-pairs with offspring^c</i>	13,881	46.80	7.54
<i>Spouse-pairs without offspring^c</i>	1,976	36.04	14.54

Table 5.1. Composition of families *N*: generally denotes number of individuals unless indicated by superscript. *b*: *N*=number of pedigrees with at least 2 individuals, *c*: *N*=number of spouse-pairs

Voluntary Exercise Behavior

Voluntary exercise behavior was assessed using survey questions in nearly all NTR questionnaires discussed above. Participants were first asked whether they regularly participate in

exercise in their leisure time (“Yes” or “No”). If the response was affirmative they were asked (1) which sport they participate in, (2) how many years they have been doing so, (3) how many months a year they do so, (4) how many times a week on average they do so, (5) how many minutes on each occasion they exercise on average. Metabolic equivalent of task (MET) values were assigned to each exercise activity following Ainsworth et al. (2011). This MET value reflects the energy expenditure of the type of exercise as a multiple of basal energy expenditure (approximately 1kcal/kg/hour). Using these data, all exercise activities were assigned a weekly MET-minutes value by calculating the product of (1) the intensity as the MET value, (2) the weekly frequency, and (3) the average duration in minutes. The total volume of exercise behavior of the participant (METmin) was the sum of the weekly METminutes across all exercise activities. Obligatory exercise such as physical education (PE) classes, or other non-voluntary activity such as biking as a form of transportation, as well as seasonal exercise, such as skiing during winter only, were excluded, as they are not part of regular voluntary exercise behavior. Weekly METmin scores for the exercise domains were calculated in a similar fashion, but with selective inclusion of the types of exercise activities that fit within each of the domains, i.e., competitive or non-competitive team-based or solitary activities, and internally or externally paced activities. The complete list of classification for each type of exercise is detailed in Supplementary Table 5.1. Test-retest reliability of total METmin was 0.82 as computed among 200 individuals who completed the questions about exercise in December 2004 and again 6 months later. Furthermore, using analysis of tracking coefficients of total METmin as well as the scores across the six domains showed moderate to high temporal stability for total volume of exercise across periods varying from 2 to 22 years, ranging from .38 to .77 with a median of .57 (van der Zee, van der Mee, et al., 2019).

Statistical Analyses

To obtain a first impression of familial resemblance for exercise behaviors, correlations were estimated for MZ and DZ twin pairs, for biological sibling pairs, for father–offspring and for mother–offspring pairs and calculating the Pearson’s correlation of the METmin variables of the two. This was repeated for every exercise domain. Since we have previously found significant sex, age and sex*age effects on the total volume of exercise behavior (van der Zee et al., 2019), we first used linear regression to correct for age, sex and the age*sex effects on exercise behavior. The Pearson’s correlations were based on the regression residuals. Two different spouse correlations were computed: one for parents of twins and one for twins and their spouses, who on average were 9 years younger than the parents of twins.

Variance components attributable to additive genetic factors (A), household influences (C), non-additive genetic factors (D), and unique environmental factors (E) were estimated using the Mendel software package (Lange et al., 2013). In all analyses, age, sex and age*sex were included as fixed effects rather than regressing them out beforehand as we did for the kinship correlations. As detailed in Boomsma et al. (2018), the algorithm, which takes the NTR administrative database as input, provides as output the pedigree structures in standard pedigree format, as used in software, such as Mendel or Merlin (Abecasis et al., 2002). Mendel has an obligatory field to indicate the presence of MZ twins in the pedigree. Optionally, extra fields can be included, to indicate whether persons share the same household within a pedigree. Whereas genetic relations do not change, household sharing can depend on the time of assessment of the exercise behaviors. Dutch offspring typically share a household with their parents and siblings (if any) until around age 18. After about 18 they establish their own households, which can be shared with their own spouse. Sharing a household was defined in four different ways:

Full Household: These household factors contribute to the resemblance of spouses, all parent-offspring pairs, and all twin and non-twin siblings pairs, with twin and non-twin offspring restricted to those under 18. Note that these effects are treated as age and birth-cohort invariant, i.e., they are the same for twins/siblings and their spouses in the pedigree as for the parents of twins/siblings.

Spouse Household: These household factors only contribute to spouse resemblance.

Sib Household: These household factors only contribute to the resemblance of twins and non-twin siblings that have shared a household up to age 18.

Twin Household: These household factors are specific to twins who have shared a household up to age 18.

To test for the sources of spouse resemblance, we used the approach suggested by van Grootheest et al. (2008), as shown in Figure 5.1, and briefly outlined in the introduction. Full maximum likelihood estimation was used in OpenMx (Neale et al., 2016) to obtain the variance-covariance matrix for the six family members expressed in Figure 5.1, separately for MZ, same-sex DZ twin families. Opposite-sex DZ twins were excluded from this analysis as the opposing sex of twins and their spouses would bias the results of r_2 and r_3 , whereas in MZ and same-sex DZ twins the comparison is always either between same-sex or different-sex pairs. Age, sex, and the age*sex interaction were included as covariates in this model, and all correlations were constrained to be equal across MZ and DZ twins when no direct comparison was made (i.e., r_1 , r_4 , the 4 parent offspring correlation, and a residual correlation of parents to offspring-spouses). The correlations of interest obtained from the estimated variance-covariance matrix convey the resemblance between twins and their spouses (r_1), twins and the spouses of their co-twins (r_2), the spouse of twin 1 and the spouse of twin 2 (r_3), and the parents of the twins (r_4).

First, to confirm the presence of spousal resemblance, both the hypotheses $r_1 = 0$ and $r_4 = 0$ were tested by means of a 2-df likelihood ratio test. Second, to test for phenotypic assortment and social homogamy, four hypotheses were tested by means of 1 df likelihood ratio tests: (1) r_1 is equal to r_2 , vs. $r_1 > r_2$; (2) r_2 is equal to r_3 , vs. $r_2 > r_3$; (3) r_2 in MZ twins equals r_2 in DZ twins vs. r_2 in MZs $>$ r_2 in DZs; and (4) r_3 in MZ twins equals r_3 in DZ twins vs. r_3 in MZs $>$ r_3 in DZs. Significant effects ($p < 0.05$) favoring these four hypotheses were considered evidence for phenotypic assortment. Rejection of these hypotheses is considered to be evidence for social homogamy. The presence of marital interaction was tested by a 1 df likelihood ratio test of $r_4 = r_1$, vs. $r_4 > r_1$.

As a post-hoc test of the influence of phenotypic assortment on the estimates for the narrow-sense heritability (i.e., the additive genetic variance component) we performed mid-parent to offspring regression. We computed the mean parental values for exercise behavior (correct for age, sex and age*sex), and regressed these on the same exercise phenotype in one randomly selected child per family. In contrast to other estimations of narrow-sense heritability, this test is not sensitive to phenotypic assortment, and will not lead to biased estimation of additive genetic variance (Falconer & Mackay, 1996). Because the estimates for A for exercise behavior have been shown to decrease across the adult life span (Vink et al., 2011), we computed mid-parent to offspring regression in four age bins (20-45, 46-50, 51-55, 55-70 years).

Results

Means and standard deviations of the various exercise domains, as well as age for each family relation (parent, child, or twin) split by sex are included in Supplementary Table 5.2. All kinship correlations and the number of pairs in each combination are presented in Table 5.2. For total METhr, monozygotic (MZ) twin

correlations were 0.58, and same-sex dizygotic (DZ) twin and sibling correlations varied between 0.31 and 0.42, with little evidence of sex differences. Opposite sex DZ twin and brother-sister sibling correlations were slightly lower (~0.22). Parent-offspring correlations were between 0.12 and 0.23, which might reflect that parents and offspring share 50% of the additive genetic variance, but in contrast to DZ and sibling pairs no genetic dominance variance. The same pattern of results characterizes the other exercise domains with generally stronger familial resemblance estimates for team-based, competitive, and externally paced activities than for solitary, non-competitive, and internally paced activities.

<i>Correlation</i>	<i>Npairs</i>	<i>Total</i>	<i>Team</i>	<i>Comp</i>	<i>Sol</i>	<i>Ncomp</i>	<i>Pacel</i>	<i>PaceE</i>
<i>All Spouses</i>	13,002	0.31	0.50	0.42	0.31	0.30	0.32	0.44
<i>Parents of twins</i>	11,879	0.32	0.52	0.45	0.32	0.30	0.32	0.46
<i>Twins - spouses^a</i>	1,767	0.28	0.37	0.31	0.29	0.26	0.29	0.33
<i>MZM</i>	1,280	0.58	0.70	0.67	0.50	0.52	0.42	0.67
<i>MZF</i>	2,589	0.58	0.77	0.72	0.56	0.55	0.43	0.72
<i>DZM</i>	824	0.37	0.55	0.45	0.44	0.52	0.32	0.45
<i>DZF</i>	1,468	0.42	0.58	0.53	0.42	0.42	0.28	0.54
<i>DOS</i>	1,857	0.23	0.35	0.24	0.23	0.23	0.20	0.27
<i>Brother-brother</i>	862	0.31	0.51	0.40	0.38	0.46	0.28	0.40
<i>Brother-sister</i>	3,281	0.22	0.30	0.23	0.19	0.19	0.16	0.24
<i>Sister-sister</i>	1,885	0.39	0.58	0.51	0.35	0.35	0.25	0.52
<i>Mother-daughter</i>	11,451	0.23	0.38	0.32	0.22	0.22	0.20	0.33
<i>Mother-son</i>	11,025	0.12	0.16	0.12	0.18	0.20	0.14	0.13
<i>Father-daughter</i>	9,465	0.21	0.34	0.27	0.20	0.20	0.17	0.29
<i>Father-son</i>	9,137	0.20	0.20	0.19	0.22	0.23	0.20	0.19

Table 5.2. Kinship Correlations. MZM: monozygotic male pairs; MZF: monozygotic female pairs; DZM: dizygotic male pairs; DZF: dizygotic female pairs; DOS: dizygotic opposite sex pairs; Total: Total METmin; Team: Team METmin; Comp: Competitive METmin; Sol: Solitary METmin; Ncomp: Non-competitive METmin; Pacel: internally paced METmin; PaceE: Externally paced METmin. ^a: if twins had twin offspring they were used in this row only, and not reused as parents of twins.

Mendel's estimates of genetic and environmental effects

Full results for all exercise domains and models tested are included in Supplementary Table 5.3. In all exercise domains, the best fitting model was the model including additive genetic, non-additive genetic (dominance), household, and unique environmental variance (ACDE) components. This was true across all four household definitions, indicating that heritability estimates are not very sensitive to how a shared household component is modelled. A summary of the model using the full household definition is presented in Figure 5.2, and

a representation of the other models is presented in Supplementary Figure 5.1. Broad-sense heritability of total METmin was 40%. The broad-sense heritabilities of team-, competitive- and externally paced METmin (46%, 43%, and 44%, respectively) were consistently higher than the broad-sense heritabilities of solitary-, non-competitive-, and internally paced METmin (33%, 30%, and 29%, respectively). These increases in heritability are largely explained by an increase in non-additive genetic effects. The effects of shared household components largely depended on its definition, with estimates of C for, e.g., total volume being low in the sibling (4%) and twin (8%) household models, and moderate in the full (20%) and spousal (24%) household models. The C component in the latter two models was driven by the spousal correlations.

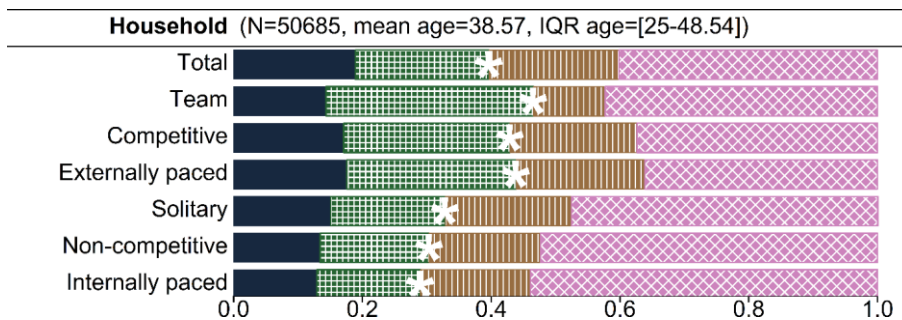


Figure 5.2. Proportion of variance explained by **additive genetic (A)**, **non-additive genetic (D)**, **shared environmental (C)**, **unique environmental (E)** factors and broad sense heritability (*) for different classes of exercise. The C component reflects the environment shared by spouses.

Causes of spousal resemblance

The ML estimate of twin - spouse correlation for total METmin was 0.19 in the subsample used for the analysis of sources of spousal resemblance. The average age of the twins and spouses in this subsample was 37.3 years. Spouse correlations in parents of twins, who were on average 46.8 years old, were significantly higher ($r = 0.35$, $p = 5.77 \times 10^{-12}$), indicating marital interaction may contribute to spousal resemblance. Table 5.3 contains a summary of the hypotheses tested for the cause of spousal resemblance in the total volume of exercise behavior. Similar tables for the six different types of exercise activities can be found in Supplementary Tables 5.4 to 5.9. Spousal resemblance was significant across all exercise phenotypes (p 's < 0.05) which is in line with the results from the different household models assessed in Mendel. The hypothesis of marital interaction, i.e., the correlation between spouses living together for a longer time (parents of twins) is larger than the correlation between those living together for a shorter time (twins and their spouses), was also supported across *all* exercise domains. The effect of marital interaction appeared to be particularly strong for team-, competitive- and externally paced sports activities.

Across all exercise domains, the support for social homogamy was greater than the support for phenotypic assortment. Evidence for phenotypic assortment was limited to the greater resemblance of twins and their own spouses (r_1) than the resemblance of twins and the spouses of their co-twin (r_2). We note that our data cannot discriminate between assortment at the time of mate selection and marital interaction as the source of this higher resemblance.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.20>0	82.46	1	1.08×10^{-19}	√			
$r4 > 0$	10,711	0.35>0	825.05	1	1.94×10^{-181}	√			
$r1 > r2$	1,420	0.20>0.11	17.02	2	2.02×10^{-4}		√	-	
$r2 > r3$	419	0.11>0.08	0.69	2	0.71		-	√	
$r2_{MZ} > r2_{DZ}$	465	0.11>0.11	0.01	1	0.92		-	√	
$r3_{MZ} > r3_{DZ}$	157	0.06>0.12	0.39	1	0.53		-	√	
$r4 > r1$	1,608	0.35>0.20	47.41	1	5.77×10^{-12}				√

Table 5.3. Spousal resemblance and its sources in total volume of exercise. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Influence of phenotypic assortment on additive genetic effects

Regression coefficients obtained in the mid-parent offspring regression on all exercise phenotypes are displayed in Table 5.4. These provide a direct estimate of the narrow-sense heritability and are presented along with the narrow-sense heritability estimates obtained in the full household model analysis in Mendel. The regression coefficients from mid-parent regression in each phenotype were very close to the narrow-sense h^2 estimates from the extended family model, at each age bin tested. This shows that if phenotypic assortment was present, it had little to no influence on the Mendel estimate of the A variance component.

Parental age cutoffs	20-45yrs	45-50yrs	50-55yrs	55-70yrs	
$M_{\text{age parents}}$	42.67	47.85	52.59	59.68	
$M_{\text{age offspring}}$	19.00	20.09	22.08	27.48	
N_{pairs}	725	1369	1463	1238	Mendel narrow-sense h^2
Total exercise	0.22	0.18	0.22	0.18	0.19
Team-based	0.21	0.18	0.13	0.14	0.14
Competitive	0.27	0.21	0.19	0.12	0.17
Externally paced	0.23	0.19	0.18	0.13	0.18
Solitary	0.23	0.15	0.19	0.19	0.15
Non-competitive	0.22	0.13	0.18	0.13	0.13
Internally paced	0.21	0.13	0.18	0.10	0.13

Table 5.4 Narrow sense heritability, estimated based on mid-parent offspring regression and from modelling full pedigree data in Mendel. N_{pairs} : Total number of complete pairs (at least one parent and at least one child) used in the regression. Age bins are based on the mean age of the parents. Estimates represent the coefficient from linear regression. Estimated A represents the estimate of A from the extended-family model tested in Mendel.

Discussion

We examined the sources of individual differences in voluntary exercise behaviors in the Netherlands using an extended twin pedigree design. Broad sense heritability estimates for total volume of exercise ranged from 34% to 41% in models using four different definitions of household sharing. Across the various classes of exercise activities, genetic contribution was largest to team-based, competitive and externally paced activities ($39\% < h^2 < 47\%$) with lower broad sense heritability for solitary, non-competitive and internally paced activities ($26\% < h^2 < 34\%$). These differences in heritability are largely explained by a larger component of non-additive genetic effects for team-based over solitary activities, a 7% increase for competitive over non-competitive activities, and an 8% increase for externally over internally paced activities. Results from the extended twin pedigree design further suggested that a shared sibling household (typically up till age ~18) explains 4-8% of the variance in adult exercise behavior, whereas sharing a household by spouses yielded higher estimates of the C variance component (20-24%) as it had to incorporate the spousal resemblance. The total spouse correlation was 0.32 for total exercise behavior and varied between 0.30 and 0.50 across the specific classes of exercise activities, which was best explained by marital interaction and social homogamy, with weaker evidence for phenotypic assortment.

Our broad sense heritability estimates for voluntary exercise behavior (40%) is 10% lower than the average of 50% obtained in twin registries from multiple countries (van der Zee & de Geus, 2019), which we believe reflects the larger numbers of adolescents and young adults in these studies. Heritability of voluntary behavior has been shown to peak in late adolescence (~65%) (Huppertz et al., 2016) and then gradually decrease across the life span (Vink et al., 2011).

A new finding in the current study is the clear evidence for the contribution of non-additive effects to the broad sense heritability, most prominent for team-based, competitive and externally paced activities. Previous use of extended twin designs for a variety of traits has similarly found higher non-additive and lower additive effects for behavioral traits than the classical twin design (Coventry & Keller, 2005). These non-additive genetic effects provide an explanation for the large discrepancy that has been found in the heritability estimates deriving from parent-offspring/sibling correlations in family studies compared to MZ/DZ twin based estimates in twin studies. Family studies (de Moor et al., 2011; Horimoto et al., 2011; Koopmans et al., 1994; Maia et al., 2014; Pérusse et al., 1988; Pérusse et al., 1989; Seabra et al., 2008, 2014) have systematically reported 11% lower heritability estimates than twin-only studies. Such differences may be partly attributed to the difference in these estimates to non-additive genetic effects, which contribute to resemblances of monozygotic twins and full siblings but not to resemblance of parents and offspring or other relatives such as cousins. The contribution of non-additive genetic effects may also have implications for genome-wide association studies (GWAS), as the traditional GWAS assumes additive genetic effects rather than take non-additivity into account.

Previous studies in adults twins have reported only small shared environmental influences on voluntary exercise behaviors with a meta-analysis estimating them to be about 10% (van der Zee & de Geus, 2019). As most of the studies in this meta-analysis used the classical twin design, the C estimates will largely reflect the sharing of environmental factors by the twins when they were still living at home. In our analyses, shared environmental effects were modeled in four different ways depending on the timing of survey completion: sharing a household as spouses at the time of survey completion, ever sharing a household either as siblings or as parents and offspring, sharing a

household as siblings, or sharing a household as twins. The latter two definitions of shared environmental effects assume that such effects linger after twins and siblings are separated from each other and form their own households (unshared by relatives). Our results using the SibHousehold and TwinHousehold models support the existence of a small impact of sharing a household until late adolescence on the total volume of exercise behavior, with estimates (4-8%) corresponding quite well with the meta-analysis.

In contrast, much larger shared household effects were found (20-24%) when using the SpouseHousehold or FullHousehold models. We surmise that these shared household effects derive largely from the spouse correlations in the twin/sibling and parental generations, which mostly reflected marital interaction across all types of exercise behaviors, including total exercise behavior. The latter contrasts with previous studies that did not find marital interaction for yes/no exercise participation (de Moor et al. 2011). The exercise-activity specific marital interaction suggests that the exercise behavior of a spouse constitutes an important environmental factor for the exercise behavior of a person. We note that marital interaction was weaker for solitary, non-competitive, internally paced activities than for team-based, competitive and externally paced activities. We further note that people tend to engage much less in team-based and competitive exercise activities over time and that solitary, non-competitive, internally paced activities are the largest source of adult exercise participation (van der Zee, van der Mee, et al., 2019). It may simply be difficult to maintain the commitments required for team-based and competitive activities without symmetrical interest and engagement of one's partner.

Marital interaction processes give rise to genotype-environment covariance, which can produce apparent shared environmental influences (Dolan et al., 2014) at the expense of additive

genetic influences. Likewise, if not explicitly modeled, phenotypic assortment may also affect A estimates, although spousal resemblance has to be fairly large to achieve noticeable bias. Phenotypic assortment can be discriminated from social homogamy by comparing the resemblances in twin and co-twin spouses (r_2) and in twin spouses and co-twin spouses (r_3) as a function of zygosity. Phenotypic assortment will make the spouses of MZ twins more alike to their co-twin and to each other than is found in the spouses of DZ twins. If non-random assortment is driven by social homogamy, r_2 and r_3 will *not* differ between MZ and DZ twins. Across all exercise phenotypes, social homogamy was favored over assortment at mate selection as the main source of spousal resemblance, but we note that social homogamy is tested as the null-hypothesis and power for detecting small-sized phenotypic assortment was low. Converging evidence that phenotypic assortment plays a minor role came from the mid-parent offspring regression analyses. The mid-parent offspring regression yields an estimate of narrow-sense heritability that is insensitive to assortment (Falconer & Mackay, 1996). Comparison of these estimates to the heritability estimates from Mendel showed that the latter were not overly biased by phenotypic assortment.

We acknowledge various limitations in our approaches. First, our results are based on twin families, and we do not know if and to what extent determination of exercise behavior in these families differs from that in non-twin families. However, we have noted previously (van der Zee, Schutte, et al., 2019) that there are no differences between the twins and the singleton siblings, and that the prevalence of the MET scores for regular voluntary exercise behavior in the Dutch twin families is very consistent with the prevalence of voluntary leisure time physical activity reported by 5 large-scale studies in Europe. Thus the results of the current study may be generalizable to the Dutch population at large.

Second, the way we carved up the total weekly volume into the six classes of exercise activity (competitive, non-competitive, team-based, solitary, internally paced, and externally paced) is far from ideal. Although not completely overlapping, these classes were not independent, in that the same activity, e.g., soccer would count in the team-based, competitive, and externally paced (paced) weekly exercise volumes.

A third limitation is the assumption that the same genes are expressed across sex and age. Parents and offspring's phenotypes were assessed at different ages. If the genetic correlation across the lifespan would be less than one for phenotypes that are analyzed this would result in a 'too low' parent-offspring correlation, compared to the sibling and DZ pair correlations, potentially causing a wrong conclusion about the presence of genetic dominance. There was some suggestion for a sex limitation model, but less so in the parent-offspring than in the sib data.

Fourth, we used the Mendel software as an efficient way to model the multigenerational familial resemblances, accepting that some effects could not be specified in the genetic model. A different approach would have been to use the 'Cascade' model (Keller et al., 2009). This model allows testing of all variance components as well as specific tests of social homogamy vs phenotypic assortment, and can even be made to incorporate vertical transmission (although we have encountered no actual examples of this). Using the simpler 'Stealth' model on the total volume of exercise behavior we previously found no evidence for vertical (or cultural) transmission suggesting that there is no direct 'copying' of parental exercise habits by the offspring (de Moor et al., 2011). This appears to be true for a large number of behavioral traits (Eaves, 2009) and we assumed here that it also applies to the exercise activities in the specific classes. It could be reasonably argued that for team sports this assumption may not hold.

In summary, regular voluntary exercise behavior, regardless of what type of exercise, is a moderate to highly heritable trait with substantial contribution by non-additive genetic factors. Competitive-team-based and externally paced exercise activities appear to be more heritable compared to non-competitive, solitary and internally paced activities, largely due to an increased effect of these non-additive genetic factors. In childhood and (early) adolescence the environment shared by siblings is a major contributor to exercise behavior (Huppertz et al., 2016) but having shared that environment plays only a minor role in voluntary exercise behaviors in adulthood. In adulthood, the exercise behavior of one's life partner becomes the more relevant environmental factor.



CHAPTER

Summary and Discussion

Summary

The past years have seen a remarkable surge of scientific discoveries in human genetics, and complex-trait genetics specifically. This has been largely facilitated by the development of affordable genome-wide arrays and aided by the development of new statistical methods to use the data from these arrays for different purposes. The genetic epidemiology of regular voluntary exercise behavior is no exception to this trend. As clear indicators of this trend, the largest reviews to date of twin-, family and gene-finding studies on exercise behavior (Aasdahl et al., 2021; van der Zee & de Geus, 2019; van der Zee, Schutte, et al., 2019) have been published during my PhD project, some of which are included in this thesis. In the same time frame, four of the six genome-wide association studies on physical activity traits (Doherty et al., 2018; Klimentidis et al., 2018; Lin et al., 2018) including sports and exercise behaviors (Doherty et al., 2018; Klimentidis et al., 2018; Lin et al., 2018; van der Zee et al., 2021) saw the light and these have produced the first genome-wide significant genetic variants.

Throughout this dissertation I have employed several methods to further our understanding of determinants of regular voluntary exercise behavior, with an emphasis on genetic factors. In the first three chapters of this thesis, I explore the prevalence and stability of exercise, and review currently available literature concerning genetic epidemiology of exercise. These chapters are followed by an extended-family study, a genome-wide association study (GWAS), and finally a study on the causal effects of personality on exercise, using genetically informed designs. A recurring theme throughout this dissertation was the separation of the total volume of exercise into activities in different domains. The main findings in this thesis are summarized below, followed by a general discussion on the genetic epidemiology of exercise, and my thoughts on future developments in this field.

Prevalence and stability of voluntary exercise behavior

As mentioned in the introduction of this thesis, voluntary exercise behavior is a prime target for behavioral intervention to increase physical activity. Since the health benefits only persist as long as the exercise activities persists, the ultimate goal of such interventions is to develop life-long habits of regular exercise. In other words, the ultimate goal is to not only increase the prevalence, but also increase the *tracking* (i.e. the stability over time) of exercise behavior. The age- and sex-specific prevalence are generally reported in all studies on exercise behavior, however an assessment of tracking is more rare as it requires a large longitudinal dataset. Creating such a dataset is a costly endeavor, especially when the aim is to assess tracking across the lifespan. It is, therefore, not surprising that many previous studies on tracking of exercise focused only on a specific range, such as from childhood to adolescence (Aarnio et al., 2002; Francis et al., 2013; Pahkala et al., 2013; R. Tammelin et al., 2014).

In **Chapter 2** of this thesis, we used a large dataset ($N = 43,889$) from the Netherlands Twin Register (NTR) to assess prevalence and tracking coefficients across the largest part of the lifespan (ages 8 to 80), with varying distances between the baseline exercise measurement and follow-up (2 to 22 years). We assessed the prevalence and tracking of total weekly volume of exercise as well as of the volume of activities in six specific exercise domains: team-based, solitary, competitive, non-competitive, externally paced, and internally paced. Generalized estimating equations (GEE) were used throughout to correct for family-relatedness in the NTR sample.

The prevalence of exercise increases during childhood and early adolescence, with the highest prevalence found in mid-adolescence, around age 16 for both men and women. The largest contributor to this peak is the prevalence of team-based and competitive exercise activities, which are the dominant exercise

activities in the Netherlands till around age 25. These activities show a strong linear decline after age 16 the slope of which is attenuated around age 40. After age 25, solitary activities, often non-competitive in nature, become the mainstay of the total weekly volume of exercise behavior. The prevalence of these solitary non-competitive exercise activities, remarkably, remains relatively stable from ages 18 to 64. After age 64 the prevalence of non-competitive solitary exercise also starts to decline, though at a slower rate than team-based competitive exercise did during adolescence. Throughout the life span, men have on average 25% higher levels of total exercise than women, but the sex difference is most pronounced in adolescence and early adulthood. This is because the discrepancy in total exercise between men and women during adolescence could be largely attributed to the greater prevalence of team-based and competitive exercise in men.

The tracking of exercise, regardless of type of exercise was moderate to high (2-year tracking coefficients between .38 and .77) with slightly higher tracking coefficients in men. In accordance with previously published tracking studies (Sallis et al., 1996; Telama et al., 2006) we found tracking strength to decrease as the distance between starting age and follow-up age increased. For example, tracking coefficients for total volume of exercise had a median of .57 across all 2-year intervals down to a median of .38 for 22-year intervals. Also in accordance with previous literature we found tracking coefficients generally increased with starting age resulting in lower tracking from childhood into adulthood compared to the higher coefficients within adulthood. For example, in females the 4-year tracking coefficient of the total volume of exercise from age 10 at baseline to age 14 at follow-up was 0.43, whereas the tracking coefficient from age 48 at baseline to age 62 at follow-up was 0.81. However, the increase in tracking strength with increasing age was entirely driven by a sharp increase in tracking for solitary and non-competitive activities. For team-based

and competitive activities, tracking was fairly stable or even gradually decreased across the life span, possibly because the prevalence of such activities decreases. These results suggest that adult exercisers engaged in solitary exercise become increasingly less likely to drop out, and vice versa, that non-exercising adults become increasingly less likely to ever take up exercise, even if it is solitary self-paced and non-competitive.

To conclude, regular voluntary exercise behavior declines with age, but this is largely driven by a decrease in team-based activities. Solitary exercise activities show a much more modest decline in prevalence. The significant female disadvantage in exercise prevalence is moderated by type of exercise and age. Throughout, the moderate to high tracking coefficients confirm that exercise behavior is a rather stable individual characteristic.

Heritability of regular exercise behavior

A large volume of genetic studies has accrued in adult populations that looked at regular voluntary exercise behavior, as well as three other physical activity phenotypes, namely total physical activity (TPA), moderate-to-vigorous physical activity (MVPA), and leisure-time physical activity (LTPA). While TPA, MVPA and LTPA all encompass voluntary exercise behavior, they are much broader in also including non-exercise activities like walking, bicycling or gardening, and activities that are not fully voluntarily controlled by an individual, such as physical activity for transport or manual labor. Total physical activity places no restriction on intensity of the activity, whereas MVPA uses only activities with a minimum intensity (generally activities with an intensity value of more than 3 or 4 times the resting metabolic rate). LTPA again does not select activities based on intensity, but on whether they are performed voluntarily in leisure time and most closely resembles voluntary exercise behavior. The key distinction

being that LTPA also includes all non-exercise or sports performed in leisure time, such as walking or dancing, on top of exercise and sports activities.

Whereas the past studies on exercise genetics have unanimously shown an important genetic contribution to physical activity behaviors, estimates of heritability have varied considerably, even for a similarly defined exercise phenotype (de Geus et al., 2014; Lightfoot et al., 2018). In **Chapter 3** of this thesis, we therefore performed a systematic search and a meta-analysis of adult twin studies on regular voluntary exercise behavior, as well as three other physical activity phenotypes. Twin-studies are particularly well-suited to estimate the heritability of a trait by comparing the difference in within-pair resemblance of monozygotic (MZ) or dizygotic (DZ) twins. A greater resemblance in MZ twins compared to DZ twins suggests additive genetic factors (A) affect the variance in a trait and additional non-additive genetic factors (D), if the difference is more than a factor two. This is because MZ twins share (nearly) 100% of their genetic variants, whilst DZ twins share, on average, about 50% of additive genetic and 25% of non-additive genetic variance. Conversely, if the resemblance in MZ and DZ twins does not differ significantly this suggests that common environmental factors (C) influence the variance of a trait. This is because both MZ twins and DZ twins share all of their common environmental factors, such as parenting styles or prenatal environment, by definition. Finally, the differences between MZ twins can only be ascribed to unique environmental factors (E). Of note, E also includes any phenotypic measurement error.

A set of 27 independent adult twin studies were included, some of which used objective measures (such as accelerometers), others used self-reported surveys. We meta-analyzed the A and C estimates of each study (almost no D was reported) for males and females separately and corrected for the original study sample size.

Contribution of A was significant and substantial in all traits, with the lowest meta-analytic estimates found for MVPA ($A_{\text{males}} = 0.41$, $A_{\text{females}} = 0.44$), and the highest estimates found for TPA ($A_{\text{males}} = 0.51$, $A_{\text{females}} = 0.48$) and exercise behavior ($A_{\text{males}} = 0.48$, $A_{\text{females}} = 0.51$). The contribution of C was only found to be consistently significant in voluntary exercise behavior (meta-analytic estimate 0.10 for both sexes), but not for the broader physical activity traits. No significant sex-differences were found for any of the A and C estimates resulting from the meta-analysis.

In **Chapter 4** of this thesis, we additionally included parent-offspring and sibling correlations from family studies in our review of studies assessing the genetic and environmental contributions to regular voluntary exercise behavior. Twin studies rely on a number of assumptions, one of which is the equal-environment assumption, which states the environmental effects are equal for MZ and DZ twins. Sibling correlations and parent offspring correlations are not relying on this assumption. However, an assumption in estimating A from parent-offspring in the standard family-based design correlations is that the transmission of trait resemblance is entirely due to genetic and not to cultural transmission. In the case of cultural transmission, the behavior of parents directly influences the behavior of the offspring (i.e. parents act as a role-model), thus increasing the influence of common environmental factors. In previous work in the NTR, de Moor et al. (2011) found a minimal (3%) effect of cultural transmission in boys only, despite their participants being adolescents, for whom shared environmental factors are still significant. In keeping, the heritability estimates resulting from the family-studies on exercise that we reviewed in Chapter 4 suggest that those found in twin-only studies are indeed not overly biased.

More alarmingly, however, **Chapter 4** did find spouse correlations to be consistently significant and substantial, ranging

from 0.16 to 0.48. This indicates noticeable assortment for exercise behavior, which violates another assumption of the classical twin design, namely that the trait should not influence an individual's choice of a partner. If such assortative mating is present, and not corrected for, DZ twins in a family may share more than 50% of genetic factors influencing a trait, which in turn will cause an overestimation of the influence of common environmental factors, and an underestimation of additive genetic factors.

In **Chapter 5** we addressed assortment in combination with a final major shortcoming of the twin- and family-studies included in chapters 3 and 4. These previous studies only estimated the effects of A, C and E, but could not simultaneously assess the effects of non-additive genetic factors (D). To achieve this, we used data from 50,690 adolescent and adult participants from 19,543 nuclear pedigrees in the NTR. All family-relations amongst these individuals and within these nuclear pedigrees were known, and this knowledge was leveraged by using the Mendel software package (Lange et al., 2013). Different definitions of 'shared environment' or household effects were tested, namely full household (where C contributes to spousal, parent-offspring, twin- and sibling resemblance), spouse household (where C only contributes to spousal resemblance), sibling household (where C only contributes to resemblance of twins and siblings), and twin household (where C only contributes to resemblance of twins). While still focused on voluntary exercise behavior, we expanded on previous twin-family studies by not only estimating the contribution of the variance components to the total volume of exercise but also to subsets of activities in different domains like team-based or solitary or competitive and non-competitive exercise.

Depending on which definition of household effects was used the broad-sense heritability (h^2 , the percentage of variance explained by A and D) ranged from 34% to 41%. Higher heritability estimates were

found for team-based, competitive and externally paced exercise behavior ($39\% < h^2 < 47\%$), compared to solitary, non-competitive and internally paced exercise ($26\% < h^2 < 34\%$), and were largely attributable to an increased contribution of non-additive genetic factors. Across all exercise domains the contribution of C strongly depended on which definition was tested, with low estimates found under the twin- or sibling household definitions, and higher estimates for the spouse- and full household definitions. For total volume of exercise, for example, the percentage of variance explained by sibling household effects was 4%, by twin household effects 8%, by full household effects 20%, and by spouse household 24%. These large differences mainly reflected the high spousal correlations found across all exercise domains ($0.30 < r < 0.50$).

Chapter 5 also examined the causes of spousal resemblance for regular exercise behavior, with a particular interest on how they could bias twin models. The only study that had examined spousal resemblance of exercise behavior was published by de Moor et al. (2011), who found that this resemblance was best explained by phenotypic assortment. To re-assess the sources of this spousal resemblance we adopted the approach outlined by van Grootheest et al. (2008) in Chapter 5. Using this model allowed us to test three distinct sources of spousal resemblance in exercise behavior. First phenotypic assortment, which describes preferential mating between partners that more resemble each other's exercise behavior. Second social homogamy, which refers to similar partner selection based on sharing a milieu in which exercise is common. Finally marital interaction, which describes partners growing more similar over time. This could mean that the non-exerciser starts exercising, influenced by the other, or vice versa. Our results suggested marital interaction was a significant contributor in all exercise domain, and there was more evidence in favor of social homogamy over phenotypic assortment. This increases

confidence in twin studies of voluntary exercise behavior that will be most strongly biased by phenotypic assortment, to a lesser extent by social homogamy, and even less by marital interaction.

To conclude, results of chapters 3-5 are in line with those of previous twin and family studies regarding the heritable nature of regular voluntary exercise behavior as well as broader physical activity traits in adulthood, and the near absence of lingering effects of being raised in a shared family environment. Like so many other behavioral traits, "about half of the variance" in adult exercise behavior can be explained by heredity. This heritability, however, is a result of both additive, and non-additive effects, particularly but not exclusively for team-based, competitive and externally paced exercise. Marital interaction seems to be consistent source of influence on spousal resemblance in regular voluntary exercise behavior and there is likely an additional role for social homogamy. These effects are of greater influence than phenotypic assortment.

Gene-finding in regular voluntary exercise behavior

As mentioned in the introduction of this thesis discovering the genetic variants underlying the heritability of regular voluntary exercise behavior has proven to be difficult, despite the well-established moderate-to-high heritability. A large number of candidate-gene studies have been performed in which a single or a few genetic variants were assessed for an association with regular exercise or broader physical activity traits (see review in Chapter 6 but also Aasdahl et al. (2021)). Only very few candidate genes, however, have been independently replicated and then not even always at the level of a specific variant but rather at the gene level. A genome-wide association study (GWAS), where millions of genetic variants are tested simultaneously, is a more robust and hypothesis-free method for identifying genetic variants. The first three GWASs on regular

voluntary exercise behavior, published by de Moor et al. (2009), Kim et al. (2014) and Lin et al. (2018), did not yield any significant results. The two GWASs that followed, published by Klimentidis et al. (2018) and Hara et al. (2018), did yield the first genome-wide significant hits for sports and exercise behaviors. Genetic variants for specific types of exercise activities, however, were not tested.

In **Chapter 6** of this thesis, we performed a GWAS of the total weekly volume of exercise, as well as a GWAS for activities in the team-based, solitary, competitive, non-competitive, and externally/internally paced domains as defined previously. We used a sample of the NTR (N = 14,626) for which genome-wide data in the form of millions of single nucleotide polymorphisms (SNPs) was available as well as survey data on exercise activities.

No genome-wide significant SNPs were found for total, team-based, solitary, competitive, externally paced and internally paced exercise. For non-competitive exercise five novel genome-wide significant SNPs were found. Four of these variants (*rs11817437*, *rs1276262*, *rs11812727*, *rs34897771*) were located in an intergenic region on chromosome 10 and have not been found in any previous genetic study of exercise behavior. One of these significant variants (*rs147244851*) was located in the *Glypican-5 (GPC5)* gene. Though this gene has previously been found to be associated with sedentary behavior (Comuzzie et al., 2012), the variant found in our GWAS on exercise behavior was different from the variant associated with sedentary behavior. Since there is no evidence for either our exercise variant, or the previous sedentary behavior variant affecting gene expression, we cannot say with certainty that the direction of the effect found in these two GWASs is congruent.

We used our suggestive ($p < 5 \times 10^{-6}$) GWAS results to perform several functional annotation analyses. Through these analyses one of the variants (*rs62620995*) found for total volume of exercise was

identified as a missense (gene-product altering) variant in the *DCSTAMP* gene. This gene plays a crucial role in bone-development (Kukita et al., 2004), furthermore the same variant found in our GWAS has been shown to affect *DCSTAMP* gene expression and osteoclast (bone-resorbing cells) morphology (Laurier et al., 2017). Across the different types of exercise activities, the suggestive GWAS results were consistently enriched for genes that were related to a number of red blood cell phenotypes, such as glycated hemoglobin levels, mean corpuscular volume, and heme metabolism.

In chapter 6 we also aimed to replicate the 103 genetic variants identified in previous candidate-gene studies and test all these variants (or a genetic proxy of these variants) for association. This replication used a much more relaxed p -value than the GWAS, namely $0.05/103$, i.e. the 'standard' α corrected for multiple testing. Strikingly, no significant evidence was found for replication of any of the previously reported genetic variants.

To conclude, in chapter 6 we identified novel genetic variants for regular voluntary non-competitive exercise activities specifically. Results of this chapter tentatively suggest bone development and red blood cell physiology to be biological determinants of voluntary exercise behaviors.

The pathways from genetic variation to regular voluntary exercise behavior

The recent discovery of significant genetic variants for physical activity traits, including regular voluntary exercise behavior, allows us to use new methods that leverage these variants to test causal hypotheses on the role of potential 'intermediate phenotypes' on the path from genes to exercise behavior. Personality, a trait known to be heritable, is one of these potential determinants of regular voluntary exercise. There is robust evidence for an association between these

two behavioral traits (Rhodes & Smith, 2006; Wilson & Dishman, 2015). The oldest, and still predominant perspective on this association is that it reflects a causal effect of personality traits on exercise behavior (Flemming, 1934), though an inverse causal effect has also been hypothesized (Stephan et al., 2014), and there is much room for genetic and environmental confounding. Testing the causal hypothesis, however, is not possible with traditional methods such as a controlled trial, as we cannot directly experimentally modify a subject's personality. This is where new genetically informed designs come in, including those based on twin-families and/or GWAS derived variants.

In **Chapter 7** we used a number of these designs to test the causal effects of the 'big five' personality traits (neuroticism, extraversion, agreeableness, openness and conscientiousness) on the total volume of exercise behavior, as well as on the volume of competitive/team and non-competitive/solitary exercise activities. First, we assessed the cross-sectional and longitudinal associations between the five personality traits and the various exercise behaviors. Second, as a direct test of causality we regressed the intrapair differences in MZ twins in exercise behaviors on the intrapair difference in the personality traits, thereby controlling for possible genetic and shared environmental confounding. Third, we tested a crucial requirement to uphold the causal hypothesis, namely that all genetic and environmental correlations between personality and exercise behavior would be significant. This was done in two different twin-sibling models, each with its own strengths. In the first model, to reduce impact of measurement error, we used the longitudinal data (two observations per participants) in a bivariate model as multiple indicators of the 'true phenotype'. In the second model, to reduce impact of reverse causality, we used longitudinal data in a prospective design, such that personality at baseline was a predictor for exercise behavior at follow-up. We separately re-assessed the genetic

correlation in independent data, using the available leave-NTR-out GWAS summary statistics for personality (de Moor et al., 2015; Lo et al., 2017) and for sports and exercise behavior (Klimentidis et al., 2018). Finally, the summary statistics from these GWASs were used to generate polygenetic scores (PRS) for personality traits and exercise behavior to be used as genetic instruments in a direct test for causality using the Mendelian randomization direction of causation (MR-DoC) model (Minică et al., 2018).

Results provided the strongest support for the causal hypothesis, i.e. by resisting falsification, for the association between extraversion and total volume of exercise, closely followed by the association between conscientiousness and non-competitive/solitary exercise and conscientiousness and total volume of exercise. Of note, we failed to show a causal effect of neuroticism on exercise behavior, which is in line with a previous cross-lagged panel analysis by de Moor and de Geus (de Moor & de Geus, 2018). Interestingly there was some evidence for a positive association between openness and non-competitive/solitary exercise, but no association between openness and total volume of exercise, likely due to the (non-significant) negative associations between openness and team-based exercise. Reverse causal effects of exercise behavior on extraversion, conscientiousness and openness were found consistently, although the effect sizes for such reverse causality were consistently smaller in our strongest estimator of the causal effect, the MR-DoC model.

From the results of chapter 7 we conclude that there is likely a bidirectional causal relationship between the personality traits extraversion, conscientiousness and openness to experience and regular voluntary exercise activities.

Discussion

The main conclusions and contributions of this thesis can be divided into three main topics, discussed separately below. First, the prevalence and stability of exercise, which mainly concerns chapter two, and the other chapters to a lesser extent. Second, the genetic epidemiology of voluntary exercise, where chapters 3, 4 and 5 mainly address the heritability, chapter 6 addresses gene-finding, and chapter 7 serves as an example of how this knowledge can be used to further study the pathways from genes to voluntary exercise behavior. Finally, the added value of a subdivision of total weekly exercise into activities in specific exercise domains, which has been a common theme throughout this thesis.

Exercise prevalence and stability

The results of chapter 2, as well as exercise descriptive statistics in other chapters provide yet more evidence that the weekly volume of regular exercise decreases with age and depends on sex. The peak of exercise behavior is in mid-adolescence, after which it decreases sharply until at about age 40 where it shows a more gradually slowing downward trend that re-accelerates around age 65. Males tend to exercise more than females at all ages although the rate of decrease after mid-adolescence is greater in males. These findings are by no means novel, and this pattern is a well-known characteristic of exercise behavior (Azevedo et al., 2007; Eime et al., 2016; Hirvensalo & Lintunen, 2011; R. Tammelin et al., 2014). The results of this thesis do, however, shed some new light on this pattern by splitting exercise activities into the various domains introduced previously. Our results indicate that the strong decrease in exercise after mid-adolescence is almost entirely due to a decrease in team-based competitive exercise in both males and females, whereas solitary non-competitive exercise remains relatively stable. This is in line with what was stated earlier by

Telama et al. (2005) based on work by Burton (1988): “there are large numbers of young athletes who would prefer to continue competitive sport but do not do so because they are screened out because of low achievement or because they perceive a sport as too demanding in the relation to their perceived ability”. The strong emphasis on the *perceived* demand and *perceived* ability is further in line with a pathway model by de Geus (2020), which suggests a feedback loop between exercise behavior and perceived ability, where high perceived ability acts as positive reinforcement for exercise behavior, but low ability as punishment.

The above patterns in exercise prevalence suggest that the transition from competitive team-based sports to solitary exercise is currently a ‘weak link’ from a public health perspective. This is where a major drop-out occurs. Social roles may start to interfere with team-obligations and/or the level of organized team sports for adults is not as advanced as that for children and adolescents. It is not clear why many exercisers do successfully switch to other exercise activities, whereas others don’t. Interestingly, the perceived value of competitive elements does not seem to change. We found a decreasing correlation between team-based and competitive exercise in parallel to an increasing correlation between solitary and competitive exercise throughout adulthood. Individuals favoring a competitive element tend to switch from a team-based (e.g. field hockey or soccer) to a competitive solitary exercise (e.g. tennis or squash) where they still obtain the perceived benefits of competition.

Exercise behavior that survives the transition into adulthood shows an increasingly higher temporal stability. Adult regular exercisers seem to have found a set of exercise activities that is sufficiently reinforcing to be maintained, possibly because it optimally matches their genotypes.

Genetic epidemiology of exercise

Previous findings suggest that the heritability of exercise behavior increases from childhood to adolescence, with a peak at around 18 years (Huppertz et al., 2016; Vink et al., 2011). As reviewed in Schutte et al. (2018), this occurs in parallel to a large change in the contribution of shared environmental influences. During childhood, sibling resemblance in exercise behaviors is strongly determined by the shared environment in which they grow up, but this shared environmental influence strongly wanes during adolescence. The strong decline of contribution of shared environmental factors may be due to the parental motivation increasing the volume of exercise behavior in their children (Beets et al., 2010). The effect of this parental motivation does decrease over time, giving way to increased influence from peers and coaches (Chan et al., 2012).

When the adolescents become young adults, heritability appears to decrease again to reach the levels reported in chapters 3 and 4, where we conclude that across the full adult life span about half of the variance in exercise behavior is contributable to genetic factors. Fine-grained analysis of the adult trajectory (as is available for children and adolescents) is currently lacking. However, various indicators suggest that this reflects a decrease in heritability from the peak in adolescence to lower levels in later stages of adulthood where the decrease becomes asymptotic. For example, the estimate of 48% from the meta-analyses in chapter 3 is higher than our finding in chapter 5, where we find a slightly lower heritability of roughly 40%, depending on the type of exercise. This is likely due to the large proportion of studies in the meta-analysis, with a relatively low mean age (~28) compared to the extended twin-family study in chapter 5 that had a mean age of 40 years.

This decreased influence of genetics is paired to a gradual increased influence of person-specific environmental influences.

There is a huge number of factors that can come into play in exercise behavior in adulthood such as entering a stable relationship, having children, job demands, caretaking obligations, or health problems (Dishman et al., 1985; Seefeldt et al., 2002; Simonen, Videman, et al., 2003). Furthermore, as identified in our extended twin-family study, we find a significant contribution of spouses on each other's exercise behaviors. Assuming individuals do not share a household with their spouse before adulthood and given the significance of marital interaction we find in chapter 5, the spousal influence on exercise behavior after partnering up may slowly increase up to 24% of explained variance.

Combining all results obtained in the NTR cohort I would like to propose an extension to the figure by Huppertz et al. (2012) showing the change in relative contributions of genetic and environmental factors to the total volume of regular voluntary exercise behavior as a function of age.

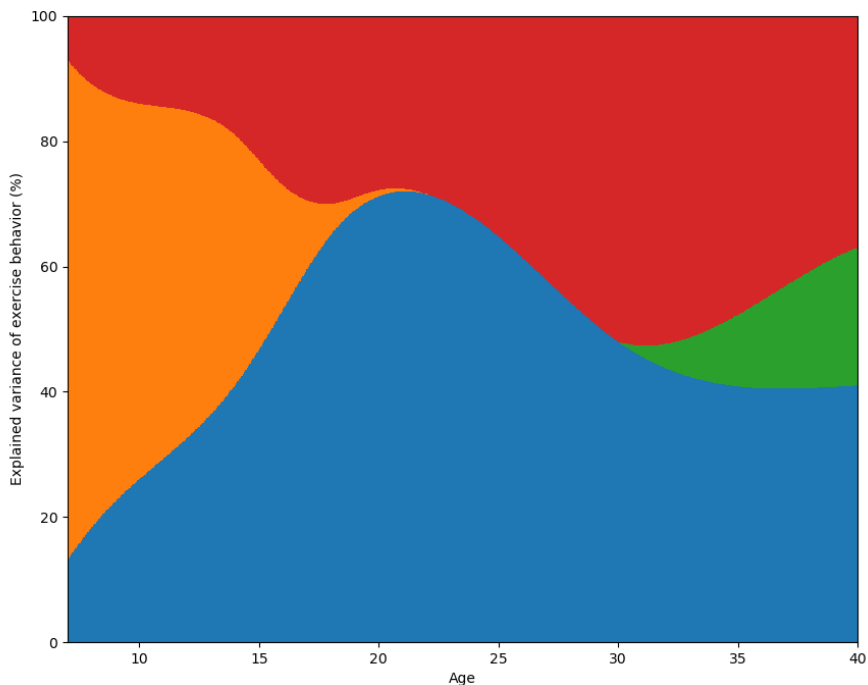


Figure 8.1. Percentage of variance in regular exercise behavior explained by *unique environmental factors*, *environmental factors shared by siblings*, *genetic factors*, and *environmental factors shared by spouses* over time.

It is important to note that the genetic factors displayed in my Figure 8.1 includes both additive, and non-additive genetic factors. Due to the limitations of the classical twin model, only one of common environmental factors, or non-additive genetic factors can be included in the model. If non-additive genetic factors are not specifically defined in the model, their contribution to the variance will end up in the additive genetic component. Given our finding that about half of the heritability (and even more so in team-based and competitive exercise) is attributable to non-additive genetic factors it seems likely that these factors also play a role earlier in life. More research is needed to accurately separate non-additive from additive genetic factors

throughout the lifespan, so for now the blue-colored area reflects broad sense heritability.

Four main tenets are visualized in this figure. First, the earlier mentioned strong decrease in the contribution of **environmental factors shared by siblings** from childhood (age 7) to late adolescence, to the point where these factors are no longer a significant contributor (around 16 years). Second, a strong increase in contribution of **genetic factors** up to a peak heritability of 70% in late adolescence and early adulthood (around 20 years) that levels off to 40% at age 40. Third, the near linear increase in the influence of **unique environmental factors** across the life span. Fourth, **spousal factors** become an important component of these environmental factors from age 30 onwards and form a substantial (de)motivator to engage in exercise after age 35.

There are different possible explanations for the sharp increase in the relative importance of genetic factors during adolescence followed by a gradual decrease to middle adulthood. First, the changes in the percentage of variance explained by genetics may simply be a result of changes in the importance of common and unique environmental factors. In other words, the *true* genetic effects may not change, only their relative contribution. However, a true increase in absolute genetic variance was demonstrated from childhood to adolescence (Huppertz et al., 2016) making this explanation unlikely. That unique environmental influence start to have a cumulative effect from adolescence towards middle adulthood makes more sense and a change in the relative contribution of E and A could explain part of the gradual decrease in heritability in this period.

However, the peak in adolescence and the decline in adulthood could also be related to the change in the prevalence of team-based and competitive exercise activities. It is very high in adolescence but wanes in adulthood. Because we have found team-based and competitive exercise to have an overall higher heritability in chapter 5,

decreased participation in primarily these types of exercise activities would lead to a proportional decrease in heritability of total volume of exercise. Second, the decreasing heritability may be a direct result of different genetic effects coming into play at different ages. In other words, a *true* change in the genetic effects may occur. Such a change may be related to a behavioristic model for the genetic determinants of exercise behavior presented in de Geus (2021). Core determinants of exercise behavior are grouped in two instrumental conditioning loops continuously influencing the adoption and maintenance of regular exercise activities. One loop is related to the affective responses during and after exercise, which is linked to genetic effects on the neurobiological impact of exercise on reward/punishment circuits; the other loop is related to the rewarding effects of being able to perform well on a valued activity, which is linked to genetic effects on core elements of exercise ability including fitness, strength, low injury sensitivity and body composition.

The difference in heritability estimates found for different types of exercise activities may be the result of different genetic effects on these types of exercise. Team-based competitive activities would be favored by genetic variants influencing exercise ability whereas solitary and non-competitive activities would be favored by genetic variants influencing the affective response to exercise. In other words difference in heritability estimates can reflect that these activities are, at least partly, influenced by different genetic variants. If this is the case, then we would expect (1) to find different GWAS results for team-based and competitive exercise compared to solitary and non-competitive exercise, and given the changing proportions of different types of exercise behavior across various ages (2) to find different GWAS results for total exercise behavior depending on the age of the sample.

In line with these expectations, we find different results for the different types of exercise activities in our GWAS in chapter 6, especially when comparing team-based competitive exercise activities to solitary non-competitive activities. Furthermore, we find no direct overlap between our GWAS results in a sample with a mean age of 31 and the self-reported total volume of exercise behavior in the largest GWAS available for self-reported sports and exercise behavior in the UKB, which is a sample aged 40-69 years. Nor did we find overlap with the variants detected in the second largest GWAS by Hara et al. (2018) in participants with a mean age of 55. Furthermore, the genome-wide significant variants found in the UKB by Klimentidis et al. (2018) appeared to be largely brain-related. In contrast our GWAS in younger population, found variants related to red blood cell phenotypes.

It is attractive to think that our GWAS tapped more into the genetic variants influencing ability whereas the UKB GWAS tapped more into genetic variants influencing the affective response to exercise. There is a clear association between red blood cell physiology and exercise ability (Mairbäurl, 2013) mainly due to their role in oxygen-delivery to peripheral muscle. A case in point is the story of Eero Mantyranta, who had stellar biathlon capability due to a rare mutation in the EPO receptor gene (Enriquez & Gullans, 2012). It is therefore not surprising that red blood cell increasing substances such as erythropoietin (EPO) are banned from professional sports as performance-enhancing drugs (World Anti-Doping Agency, 2021). Thus it seems very plausible that individuals with a genetic makeup for an increased number (or improved physiology) of red blood cells perform better compared to their peers. The perception of higher ability would in turn make these individuals more likely to continue exercising as part of (competitive) team sports activities, in line with de Geus (2020) as discussed earlier.

Clearly, this is utter speculation. There are multiple other possible sources of the differences between the handful of exercise GWASs, most notably the modest sample size in our NTR GWAS. Apart from insufficient power, there is potential bias due to selective participation (both in the UKB and NTR cohorts) resulting in population stratification and poor harmonization of instruments used to establish voluntary exercise participation. The different findings might also be the result of different moderation of genetic variants across different countries (i.e., gene-environment interaction). Larger GWAS on the various types of exercise in different populations and at different ages are very much needed to progress our understanding of the molecular genetic basis of voluntary engagement in regular exercise behaviors and its change across the lifespan.

Exercise domains

The main exercise phenotype used throughout this thesis was the total amount of sports and exercise activities weekly, recast as a measure of energy expenditure on these activities. This involves the use of fixed intensity codes for specific activities based on the average values obtained in past experimental studies (Ainsworth et al., 2011; Ridley et al., 2008). This had the advantage of making our exercise phenotype comparable to those used in a large number of studies in the extant literature. A disadvantage of this measure, compared to e.g. number of minutes weekly spent on exercise, is that it introduces measurement error because individuals may perform these activities at different actual intensity levels based on differences in motivation or efficiency related to body composition and/or motor competence. However, acknowledging this disadvantage, we could now at least compare our results to a large body of past work that also used a METminutes-based score.

The additional use of energy expended on team-based, solitary, competitive, non-competitive, externally paced and internally paced exercise activities was more challenging in this regard. The inclusion of these separate exercise domains was inspired by van der Mee et al (2017) and has become a common theme throughout this thesis. As a consequence, many results presented in this thesis, i.e. those related to these domains specifically, cannot be directly compared to existing literature, as to my knowledge almost no previous genetic studies have used these domains. However, I believe the results presented in this thesis strongly justify the use of these separate domains, as they yield differential and novel findings, compared to total volume of exercise alone. Most strikingly was the differential course across the life span of team-based, competitive and solitary, non-competitive activities in chapter 2 as well the larger broad sense heritability of the former in chapter 5 due to a more substantial non-additive component.

Do all these domains need to be included in the analyses? It may depend on the application. Because of the clear meaning the different domains have for professionals and the clear role these may play in possible interventions it is my recommendation to adhere to these domains when the aim of future research is directly aimed at developing or improving exercise interventions. For genetic research, we did note substantial redundancy between team-based, competitive and externally paced activities on the one hand, and solitary, non-competitive, and internally paced activities on the other hand. Internally (self) paced versus externally paced, in particular, did not add a lot to the domain solitary vs team-based. However, when examining the role of the genetics of executive functioning on exercise preference this distinction did prove to be meaningful (van der Mee et al., 2017). Somewhat more distinction exists between the team-based vs solitary domain and the competitive and non-competitive domain, although substantial overlap was found for these dimensions too. Even

so, the inclusion of the full set of team-based versus solitary and competitive versus non-competitive may be maintained when research concerns, for instance, the role of personality in exercise (H. J. Eysenck et al., 1982).

Whereas some research questions may require all three exercise domains to be used in full, evidence from both the phenotypic and genotypic analyses performed throughout this thesis suggest that two underlying factors capture the six METminutes values across the three exercise domains rather well. These latent factors can be approximated by using the team-based versus solitary activities but an actual factor score computed across the six different exercise phenotypes, as used in chapter 7 may be optimal. On top of the inclusion of the separate domains or the two factor scores, the total volume of exercise behavior should also be included since (1) the correlations between total volume and the two factors or the full set of the six METminutes scores are only moderate and (2) the vast majority of previously published literature only includes total volume of exercise behavior, as discussed earlier, thus allowing for a more direct comparison to past findings.

Future directions for exercise phenotyping

Throughout this thesis self-report, or parent-report in children included in chapter 2, was used to measure the time spent on all exercise activities. As discussed in multiple chapters of this thesis, voluntary exercise activities are salient and thus reliably recalled by self-report in surveys. Total physical activity on the other hand is much harder to accurately recall retroactively, it is too easy to significantly over- or underestimate the time spent being physically active in a day, let alone a week. It is therefore not surprising that the accelerometer (and pedometer to a lesser extent) has all but replaced the self-report survey in studies on physical activity (Silfee et al., 2018).

Nowadays the vast majority of the population carries highly valid accelerometers with them everywhere all the time, at least one in (nearly) every smartphone, and sometimes additional ones in devices such as fitness bands or smartwatches. The large amount of data generated by these devices provides a lot of opportunity for future research. Major challenges, however, are to *obtain* the data from the often commercial suppliers like Fitbit, Google, Apple or Polar, and to *standardize* across the many proprietary versions of the hard- and software that regularly spring into life. For this reasons, many researchers have resorted to dedicated research devices for accelerometer signals, of which the Actigraph seems most popular, paired to scoring standards and open software solutions in R to do so (Miguelles et al., 2021). Unfortunately, where total physical activity was harder to measure through self-report, voluntary exercise behavior cannot be assessed by relying solely on an accelerometer. Since the accelerometer only records raw movement on three axes, it is perfectly suited to measure total physical activity, however without a record or log about what type of activity was performed (and why), there is no easy way to tell which bout of activity is attributable to voluntary regular exercise behavior.

The future is bright here though, as innovative machine learning methods become increasingly capable at recognizing patterns in vast quantities of unstructured data, making them very promising methods to accurately detect exercise bouts from raw accelerometer data (Hoogendoorn & Funk, 2018). Ongoing research to make these classifiers more and more accurate are making it feasible to use accelerometers in large-scale exercise studies in the future. The benefits of this are plenty, for example we can more accurately estimate the exact amount of time an individual is engaged in exercise, and how often. Additionally, as these models develop, they will inevitably produce a better estimate of the true energy expenditure

during exercise compared to survey-based data in conjunction with MET-constants (Freedson et al., 2011; Lawal & Bano, 2020; Staudenmayer et al., 2009; Yen & Lin, 2020).

Another exciting avenue for research is brought about when accelerometers are combined with short self-report queries that are sent out on an hourly basis as part of people's daily lives, also known as ecological momentary assessment (EMA). Smartphone-based EMA can measure an individual's intent to engage in, attitudes towards *voluntary* exercise, and experienced enjoyment. Combining EMA with accelerometers can accurately assess the differences in people's reported or intended exercise activities, acute psychological effects of exercise, and momentary determinants of exercise, together with the objective volume of exercise they engage in (Dunton et al., 2015; Liao et al., 2017; Liao et al., 2015; Maher et al., 2017).

In spite of these exiting developments, survey-based research into exercise behavior will retain its value in the foreseeable future. No matter how good the accelerometers and the accompanying (machine learning) models become at estimating time and energy spent on exercise, the scale of the samples required for genetic analyses may not be easy to obtain with these methods due to the challenges mentioned previously. Also, various trait-like characteristics are still well captured by surveys like personality or attitudes. One other relevant trait that we recently tackled is an individual's exercise *liking*. In over 157,000 individuals from the UK Biobank, we sought to complement and extend previous findings on the genetics of physical activity behaviors by performing genome-wide association studies of liking of several exercise-related behaviors plus an additional derived overall activity-liking trait. We identified a total of 17 loci, along with an additional eight for the overall trait, only some of which overlap with loci previously identified for physical activity behavior. Replication in over 7,000 adults from the NTR showed directional consistency in 13

out of 17 loci (Klimentidis et al., 2021). If the aim of a future study is to aid the development of more personalized exercise interventions, an individual's exercise liking and attitudes towards the behavior are, in my opinion, at least as important (if not more so) as the objective energy expenditure.

Future directions for finding molecular determinants of exercise behavior

As sample sizes increase, future GWASs will be able to tell us more about the complex genetic underpinnings of exercise behavior, particularly when cohorts combine forces in meta-analyses. Throughout this thesis I have shown that these meta-analyses would do well to take the changing composition of total exercise behavior into account. 'Total exercise' at age 20 is not strictly the same behavior as 'total exercise' at age 60, which may make meta-analysis of studies across different ages more challenging. Additionally, as discussed previously, a GWAS of exercise activities is likely sensitive to selection bias compounded by population stratification. Luckily the development of genetic methods does not seem to be slowing down and new methods to tackle issues like this are being developed or have already been developed. For example to tackle the issue of different compositions of total volume of exercise across the various dimensions, future research could employ the multivariate GWAS meta-analysis approach as described by Baselmans et al. (2019). Additionally, to tackle the issue of stratification or indirect genetic effects future research could use a within-sibling GWAS (Howe et al., 2021).

Variations in the DNA code, the focus in this thesis, are not the only possible molecular underpinnings of voluntary exercise. There is likely a strong relationship between epigenetic mechanisms and voluntary exercise behavior as well (van Roekel et al., 2019; Voisin et al.,

2015). Epigenetics does bring up the thorny issue of causality. In genetics, the direction of causality is simple, as genetic variants can (indirectly) affect behavior in many ways but the reverse is near impossible (barring extremely rare genetic mutations due to things like radiation). In epigenetics, this is not as simple because epigenetic changes such as DNA methylation or histone modification may well have a causal effect on exercise behavior, but the reverse may just as well hold, or the effect may be bidirectional creating an epigenetic feedback loop (Lightfoot, 2020). Further complicating the epigenetics of exercise is the fact that epigenetic profiles are different in different cell types (Maurano et al., 2012). Nevertheless, I believe epigenetics has great potential in exercise behavior as it can lead to more insights into the molecular underpinnings of the health benefits of exercise. Longitudinal epigenetic assessments combined with longitudinal measures of (objective) exercise behaviors can likely aid in distinguishing these two directions of causality. Using twin samples this can be further aided by an MR-DoC design.

Another avenue through which we may well learn more about the biological underpinnings of the health benefits of exercise behavior is the gut-microbiome. The interest in the complex ecosystem of bacteria and other micro-organisms in the gut is relatively young and the immense diversity of the gut-microbiome with over 3 million unique genes from over 1000 unique bacterial species (Qin et al., 2010) poses significant challenges for future research. This diversity is in turn affected by a combination of host genetics (Kurilshikov et al., 2021), and numerous environmental factors (Rothschild et al., 2018), and these effects can vary between species, posing further challenges. Despite these challenges, however, numerous studies in both humans and animals have already found evidence for associations between exercise and the gut-microbiome (see Mailing et al. (2019) and Dalton et al. (2019) for review).

To summarize, I think there is a lot to look forward to in the field of exercise genetics. With the combined growth in popularity of daily-wear accelerometers, advancements in methods to accurately label this data and advancements in EMA methods, there is a wealth of new data just on the horizon. By combining this data with novel and increasingly bias-resistant genetic methods in ever increasing sample sizes, and expanding from the genomic to other multi-omics levels, we stand to learn a lot more about the molecular determinants of exercise behaviors. Combining these results across cohorts in large-scale meta-analyses will yield the required statistical power to detect the small effects that are inherent to any highly polygenetic behavior. If, on top of that, future research also analyzes the different types of exercise activities separately, this will likely not only yield more scientific findings, but also provide avenues for personalized interventions that have higher success rates than those currently on offer.



Appendix

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Age	Total		Team		Sol		Comp		Ncomp		EP		IP	
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD
8	527	517	170	374	357	409	232	423	294	366	230	421	194	336
10	766	667	383	596	382	464	487	628	279	386	486	636	124	304
12	872	798	427	704	445	556	556	742	316	486	549	741	157	396
14	984	908	528	820	456	606	663	865	321	514	659	870	160	394
16	1057	1047	540	857	518	764	665	912	392	676	658	906	225	529
18	1046	1186	479	891	567	915	584	956	462	825	578	960	317	702
20	912	1108	373	808	539	830	444	866	468	757	444	890	345	635
22	907	1066	314	737	594	853	391	807	516	800	391	826	413	701
24	921	1116	287	702	633	941	360	768	561	877	359	779	475	812
26	834	962	206	549	628	847	276	608	558	804	272	605	488	762
28	762	903	171	506	591	785	251	607	511	713	248	606	453	678
30	719	932	163	510	556	785	225	587	494	725	221	574	434	706
32	701	900	124	415	577	798	189	486	512	751	191	502	451	698
34	619	780	99	352	520	717	171	458	448	665	169	454	403	631
36	551	728	63	275	488	677	123	364	428	643	125	380	374	583
38	552	734	63	265	489	695	128	370	424	657	128	369	378	628
40	552	716	57	253	495	670	131	363	422	633	130	362	377	603
42	549	693	56	238	493	659	145	380	403	597	143	376	364	570
44	543	712	51	239	492	674	147	393	395	602	145	389	355	582
46	544	696	46	196	497	672	149	383	395	600	147	380	358	577
48	562	743	41	183	520	725	145	381	417	652	143	379	380	634
50	576	761	37	173	539	743	134	374	441	672	132	372	402	639
52	586	833	31	171	555	810	123	376	463	744	119	359	420	705
54	602	899	34	170	569	871	133	382	469	806	131	380	428	778
56	598	877	35	213	562	833	138	403	460	761	133	398	427	731
58	559	784	20	134	539	770	118	359	441	674	114	353	403	650
60	556	825	18	131	537	799	121	382	434	709	116	372	395	672
62	560	911	21	151	539	881	116	352	444	830	110	347	409	795
64	597	837	13	114	584	824	132	427	465	704	125	414	435	680
66	543	868	13	100	530	864	118	366	425	779	112	357	403	767
68	448	628	10	82	439	623	101	327	347	553	95	317	313	522
70	469	756	15	92	454	753	123	402	345	656	114	388	319	637
72	399	576	12	88	387	557	119	378	280	465	94	338	283	475
74	433	740	6	55	428	734	114	374	319	582	101	365	311	583
76	319	549	18	161	301	488	106	390	213	383	90	354	198	350
78	336	643	0	0	336	643	48	287	288	597	42	283	279	582
80	267	516	4	37	263	514	56	234	211	485	43	221	224	487
82	190	315	0	0	190	315	7	50	183	307	0	0	181	313

Supplementary table 2.1. Mean, and standard deviation (SD) of MET-minutes in the 7 exercise dimensions over age. Comp: Competitive; Ncomp: non-competitive; EP: externally paced; IP: internally paced.

	2-year		8-year		14-year		20-year	
	Range	Median	Range	Median	Range	Median	Range	Median
Within domain								
Total								
Males	0.4-0.77	0.56	0.21-0.78	0.42	0.13-0.72	0.36	0.09-0.59	0.36
Females	0.37-0.71	0.53	0.23-0.64	0.39	0.2-0.65	0.32	0.26-0.5	0.35
Team								
Males	0.38-0.81	0.63	0.16-0.67	0.46	0.24-0.58	0.42	0.06-0.41	0.28
Females	0.52-0.98	0.7	0.14-0.79	0.48	0.15-1	0.65	0.03-0.72	0.23
Competitive								
Males	0.48-0.84	0.63	0.28-0.74	0.47	0.26-0.61	0.45	0.19-0.42	0.26
Females	0.53-0.83	0.69	0.36-0.7	0.49	0.26-0.91	0.45	0.21-0.66	0.37
Externally paced								
Males	0.47-0.88	0.64	0.29-0.72	0.51	0.28-0.6	0.45	0.21-0.43	0.26
Females	0.52-0.83	0.67	0.35-0.7	0.52	0.25-0.8	0.42	0.21-0.67	0.36
Solitary								
Males	0.24-0.77	0.54	0.11-0.8	0.4	0.08-0.82	0.42	0.18-0.75	0.4
Females	0.3-0.72	0.51	0.2-0.66	0.35	0.11-0.68	0.26	0.07-0.53	0.26
Non-competitive								
Males	0.26-0.78	0.56	0.06-0.93	0.37	0.05-0.92	0.36	0.07-0.81	0.43
Females	0.28-0.7	0.46	0.17-0.69	0.32	0.07-0.57	0.24	0.04-0.5	0.16
Internally Paced								
Males	0.22-0.75	0.55	0.12-0.87	0.39	0.04-0.84	0.34	-0.09-0.8	0.43
Females	0.26-0.77	0.44	0.15-0.73	0.33	0.06-0.42	0.23	0.01-0.48	0.1
Between domains								
Team								
Males	0.12-0.52	0.25	0.06-0.33	0.22	0.06-0.35	0.16	0.03-0.22	0.12
Females	0.01-0.5	0.24	0.03-0.38	0.22	0.03-0.35	0.17	0.03-0.4	0.19
Competitive								
Males	0.24-0.51	0.36	0.14-0.4	0.28	0.13-0.38	0.22	0.04-0.32	0.21
Females	0.27-0.49	0.33	0.18-0.42	0.29	0.11-0.4	0.2	0.13-0.35	0.24
Externally paced								
Males	0.23-0.52	0.37	0.14-0.39	0.28	0.13-0.37	0.26	-0.46-0.31	0.21
Females	0.26-0.47	0.33	0.18-0.42	0.29	0.11-0.41	0.2	0.13-0.37	0.24
Solitary								
Males	0.07-0.72	0.46	0.01-0.77	0.33	0.06-1.23	0.56	0.12-0.67	0.32
Females	0.14-0.7	0.48	0.03-0.64	0.31	0.03-0.66	0.28	0.02-0.52	0.26
Non-competitive								
Males	0.03-0.66	0.39	0.05-0.72	0.29	0.02-0.74	0.37	0.1-0.63	0.41
Females	0.11-0.58	0.4	0.03-0.71	0.26	0.03-0.46	0.2	0-0.44	0.2
Internally Paced								
Males	0.06-0.64	0.4	0.03-0.74	0.27	-0.01-0.84	0.41	-0.11-0.62	0.36
Females	0.04-0.57	0.37	0.02-0.76	0.25	0.08-0.44	0.2	0-0.41	0.22

Supplementary Table 2.2 95-percentile ranges, and medians of tracking coefficient

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing	
Aerobics	Aerobics	Aerobics		no	no	4	
		Combi-fit		no	no	4	
	High impact	Grit		no	no	4	
		High impact		no	no	4	
		HIIT		no	no	4	
		Insanity		no	no	4	
		Labooca		no	no	4	
		Tae Bo		no	no	4	
	Low impact	Aeronatics		no	no	4	
		BBB		no	no	4	
		Callanetics Low impact		no	no	4	
		Steps		no	no	4	
			Body Steps		no	no	4
			Steps		no	no	4
Acrobatics/gymnastics	Acrobatics	Acrobatic Rock-n-Roll		Can be	Can be	3	
		Acrobatics		Can be	Can be	3	
		Tumbling		Can be	Can be	3	
	Cheerleading	Cheerleading		yes	yes	3	
	Color Guard	Color Guard		Can be	Can be	3	
	Figure Scating	Figure Scating		Can be	yes	3	
	Gymnastics	Cesar therapy		no	no	4	
		Competitive		Can be	yes	4	
		Gymnastics		no	no	4	
		Heart Disease		no	no	4	
		Mensendieck		no	no	4	
		Pregnancy		no	no	4	
		Recovery		no	no	4	
		Rhythmic		Can be	no	3	
		Voltige		Can be	Can be	3	
Platform diving	Platform diving		no	yes	3		
Aiming based	Archery	Archery	yes	no	Can be	4	
	Billiards	Billiards	yes	no	yes	4	
	Bowling	Bowling	yes	Can be	yes	4	
		Jeu de boules	yes	Can be	yes	4	

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing
		Petanque	yes	Can be	yes	4
	Curling	Curling	yes	yes	yes	4
	Darts	Darts	yes	no	yes	4
	Frisbee	Frisbee		yes	Can be	3
		Ultimate frisbee		yes	Can be	3
	Golf	Golf		no	Can be	4
	Shooting	Gun	yes	no	Can be	4
		Rifle	yes	no	Can be	4
Air based sports		Hang gliding		no	no	3
		Sky diving		no	no	3
Ball games	Baseball	Baseball		yes	yes	1
		Softball		yes	yes	1
Ball	Basketball	Basketball		yes	yes	1
		Basketball		yes	yes	1
		Basketball		yes	yes	1
	Cricket	Cricket		yes	yes	1
	Handball	Handball		yes	yes	1
	Hockey	Hockey		yes	yes	1
		Hockey		yes	yes	1
		Ice Hockey		yes	yes	1
		In-line Hockey		yes	yes	1
		Water Hockey		yes	yes	1
	Korfball play	Korfball play		yes	yes	1
	Polo	Polo		yes	yes	1
	Rugby	Rugby		yes	yes	1
		Rugby		yes	yes	1
	Soccer	Beach Soccer		yes	yes	1
		Floorball		yes	yes	1
		Hall sports		yes	yes	1
		Hall sports		yes	yes	1
		Indoor soccer		yes	yes	1
		Indoor soccer		yes	yes	1
		Soccer		yes	yes	1
	Volleyball	Beach Volleyball		yes	yes	1
		Competitive		yes	yes	1

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing	
	Various	Volleyball		yes	yes	1	
		Volleyball (sitting)		yes	yes	1	
		Ball games (other)		yes	yes	1	
Cardiotraining/ endurance	Athlons	Biathlon		no	yes	3	
		Pentathlon		no	yes	3	
		Triathlon		no	yes	3	
	Cardiotraining	Cardiotraining		no	no	4	
		Elliptical trainer		no	no	4	
		Rowing machine		no	no	4	
		Spinning		no	no	4	
		Water Spinning		no	no	4	
		Cycling	Cycling (race)		no	Can be	4
			Handbiking		no	no	4
	Mountainbiking			no	Can be	4	
	Endurance	Competitive		no	yes	4	
		Endurance		no	no	4	
		Fast walking		no	Can be	4	
		Freerunning		no	Can be	3	
		Jogging		no	no	4	
		Jumping rope		no	no	4	
		Running		no	Can be	4	
		Treadmill		no	no	4	
		Trampoline		no	no	4	
Cardiotraining/ endurance (cont.)		Skating	Water jogging		no	no	4
	In-line skating			no	Can be	4	
	Rollarskating			no	no	4	
	Stationairy	Skateboarding		no	Can be	4	
		Cycling (tours)		no	no	4	
		Hometrainer		no	no	4	
		Hypoxi		no	no	4	
Climbing	Mountain	Mountain		no	no	3	
	Wall Climbing	Wall Climbing		no	no	3	
		Canyoning		no	no	3	
		Potholing		no	no	3	
Dancing	Ballet (like)	Ballet		no	Can be	3	

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing	
Dancing (cont.)	Ballroom dancing	Jazz dancing		no	no	3	
		Modern dancing		no	Can be	3	
		Ballroom dancing		no	Can be	3	
		Competitive		no	yes	3	
		Latin dancing		no	Can be	3	
		Tango dancing		no	Can be	3	
	Cultural dancing	Dancing	Belly dancing		no	no	3
			Bio dancing		no	no	3
			Body by Dance		no	no	3
			Breakdance		no	no	3
			Flamengo		no	no	3
			Hiphop dancing		no	no	3
			Salsa dancing		no	no	3
			Showdance		no	no	3
			Streetdance		no	no	3
			Country dancing		no	no	3
	Dancing aerobics	Dancing	Dancing		no	no	3
			Dancing		no	no	3
			Disco dancing		no	no	3
			Folk dancing		no	no	3
			Line dancing		no	no	3
			Aerobic dance		no	no	3
			Rock & Roll		no	no	3
Gogo dancing	Dancing	Shabam		no	no	3	
		Zumba		no	no	3	
		Gogo dancing		no	no	3	
Tapdancing		no	no	3			
Twirling		no	Can be	3			
Equestrian		Carriage driving	yes	no	Can be	3	
		Dressage		no	Can be	3	
		Horse training		no	no	3	
		Horseback riding		no	Can be	3	
Fighting sports	Boxing	Boxing		no	yes	2	
	Fencing	Fencing		no	yes	2	
Fighting sports	Martial arts	Aiki jitsu		no	yes	2	

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing	
(cont.)		Barokai		no	yes	2	
		Capoeira		no	Can be	3	
		Choi Kwan Do		no	yes	2	
		Eskrima		no	yes	2	
		Iaido		no	yes	2	
		Judo		no	yes	2	
		Jujitsu		no	yes	2	
		Karate		no	yes	2	
		Kempo		no	yes	2	
		Kickboxing		no	yes	2	
		Kickfun		no	yes	2	
		Kobudo		no	yes	2	
		Krav Maga		no	yes	2	
		Kung Fu		no	yes	2	
		Martial arts		no	yes	2	
		Ninjatsa		no	yes	2	
		Tae kwan do		no	yes	2	
		Tang soo do		no	yes	2	
		Thai boxing		no	yes	2	
		Wing Chun		no	yes	2	
	Sword fighting	Sword fighting		no	yes	2	
	Wrestling	Wrestling		no	yes	2	
Fitness training	Bootcamp	Bootcamp		no	no	4	
	Boxing, punching	Boxing, punching		no	no	4	
	Calisthenics	Calisthenics	Calisthenics		no	no	4
		Calisthenics (back	Calisthenics (back		no	no	4
		Calisthenics	Calisthenics		no	no	4
		Curves	Curves		no	no	4
		Powerplate	Powerplate		no	no	4
		Slender you	Slender you		no	no	4
		TMF heat cabine	TMF heat cabine		no	no	4
	Fitness	55+ Sport	55+ Sport		no	no	4
		Fitness	Fitness		no	no	4
		Fysiofitness	Fysiofitness		no	no	4
		Nederlands on	Nederlands on		no	no	4

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing
Fitness training (cont.)	Group fitness	7-min workout		no	no	4
		Body Attack		no	no	4
		Body Boost		no	no	4
		Body Combat		no	no	4
		Body Fit		no	no	4
		Body Five		no	no	4
		Body Heat		no	no	4
		Body Jam		no	no	4
		Body Kick		no	no	4
		Body Power		no	no	4
		Body Pump		no	no	4
		Body Shape		no	no	4
		Body Styling		no	no	4
		Bodyline		no	no	4
		Crossfit		no	no	4
		Fat attack/burn		no	no	4
		Femme Fit		no	no	4
		Group fitness		no	no	4
		Keep-fit		no	no	4
		Piloxing		no	no	4
	X-CO		no	no	4	
	Home exercises	Home exercises		no	no	4
		Video workout		no	no	4
	Pole Fitness	Pole Fitness		no	Can be	4
	Water aerobics	Water aerobics		no	no	4
	Weight lifting	Bodybuilding		no	yes	4
Weight lifting			no	Can be	4	
Weight training	Circuit training		no	no	4	
	CRXworx		no	no	4	
	Dry training		no	no	4	
	Total body		no	no	4	
	Weight training		no	no	4	
Mind games		Bridge	yes	yes	yes	4
		Checkers	yes	no	yes	4
		Chess	yes	no	yes	4

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing
		Mind Games	yes	no	Can be	4
Motor sports		Drag Racing	yes	no	yes	3
		Go carting	yes	no	yes	3
		Motor-cross		no	yes	3
Swimming	Diving	Diving		no	no	3
		Scubadiving		no	no	3
Swimming (cont.)	Lifeguard Swimming	Lifeguard		no	no	4
		Competitive		no	yes	4
		Pregnancy		no	no	4
		Relaxation		no	no	4
		Rheumatic		no	no	4
		Swimming		no	Can be	4
		Swimming (laps)		no	no	4
		Swimming		no	no	4
		Swimming (sport)		no	Can be	4
		Swimming		no	no	4
	Synchronized		no	yes	3	
	Water polo	Water polo		yes	yes	1
Racket sports	Badminton	Badminton		Can be	yes	2
		Badminton		Can be	yes	2
		Competitive		Can be	yes	2
Racket sports (cont.)	Ping pong	Ping pong		no	yes	2
	Squash	Racquetball		no	yes	2
		Squash		no	yes	2
	Tennis	Tennis		Can be	yes	2
		Tennis		Can be	yes	2
Rowing	Canoeing	Canoeing		Can be	Can be	3
		Kayaking		Can be	Can be	3
	Rowing	Competitive		yes	yes	3
		Rowing		yes	Can be	3
Tai chi/yoga	Pilates	Body Balance		no	no	4
		Pilates		no	no	4
	Tai chi	Aikido		no	no	3
		Chu Yu Do		no	no	3
		Hapkido		no	no	3

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing
Thai chi/yoga (cont.)	Yoga	Pentjak Silat		no	no	3
		Qi gong		no	no	3
		Tai Chi		no	no	3
		Baby Balance		no	no	4
		Ismakogie		no	no	4
		Stretching		no	no	4
		Tacoyo		no	no	4
		Yoga (hatha)		no	no	4
		Yoga		no	no	4
		Yoga (power)		no	no	4
Yoga (Surya)		no	no	4		
Track-and-field	Jumping	Hurdles		no	Can be	3
		High jump		no	Can be	3
		Fierljeppen		no	Can be	3
		Long jump		no	Can be	3
		Pole vault		no	Can be	3
	Running	Sprinting		no	Can be	4
	Throwing	Discus Throwing		no	yes	3
Walking based	Hiking	Fitwalking		no	no	4
		Hiking		no	no	4
		Mountain hiking		no	no	4
		Marching		no	no	4
		Nordic Walking		no	no	4
		Orienteering		no	no	4
		Survival trail		no	Can be	3
	Referee/coach	Referee		no	no	4
	Sport coach		no	no	4	
Water activities	Fishing	Fishing	yes	no	Can be	3
		Jet-skiing		no	no	3
		Water skiing		no	Can be	4
	Kiting	Kite flying	yes	no	no	3
		Kitesurfing		no	Can be	3
		Competitive		no	yes	3
Water activities (cont.)	Sailing	Sailing		no	Can be	3
		Yachting		no	no	3

Exercise domain	Subdomain	Reported activities	Excluded	Team sport	Competitive sport	Internal/ External pacing
	Surfing	Flowboarding		no	no	4
		Paddleboarding		no	no	4
		Surfing		no	no	4
		Wakeboarding		no	Can be	4
		Windsurfing		no	Can be	3
Winter activities	Cross Country	Cross Country		no	Can be	4
	Ice Skating	Ice Skating		Can be	Can be	4
		Ice Skating (long)		Can be	yes	4
		Ice Skating		Can be	yes	4
		Ice skating (short)		yes	yes	4
	Skiing	Ski-gym		no	no	4
		Skiing (indoor)		no	Can be	4
		Snowboarding		no	Can be	4

Supplementary Table 5.1. Classification of various types of exercise

This is a complete list of the exercise activities that were reported by the NTR participants (NB: minor variations of the same activity not listed to exhaustion). Domains and subdomains are not used in the analyses and just serve to help the reader navigate this table. Exclude means that the activity was considered below the threshold for moderate-to-vigorous intensity. **Team sports** means any sport that is or can be performed in a team-setting, where multiple individuals work together to achieve a shared objective. If a sport can be a team sport is counted as a team sport over a solitary sport. **Competitive sport** means a type of sport where a team or individual (can) competes against another team or individual to win. If a sport can be a competitive sport is counted as a team sport over a solitary sport. **Internal/external pacing** is coded as follows: 1 Highly externally paced, influences from both teammates and opponent; 2 Intermediate externally paced, influenced by opponent or teammates only; 3 Low externally paced, influenced by elements (wind/water/music/synchronic team movements); 4 Internally paced for the purposes of this thesis, categories 1 and 2 are considered externally paced, and category 4 is considered internally paced. Category 3 is excluded.

		Age	Birth year	Total	Team	Competitive	Externally paced	Solitary	Non-competitive	Internally paced
Male parents	Mean	48.21	1959	673.50	137.03	244.52	234.82	536.47	428.98	414.69
	SD	7.41	9.95	1067.79	408.11	549.25	532.82	981.62	912.07	901.12
Female parents	Mean	45.89	1962	502.92	39.95	118.27	116.63	462.97	384.65	345.91
	SD	7.68	10.10	720.78	215.11	357.05	357.31	689.37	630.01	600.38
Male children	Mean	27.03	1978	1210.77	559.08	710.40	690.19	651.70	500.38	460.05
	SD	12.00	12.68	1384.59	945.37	1055.70	1044.40	1090.23	959.64	917.58
Female children	Mean	29.48	1977	780.26	223.30	305.69	301.97	556.96	474.57	391.08
	SD	13.06	13.70	1022.47	627.34	707.39	711.73	854.72	783.18	712.11
MZM	Mean	27.26	1978	1253.26	565.40	734.03	712.84	687.86	519.22	478.73
	SD	12.41	12.82	1421.74	928.63	1078.47	1054.75	1146.86	970.73	918.54
MZF	Mean	29.88	1977	796.28	229.72	325.25	318.82	566.56	471.03	392.72
	SD	13.63	13.96	1068.76	641.64	739.33	725.18	910.94	818.66	755.74
DZM	Mean	24.89	1979	1258.62	646.01	788.97	769.86	612.61	469.65	421.32
	SD	11.17	12.22	1375.40	1039.40	1109.98	1099.72	1027.20	922.06	891.88
DZF	Mean	27.20	1979	824.07	254.63	332.94	330.97	569.43	491.13	399.36
	SD	12.00	13.07	1071.69	686.06	747.68	763.81	860.50	796.93	720.05

Supplementary table 5.2 Exercise and age descriptives per sex and family relation. MZM: Monozygotic male twins; MZF: Monozygotic female twins; DZM: Males part of a dizygotic twin pair; DZF: Females part of a dizygotic twin pair; Total: Total volume of exercise (METminutes /week) ; Team: volume of exercise in team-based activities; Comp: volume of exercise in competitive activities; Externally paced: volume of exercise in externally paced activities; Solitary: volume of exercise in solitary activities; Non-competitive: volume of exercise in non-competitive activities; Internally paced: volume of exercise in internally paced activities.

		Total		Team		Solitary		Competitive		Non-Competitive		Ext. Paced		Int. Paced	
		ACE	ACDE	ACE	ACDE	ACE	ACDE	ACE	ACDE	ACE	ACDE	ACE	ACDE	ACE	ACDE
Household	A	0.28	0.19	0.32	0.14	0.23	0.15	0.3	0.17	0.21	0.13	0.31	0.18	0.2	0.13
	C	0.2	0.2	0.09	0.11	0.19	0.2	0.19	0.2	0.17	0.17	0.19	0.2	0.17	0.17
	D		0.21		0.32		0.18		0.26		0.17		0.26		0.16
	E	0.52	0.4	0.59	0.42	0.58	0.48	0.51	0.37	0.62	0.52	0.5	0.36	0.63	0.54
	Log Likelihood	13317	13394	32470	32698	11870	11925	22595	22731	12312	12361	23165	23308	12604	12647
SibHousehold	A	0.25	0.22	0.25	0.17	0.22	0.19	0.27	0.23	0.19	0.17	0.29	0.23	0.19	0.16
	C	0.1	0.04	0.11	0.03	0.07	0.02	0.08	0.01	0.06	0.01	0.08	0	0.05	0
	D		0.15		0.26		0.14		0.21		0.14		0.23		0.14
	E	0.65	0.59	0.64	0.53	0.72	0.65	0.64	0.55	0.74	0.68	0.63	0.54	0.76	0.69
	Log Likelihood	12996	13018	32512	32615	11574	11593	22349	22407	12092	12111	22907	22974	12386	12405
SpouseHousehold	A	0.34	0.26	0.36	0.19	0.28	0.22	0.36	0.26	0.25	0.19	0.37	0.26	0.24	0.18
	C	0.25	0.24	0.19	0.16	0.25	0.25	0.26	0.25	0.22	0.22	0.27	0.26	0.21	0.21
	D		0.15		0.28		0.12		0.19		0.12		0.19		0.12
	E	0.42	0.35	0.46	0.36	0.47	0.41	0.37	0.31	0.52	0.47	0.36	0.29	0.55	0.49
	Log Likelihood	13411	13445	32543	32709	11994	12016	22720	22783	12408	12431	23295	23361	12676	12697
TwinHousehold	A	0.24	0.22	0.24	0.18	0.21	0.19	0.26	0.23	0.19	0.17	0.27	0.23	0.18	0.16
	C	0.14	0.08	0.16	0.07	0.11	0.06	0.14	0.07	0.1	0.05	0.14	0.06	0.09	0.04
	D		0.12		0.23		0.1		0.16		0.1		0.17		0.11
	E	0.61	0.58	0.6	0.53	0.68	0.65	0.6	0.55	0.71	0.68	0.59	0.54	0.73	0.69
	Log Likelihood	13010	13022	32554	32624	11590	11598	22389	22417	12106	12115	22949	22982	12397	12407

Supplementary Table 5.3. Estimates from all models tested with the Mendel software package.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.24>0	61.88	1	3.66×10^{-15}	√			
$r4 > 0$	10,711	0.71>0	2335.71	1	$< 10^{-200}$	√			
$r1 > r2$	1,420	0.24>0.12	16.61	2	2.48×10^{-4}		√	-	
$r2 > r3$	419	0.12>0.31	8.12	2	0.017		-	√	
$r2_{mz} > r2_{dz}$	465	0.12>0.12	0	1	>0.99		-	√	
$r3_{mz} > r3_{dz}$	157	0.36>0.14	2.02	1	0.16		-	√	
$r4 > r1$	1,608	0.71>0.24	656.74	1	7.66×10^{-145}				√

Supplementary Table 5.4. Spousal resemblance and its sources in team-based sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.23>0	81.91	1	1.43×10^{-19}	√			
$r4 > 0$	10,711	0.6>0	1525.94	1	$< 10^{-200}$	√			
$r1 > r2$	1,420	0.23>0.07	36.25	2	1.35×10^{-8}		√	-	
$r2 > r3$	419	0.07>0.2	4.16	2	0.12		-	√	
$r2_{mz} > r2_{dz}$	465	0.06>0.11	1.47	1	0.22		-	√	
$r3_{mz} > r3_{dz}$	157	0.18>0.23	0.19	1	0.66		-	√	
$r4 > r1$	1,608	0.6>0.23	326.41	1	5.80×10^{-73}				√

Supplementary Table 5.5. Spousal resemblance and its sources in competitive sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.26>0	93.04	1	5.12×10^{-22}	√			
$r4 > 0$	10,711	0.61>0	1664.68	1	$< 10^{-200}$	√			
$r1 > r2$	1,420	0.26>0.11	31.94	2	1.16×10^{-7}		√	-	
$r2 > r3$	419	0.11>0.2	2.58	2	0.28		-	√	
$r2_{mz} > r2_{dz}$	465	0.1>0.13	0.37	1	0.54		-	√	
$r3_{mz} > r3_{dz}$	157	0.17>0.24	0.4	1	0.53		-	√	
$r4 > r1$	1,608	0.61>0.26	314.86	1	1.91×10^{-70}				√

Supplementary Table 5.6. Spousal resemblance and its sources in externally paced sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.16>0	69.15	1	9.12×10^{-17}	√			
$r4 > 0$	10,711	0.28>0	692.13	1	1.54×10^{-152}	√			
$r1 > r2$	1,420	0.16>0.08	18.55	2	9.37×10^{-5}		√	-	
$r2 > r3$	419	0.08>0.06	0.71	2	0.70		-	√	
$r2_{mz} > r2_{dz}$	465	0.07>0.1	0.34	1	0.56		-	√	
$r3_{mz} > r3_{dz}$	157	0.07>0.03	0.18	1	0.67		-	√	
$r4 > r1$	1,608	0.28>0.16	27.8	1	1.35×10^{-7}				√

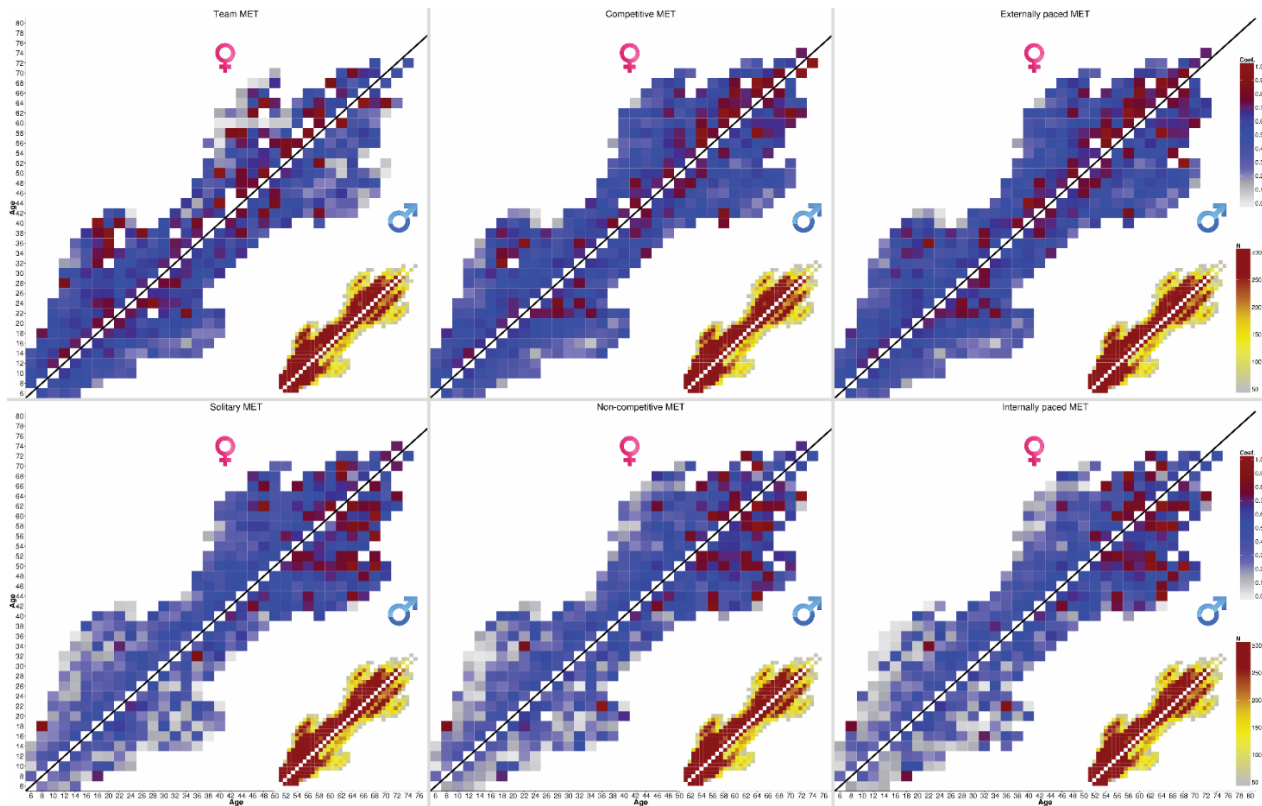
Supplementary Table 5.7. Spousal resemblance and its sources in solitary paced sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.14>0	47.22	1	6.33×10^{-12}	√			
$r4 > 0$	10,711	0.23>0	535.41	1	1.88×10^{-118}	√			
$r1 > r2$	1,420	0.14>0.06	13.19	2	1.37×10^{-3}		√	-	
$r2 > r3$	419	0.06>0.07	0.61	2	0.74		-	√	
$r2_{mz} > r2_{dz}$	465	0.06>0.09	0.43	1	0.51		-	√	
$r3_{mz} > r3_{dz}$	157	0.08>0.03	0.25	1	0.61		-	√	
$r4 > r1$	1,608	0.23>0.14	19.98	1	7.82×10^{-6}				√

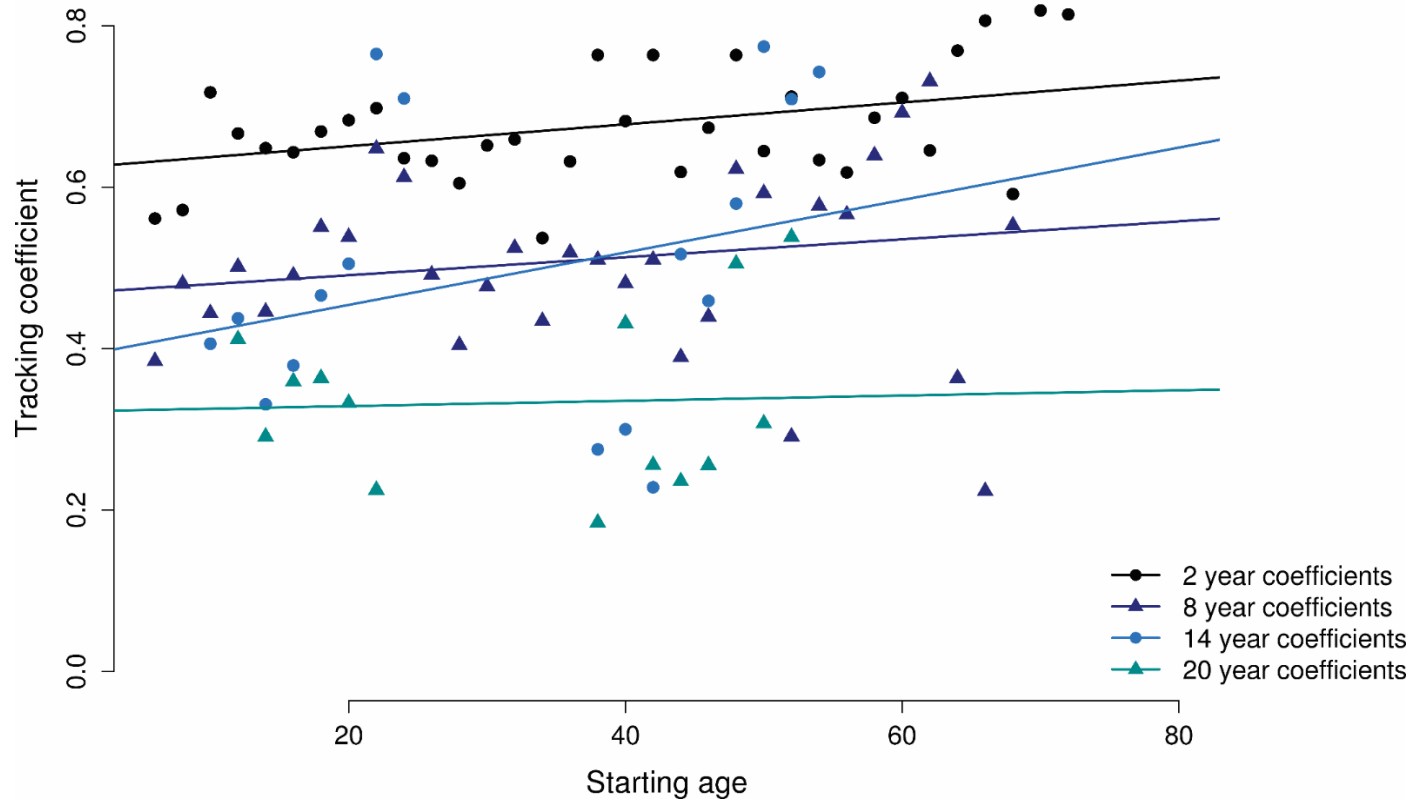
Supplementary Table 5.8. Spousal resemblance and its sources in non-competitive sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.

Hypothesis	N	Estimates	Δ -2LL	Δ df	p	Spousal Resemblance	Phenotypic Assortment	Social Homogamy	Marital interaction
$r1 > 0$	1,608	0.14>0	48.93	1	2.66×10^{-12}	√			
$r4 > 0$	10,711	0.22>0	496.66	1	5.06×10^{-110}	√			
$r1 > r2$	1,420	0.14>0.07	15.32	2	4.71×10^{-4}		√	-	
$r2 > r3$	419	0.07>0.06	0.89	2	0.64		-	√	
$r2_{mz} > r2_{dz}$	465	0.05>0.1	1.1	1	0.30		-	√	
$r3_{mz} > r3_{dz}$	157	0.08>0.03	0.23	1	0.63		-	√	
$r4 > r1$	1,608	0.22>0.14	12.1	1	5.04×10^{-4}				√

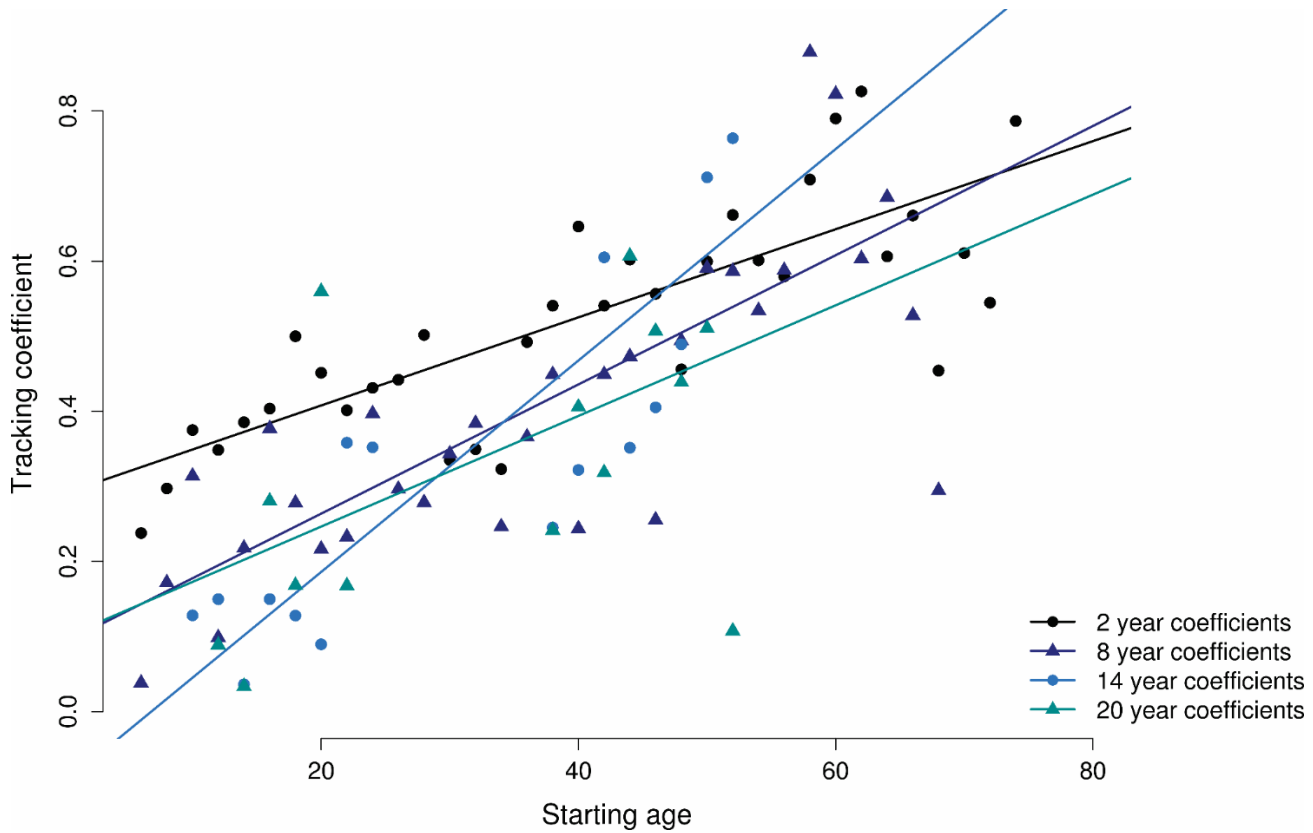
Supplementary Table 5.9. Spousal resemblance and its sources in internally paced sports activities. Hypothesis: expectations for the patterns of twin-spouse correlations ($r1$), co-twin spouse-correlations ($r2$), spouse1-spouse2 correlations ($r3$), and parent-parent correlations ($r4$) under phenotypic assortment, social homogamy, and marital interaction. Under phenotypic assortment the expected pattern of correlations is $r1 > r2 > r3$, $r2_{MZ} > r2_{DZ}$, $r3_{MZ} > r3_{DZ}$. Under social homogamy the expected pattern is ($r1 = r2 \geq r3$), $r2_{MZ} = r2_{DZ}$, $r3_{MZ} = r3_{DZ}$. Under marital interaction we expect $r4 > r1$; N: Number of complete pairs in the data (if two correlation coefficients are compared the lowest N is presented); Δ -2LL: Difference in -2 log-likelihood compared to the base model; Δ df: Difference in degrees of freedom compared to the base model, and used in the chi-squared test; p: p-value of the chi-squared difference test comparing the base model to the constrained model; √: Hypothesis supported with $\alpha = 0.01$.



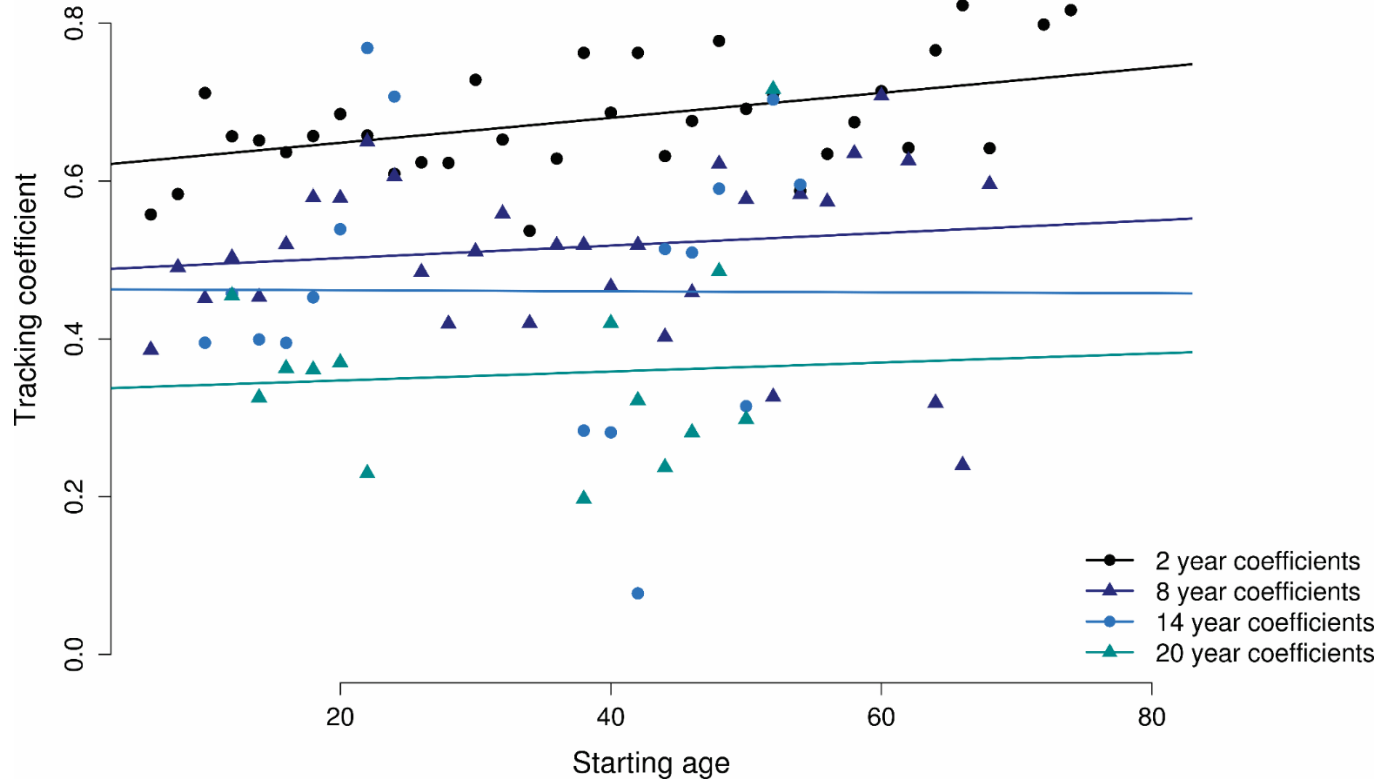
Supplementary Figure 2.1. Tracking coefficient, and sample size heatmaps of exercise domains, similar to Figure 2.3 of the main manuscript. High-resolution version available online at <https://drive.google.com/drive/folders/1i8IUQJcMmzjOQTPTGTxsFuTn8tpKIKZr?usp=sharing>



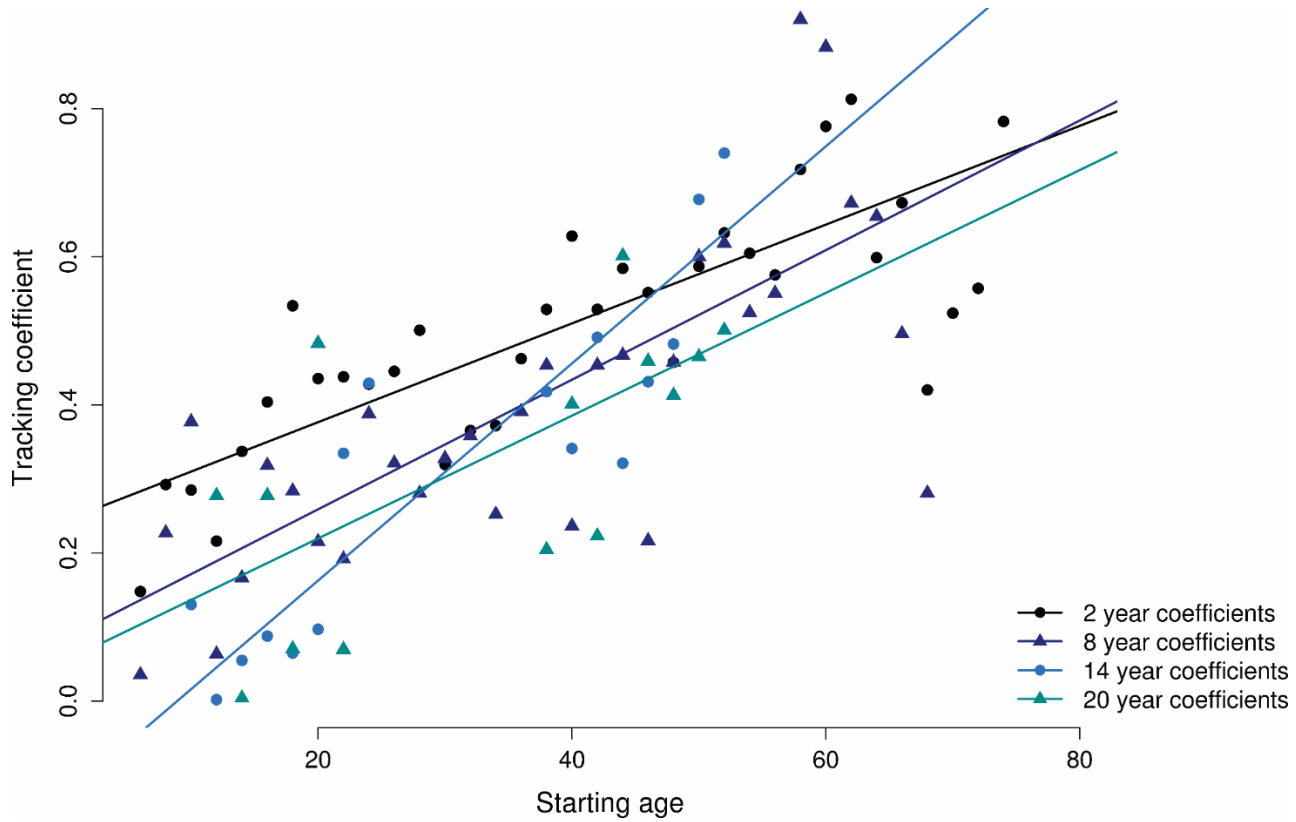
Supplementary Figure 2.2. Tracking coefficients for volume of competitive exercise behavior as a function of age at baseline.



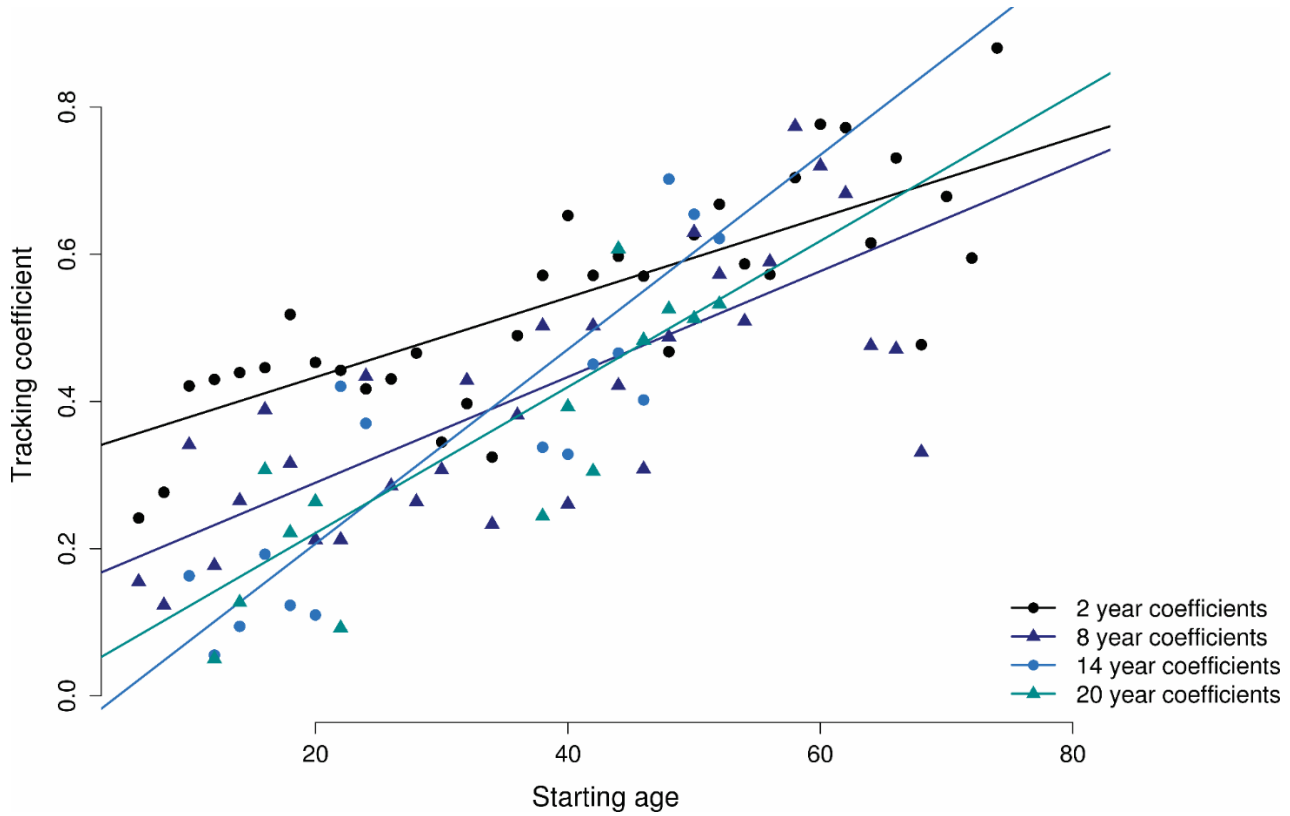
Supplementary Figure 2.3. Tracking coefficients for volume of non-competitive exercise behavior as a function of age at baseline.



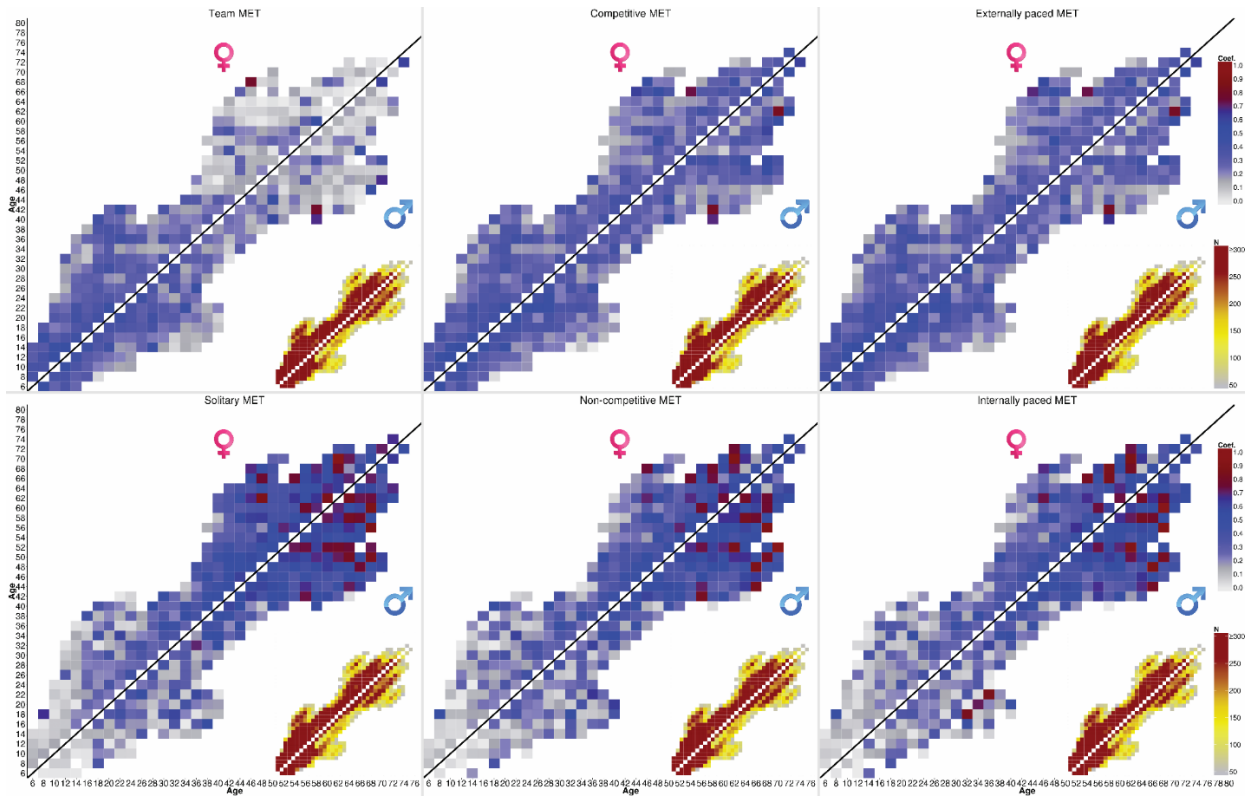
Supplementary Figure 2.4. Tracking coefficients for volume of externally paced exercise behavior as a function of age at baseline.



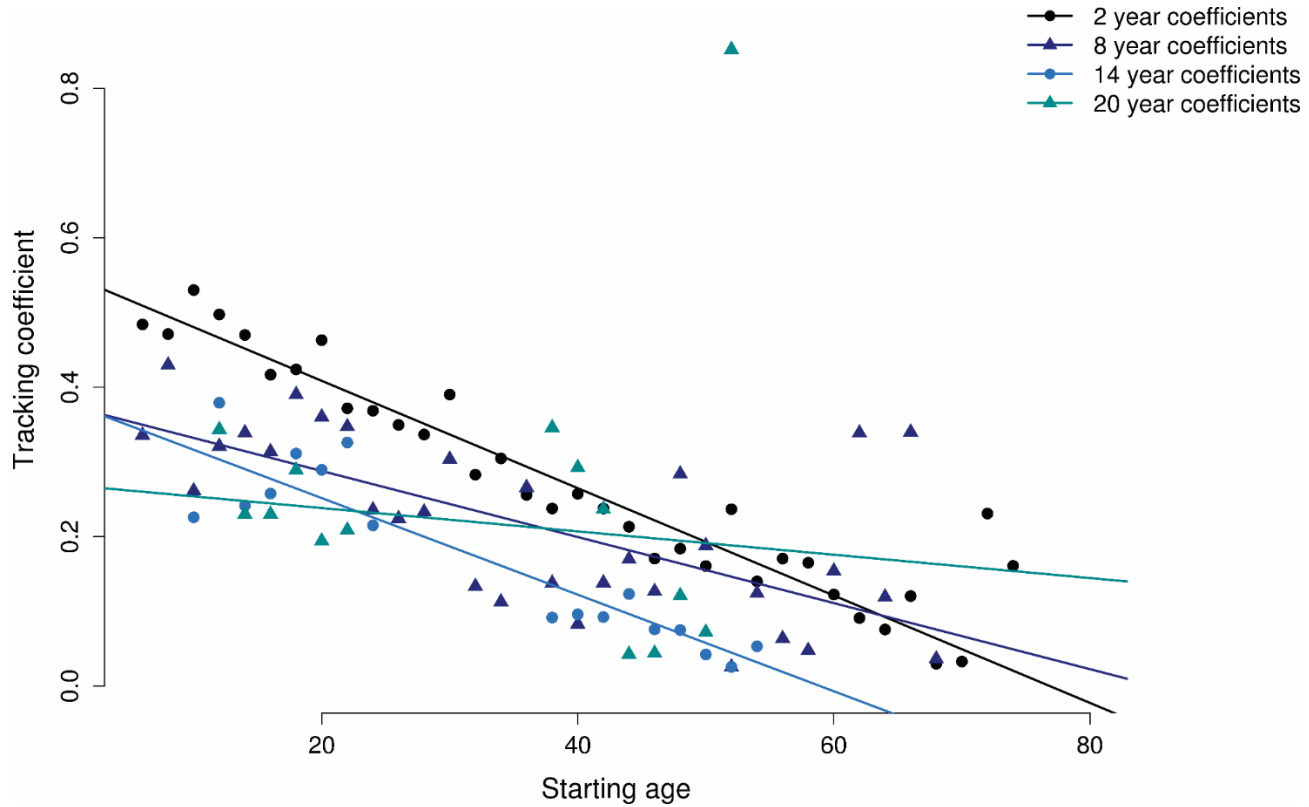
Supplementary Figure 2.5. Tracking coefficients for volume of internally paced exercise behavior as a function of age at baseline.



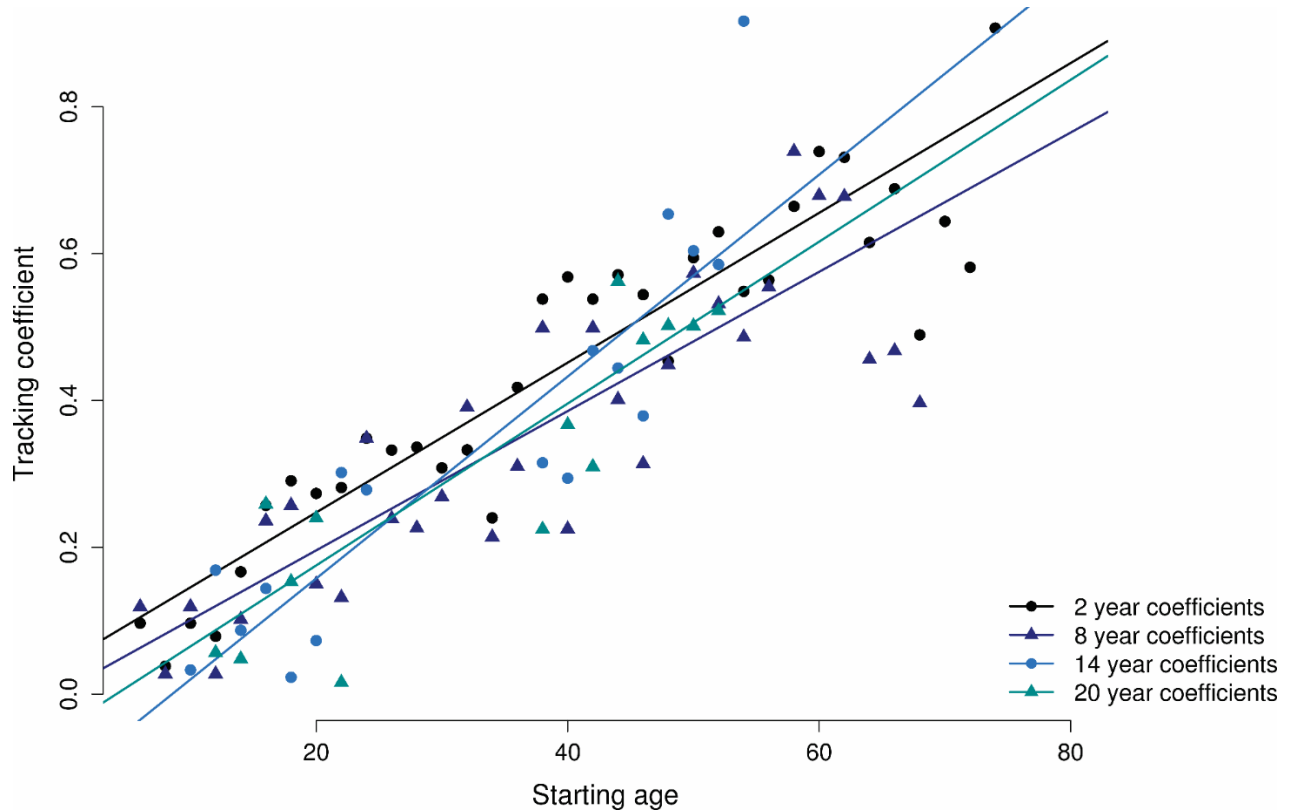
Supplementary Figure 2.6. Tracking coefficients for volume of solitary exercise behavior as a function of age at baseline.



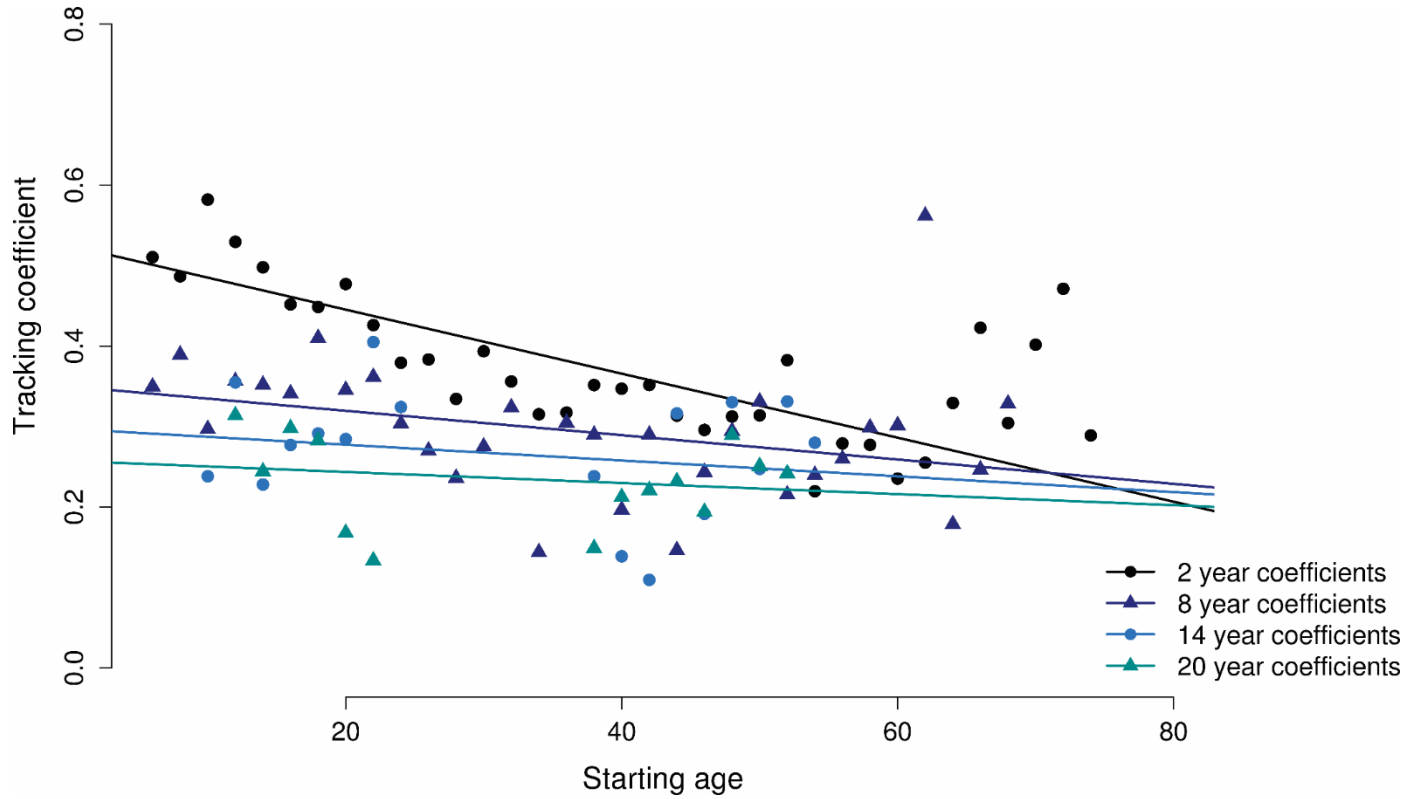
Supplementary Figure 2.7. Between-domain tracking coefficient heatmaps of exercise domains at baseline and total volume of exercise at follow-up. High-resolution version available online at <https://drive.google.com/drive/folders/1i8IUQJcMmzj0QTPtGTxsFuTn8tpKIKZr?usp=sharing>



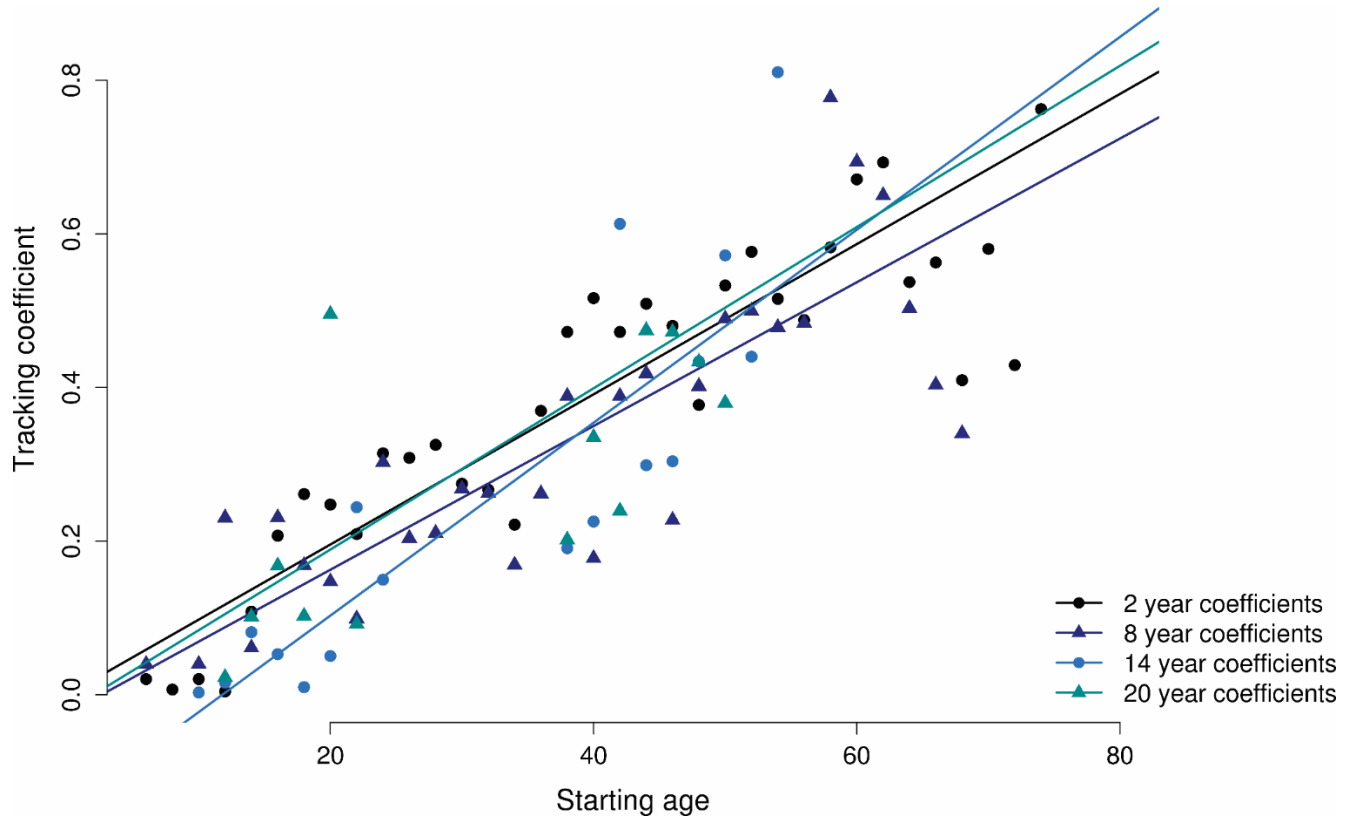
Supplementary Figure 2.8. Tracking coefficients for volume of team-based exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



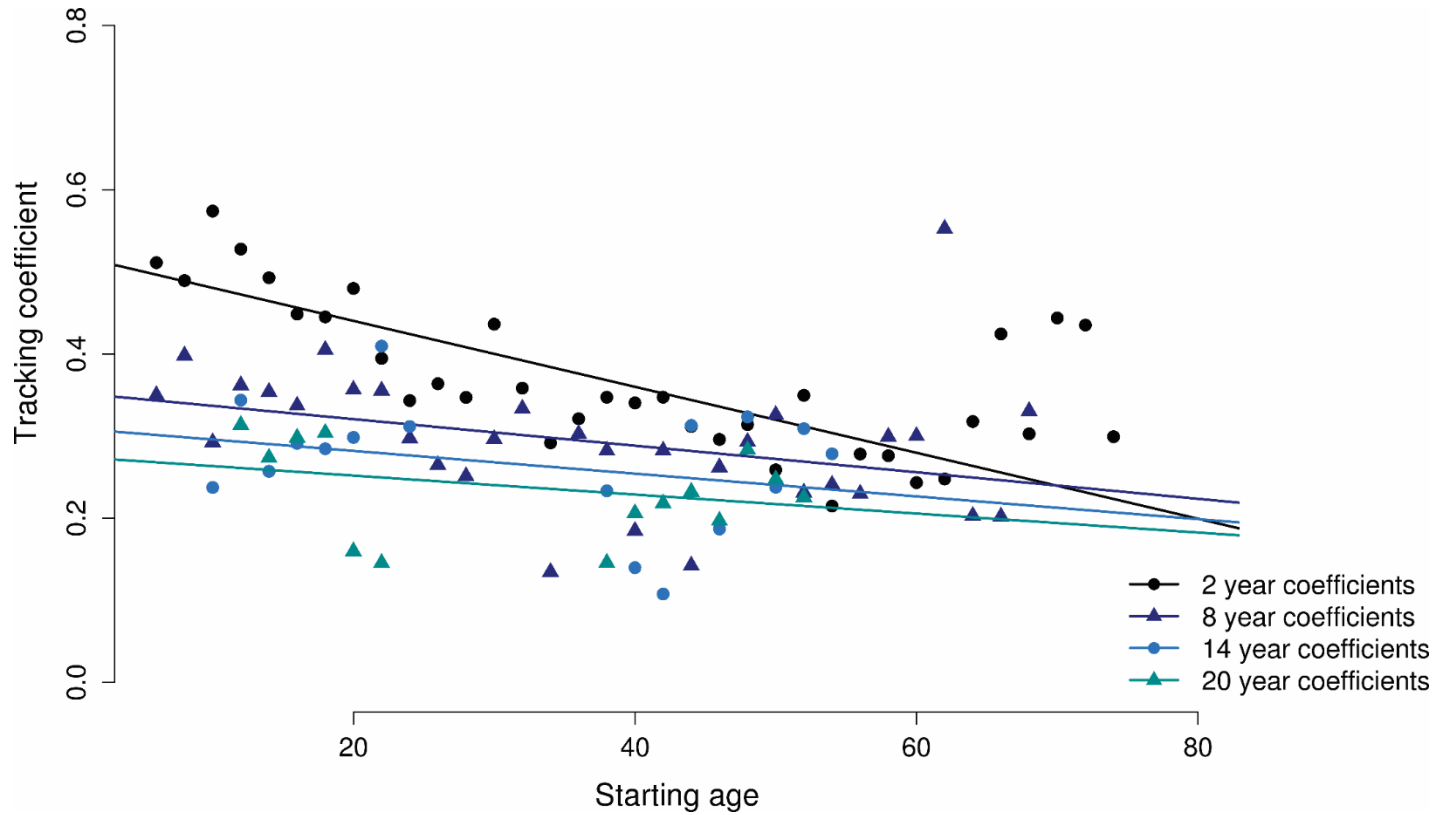
Supplementary Figure 2.9. Tracking coefficients for volume of solitary exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



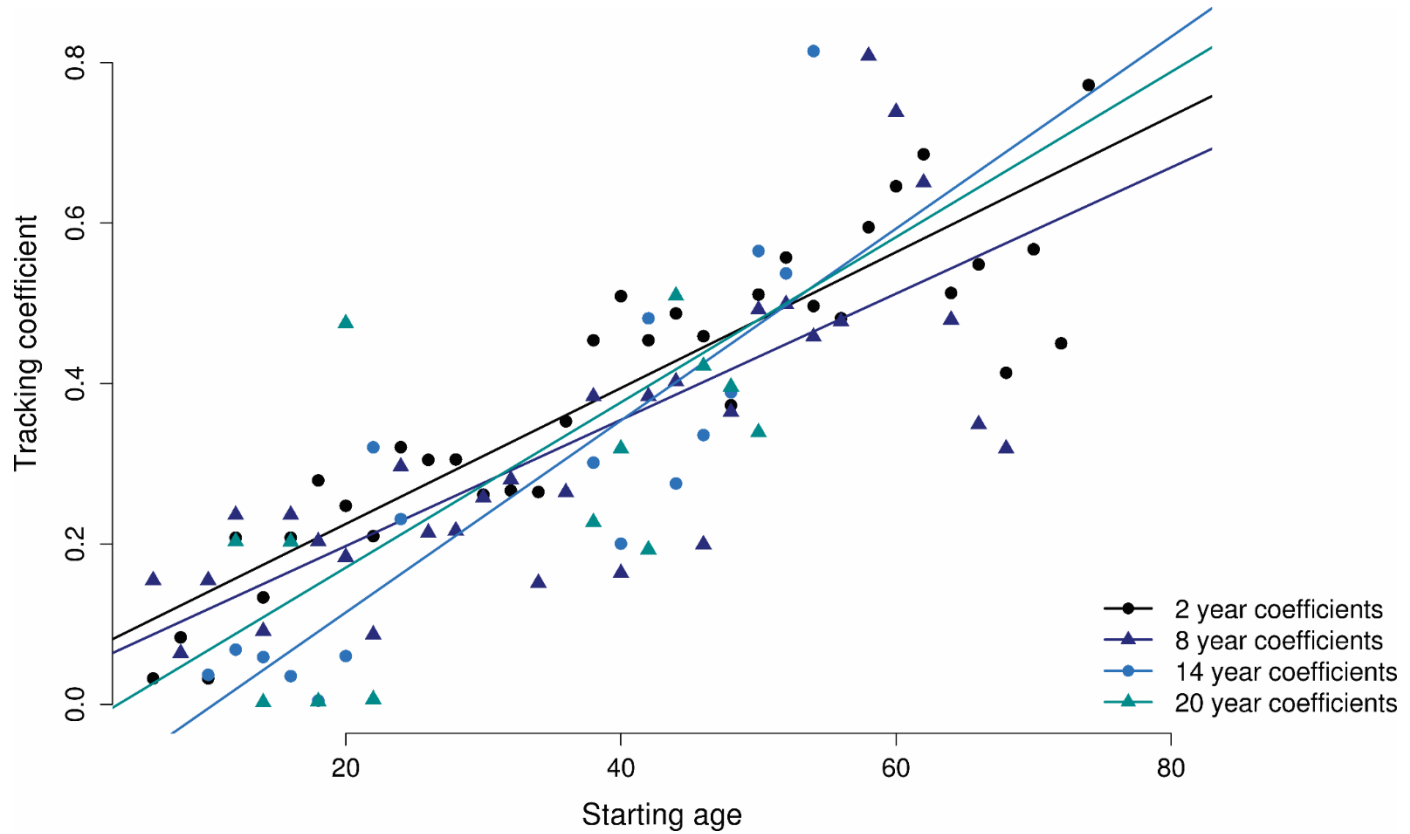
Supplementary Figure 2.10. Tracking coefficients for volume of competitive exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



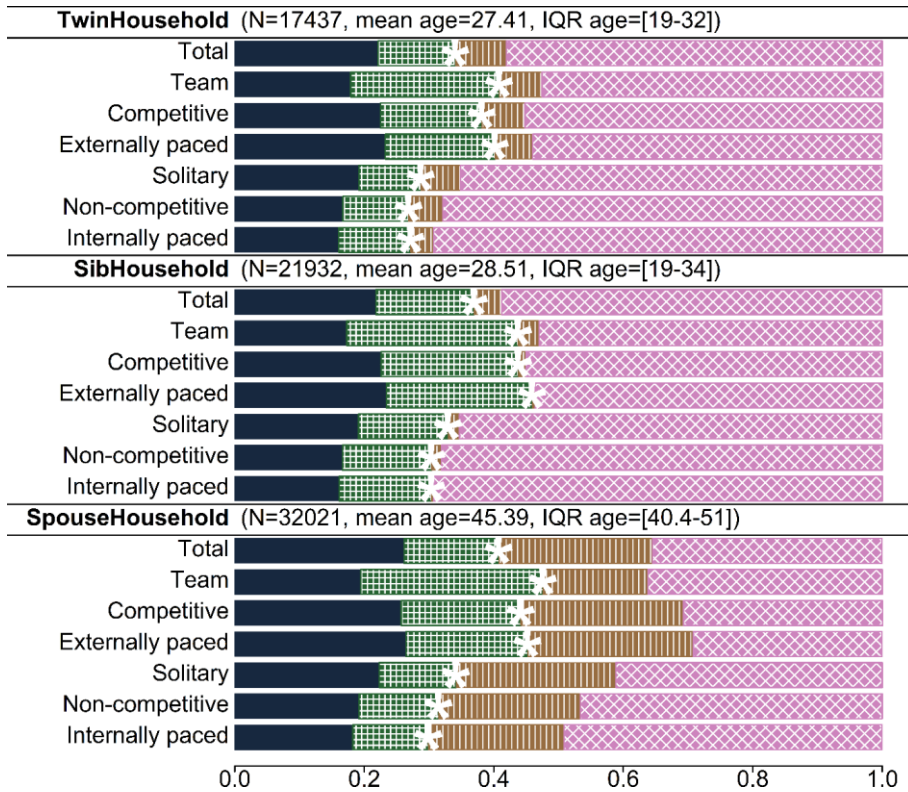
Supplementary Figure 2.11. Tracking coefficients for volume of non-competitive exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



Supplementary Figure 2.12. Tracking coefficients for volume of externally paced exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



Supplementary Figure 2.13. Tracking coefficients for volume of internally paced exercise behavior at baseline and total volume of exercise at follow-up, as a function of age at baseline.



Supplementary Figure 5.1. ACDE estimates for other household definitions: Proportion of variance explained by **additive genetic (A)**, **non-additive genetic (D)**, **common household environmental (C)**, **unique environmental (E)** factors and broad sense heritability(*) for different classes of exercise using various household definitions as shared environment.

Dankwoord

To the majority of readers, welcome to my thesis. To those of you who have actually read everything and ended up here, thank you very much, I do hope you enjoyed the content. Just a heads up before I begin, this dankwoord will switch between English and Dutch often and mid-paragraph. I tried to create some semblance of structure in what's English and what's Dutch but to no avail.

Allereerst wil ik graag alle **deelnemers aan het NTR** ontzettend bedanken voor hun bijdrage. Dit proefschrift was niet mogelijk geweest zonder de voortdurende vrijwillige inzet van de vele deelnemers. Dus bij deze, aan alle deelnemers en iedereen die geholpen heeft bij de dataverzameling, ontzettend bedankt!

Next I would like to thank my promotion committee. **Peter Beek, Yannis Pitsiladis, Jaakko Kaprio, Hidde van der Ploeg and Nienke Schutte**. I would like to thank you all sincerely for all the time and effort you have spent on my thesis. **Nienke**, ik vind het een bijzondere eer dat je op deze manier aan het einde van mijn PhD betrokken bent, aangezien je ook aan de wieg van mijn wetenschappelijke carrière hebt gestaan. Jouw enthousiasme en motivatie heeft destijds een belangrijke rol gespeeld in mijn beslissing om een PhD te gaan doen, dus ook daarvoor heel erg bedankt.

I would also like to thank my co-promoters. **Erik Ehli**, thank you so much for your mentorship and guidance, especially during my time at AIHG. It has always been a joy for me to learn from your expertise. **Jenny van Dongen**, ook jij ontzettend bedankt voor alles wat je voor mijn proefschrift hebt betekend en bedankt voor alles wat ik van jou heb mogen leren tijdens mijn PhD, zowel over (epi-)genetica als over het goed begeleiden van studenten.

Uiteraard kan in mijn dankwoord ook mijn promotor, **Eco de Geus**, niet ontbreken. Beste Eco, ik kan jou nooit genoeg bedanken voor wat je voor dit proefschrift en voor mij persoonlijk hebt betekend. Voor je intensieve hulp en steun, bij de laatste loodjes in het bijzonder, ben ik je ongelooflijk dankbaar voor. Dit geldt eigenlijk evengoed voor het gehele project. Met jouw passie en interesse wist je mij keer op keer te motiveren voor nieuwe projecten, uitgebreide analyses en noem maar op. Dus voor alles: je hulp bij het schrijven, bij analyses, je openheid voor nieuwe ideeën, voor dat ik (na wat aandringen) toch Python mocht gebruiken, voor je steun en zo veel meer, ontzettend bedankt!

I would also like to thank everyone at the **Avera Institute for Human Genetics** for the continued collaboration throughout my PhD and for making me feel at home in Sioux Falls during my time there. **Ryan**, if it wasn't for your comforting words leading up to my first visit to AIHG, odds are none of this would have happened, so thank you very much for that and all the rest you have done to help make this PhD a reality. **John, Brandon and Austin**, thank you so much for the awesome collaboration throughout my PhD. I have enjoyed working with all of you very much and I'm looking forward to a continued collaboration in the future. Noah, your humor and helpfulness made my time at AIHG even more enjoyable than it already was, so thank you for making my time at AIHG even more fun. **Jeff**, though it pained me to be named 'New-Jeff' when I came back and you knew Wonu and Eshim better than me, I consider it a compliment. It has been awesome to work with you, but more importantly I consider you as a good friend and I am grateful for all the time we spent together, looking forward to much more. **Casey**, be it the microbiome lectures on a road trip, or beers and (Dutch) nachos, I have not only learned a lot from you, but more importantly I have enjoyed every second of our great friendship.

Of course, I would also like to thank all my colleagues at **BioPsy**, for all their help writing my thesis and equally important for their support throughout. **Meike**, jij diende als mijn “gateway-drug” voor de afdeling tijdens mijn bachelor state in 2013 en sindsdien ben ik er ook niet meer weggegaan. Dankzij jou zit ik hier en mede dankzij jou blijf ik hier ook. **Dennis**, om nog maar even bij mijn begin op de afdeling te blijven. Niet alleen was jij de beste teaser voor de afdeling in het bachelorvak, jouw vriendelijkheid en humor hebben ervoor gezorgd dat ik me snel op mijn gemak voelde op de afdeling. **Dorret**, zonder jou waren veel papers in dit proefschrift niet mogelijk geweest en was mijn fijne samenwerking met AIHG misschien ook wel nooit tot stand gekomen, dus ontzettend bedankt voor al je hulp! Over hulp gesproken, **Conor**, zonder jou had ik veel van de OpenMx en R dingen in dit proefschrift nooit kunnen doen, dus nogmaals ontzettend bedankt. **Jouke-Jan**, mijn hele these is gebouwd op genetische data en niets hiervan was mogelijk zonder jou. Niet alleen vanwege je werk aan MRG maar ook door de honderden keren waarop je mij hebt geholpen, dank daarvoor. Ditzelfde geldt overigens voor **René Pool**, niet alleen bedankt voor je hulp met PRS en data, maar het is vooral ook fijn om niet de enige Pythonista op de afdeling te zijn. **Michiel**, zonder jouw hulp was er nog veel meer dan alleen wat analyses niet gelukt, dus ontzettend bedankt! **Martin**, bedankt voor het zelfgemaakte kokosnootbier en de bijzonder fijne samenwerking tijdens Analyses Toolbox het onderwijs. **Michel**, dankzij jou ben ik op vele vlakken, zowel als wetenschapper als persoon, enorm gegroeid. Ontzettend bedankt daarvoor (en voor de PostDoc positie natuurlijk). En tot slot, **Natascha**, jij maakt de hele afdeling voor mij (en ik denk voor iedereen) altijd leuker, zelfs in corona tijden. Zonder jou en zonder de sfeer had ik me in al die jaren niet zo vermaakt en zonder jouw steun was deze PhD ook niet mogelijk, dus nogmaals ontzettend bedankt!

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